

THE EFFECTS OF ATP –DEPENDENT POTASSIUM CHANNEL (K_{ATP})
AGONIST AND ANTAGONISTS ON PENICILLIN G INDUCED EPILEPSY
MODEL IN RATS

by

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THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF NATURAL APPLIED SCIENCES
OF
ABANT İZZET BAYSAL UNIVERSITY
IN PARTIAL FULLFILMENT OF THE REQUIIREMENTS FOR THE
DEGREE OF
DOCTOR PHILOSOPHY OF SCİENCE
IN THE DEPARTMENT OF BIOLOGY

JULY 2014

Approval of the Graduate School of Natural and Applied Sciences

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ABSTRACT

THE EFFECTS OF ATP –DEPENDENT POTASSIUM CHANNEL (K_{ATP}) AGONIST AND ANTAGONISTS ON PENICILLIN G INDUCED EPILEPSY MODEL IN RATS

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July - 2014, 255 Pages

Epilepsy is a neurological disease having a high incidence in the world that characterized with abrupt, extreme, rhythmic, abnormal electrical discharges. It is characterized with hypersynchronization occurring due to disturbance of equilibrium between inhibitory and excitatory systems and shifting the electrical activity towards the excitator side. Although molecular mechanism of seizures are not fully understood, functions of membrane channels are not known well. ATP dependent potassium channels have been shown to have a role in control of seizures. ATP dependent potassium channels regulate excitatory neurotransmitter release of neurons. In control of seizure, ATP dependent potassium channels play a very important role and found in most of the tissues. The physiological roles of ATP dependent potassium channels have been demonstrated in cardiac myocytes,

pancreatic β cells and muscle cells. K_{ATP} channels is effective in seizure and control of chronic epilepsy models that have been shown in many studies. In these studies, it is found that K_{ATP} opener increase seizure threshold. Aim of the study is to research the effects of K_{ATP} channel agonists (opener) and antagonists (blocker) in the penicillin model of experimental epilepsy.

Wistar albino male rats were used in this study. Groups were divided into three main groups which were; control, before-seizure and during seizure groups. Epilepsy was produced by application of 500IU 2.5 μ l penicillin intracortically. In the first step of this study, the effective dose of bepridil (ATP dependent mitochondrial potassium channel opener) and P1075 (sarcolemmal K_{ATP} opener) were determined. Bepridil, P1075, HMR1098 (sarcolemmal K_{ATP} blocker-3mg / kg), 5HD (mitochondrial K_{ATP} blocker-10mg / kg) were given before seizure and during seizure. The effect of each drug on the appearance of the frequency and amplitude of epileptic spike were determined. Differences within groups were tested by one way ANOVA. LSD test was used as a post hoc test. P values which were smaller than 0,05 were accepted as significant.

P1075 0.1mg/kg delayed seizure when it was applied before seizure ($p < 0.05$). When bepridil applied 1mg/kg in dose before and during seizure, it decreased spike frequency compared to control ($p < 0.05$). P1075 in 0.1 mg/kg dose applied before seizure and during seizure decreased spike frequency significantly compared to control group. On the other hand, P1075 0.5 mg/kg in dose applied during seizure and 0.1 mg/kg in dose applied before seizure ended seizure earlier than the control group. HMR 1098 applied before seizure started seizure earlier in respect to control. In 5HD and HMR 1098 groups, there were no significant differences in latency. When 5HD and HMR 1098 applied before seizure and during seizure they increased

spike frequency compared to control group ($p < 0.05$). As a result, K_{ATP} channel blockers in experimental penicillin model of epilepsy, increase spike wave frequency, otherwise K_{ATP} channel opener P1075 and bepridil decrease spike frequency ($p < 0.05$). At the same time while Bepridil and P1075 delayed the seizure. HMR 1098 and 5HD caused early appearance of seizure spike following penicillin treatment. As a result both sarcolemmal and mitochondrial openers have protective effect, on the other side, blockers have deleterious effect in the epileptic activity and its duration.

Keywords: Epilepsy, mito K_{ATP} , sarc K_{ATP} , Bepridil, 5-HD, P-1075, HMR-1098

ÖZET

PENİSİLİN G İLE OLUŞTURULAN DENEYSEL EPİLEPSİ MODELİNDE ATP BAĞIMLI K (K_{ATP}) KANAL AGONİST VE ANTAGONİSTLERİNİN ETKİLERİ

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Temmuz - 2014, 255 Sayfa

Epilepsi dünyada görülme oranı yüksek olan nörolojik bir hastalıktır. Ani, şiddetli, ritmik, anormal elektriksel deşarjlarla karakterizedir. İnhibitör ve eksitator sistem arasındaki dengenin eksitator tarafa bozulması sonucu oluşan hipersenkronizasyon ile karakterizedir. Nöbetlerin moleküler mekanizması tam olarak bilinmemesine rağmen nöbetlerin kontrolünde ATP bağımlı potasyum kanallarının rolü olduğu gösterilmiştir. ATP bağımlı potasyum kanalları nöronların eksitator nörotransmitter salınımını düzenler. Nöbetin kontrolünde ATP bağımlı potasyum kanalları çok önemli rol oynar. K_{ATP} kanalları birçok dokuda bulunur. Örneğin kardiyak miyositlerde, pankreatik beta hücrelerinde, kas hücrelerinde birçok fizyolojik role sahiptir. Birçok çalışmada kronik epilepsi modellerinde K_{ATP} kanallarının nöbet

kontrolünde etkili olduđu gösterilmiřtir. K_{ATP} agonistlerinin nbet eřiđini arttırdıđı ve antagonistlerinin de azalttıđı, yapılan alıřmalarla ortaya konmuřtur. İstatistiki verilere gre epilepsi hastalıđının diři ve erkek bireylerde grlme oranı eřittir. alıřmanın amacı K_{ATP} kanal agonist (opener) ve antagonistlerinin (bloker) penisilin modeli deneysel epilepsi zerine etkilerini arařtırmaktır.

alıřmada wistar albino cinsi erkek sıanlar kullanıldı. Kontrol, nbet ncesi ve nbet sırası olmak zere  ana grup oluřturuldu. Epilepsi 500 IU 2.5 µl penisilinin intrakortikal verilmesi ile oluřturuldu. alıřmanın birinci ařamasında mitokondriyal K_{ATP} - aıcısı olan bepridil ve P1075 in etkili dozları saptandı. İkinici ařamada HMR 1098 (sarkolemmal K_{ATP} bloker-3 mg/kg) ve 5HD (mitokondriyal K_{ATP} blokerı-10 mg/kg) nbet ncesi ve nbet sırasında verildi ve epileptik diken dalgaların frekansı ve genlikleri saptandı. Gruplar arasındaki farlılıklar ANOVA ile deđerlendirildi. Post hoc testi olarak ise LSD kullanıldı. $P < 0.05$ deđerleri anlamlı olarak kabul edildi.

P1075 0.1 mg/kg ve bepridil 10 mg/kg nbet ncesi uygulandıđında nbeti geciktirmiřtir ($p < 0.05$). Bepridil nbet ncesinde ve sırasında 1 mg/kg dozda uygulandıđında diken dalga frekansını kontrole gre azaltmıřtır ($p < 0.05$). P1075 nbet ncesinde ve sırasında 0.1 mg/kg dozda diken dalga sayısını kontrol grubuna gre anlamlı olarak azaltmıřtır. P1075'in 0.5 mg/kg dozda ise nbeti erken sonlandırmıřtır. 5HD ve HMR 1098 gruplarında nbete bařlama zamanları kontrole gre deđiřmemiřtir. 5HD ve HMR 1098 nbet ncesinde ve nbet sırasında uygulandıđında diken dalga frekansını kontrole gre artırmıřtır ($p < 0.05$). Bu sonulara gre K_{ATP} kanal kapatıcısı penisilin modeli deneysel epilepside nbet řiddetini belirleyen diken dalga sayısını artırırken. K_{ATP} kanal aıcısı P1075 ve bepridil diken dalga sayısını azaltmıřtır ($p < 0.05$). Aynı zamanda Bepridil ve P1075 nbeti geciktirirken HMR 1098 ve 5HD nbete bařlamayı kolaylařtırmıřtır. Sonu

olarak Hem sarkolemmal hemde mitokondrial K_{ATP} açıcılar epilepsi üzerinde koruyucu etkiye sahipken kapatıcılar ise epileptik aktiviteyi ve süresini artırmıştır.

Anahtar Kelimeler: Epilepsi, mito K_{ATP} , sarc K_{ATP} , Bepridil, 5-HD, P-1075, HMR-1098

TO MY FATHER,
Nadi SOYTÜRK

ACKNOWLEDGEMENT

I would like to express my sincere gratitude to Prof. Dr. Ömer Bozdoğan and Associate Prof. Dr. Şerif Demir for his unceasing interest, valuable guidance, encouragement and great help throughout the course of this work. I would like to thank my committee members. Prof. Dr. Nurbay Ates, Prof. Dr. Fatma Töre, Prof. Dr. Mustafa Ünal, for their critical reading of this manuscript.

I want to convey my deepest thanks to my family for their supports. I want to thank Prof. Dr. Aysel Kükner and Assistant Prof. Dr. Tülin Fırat for their technical supports. I want to thank Assistant Prof. Dr. Yıldırım Kayacan for him supports. I want to thank Associate. Prof. Dr. Alper Karakaş for him supports.

I would like to thank Ms students Oğulcan Özarslan, İsmail Akpunar, Firdevs Erim, Gürkan Özcan and Merve Toklucu for their help in the drawing of the figures in this thesis.

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LIST OF ABBREVIATIONS

K_{ATP} channel	: ATP dependent potassium channel.
SarcK_{ATP} channel	: Sarcolemmal ATP dependent potassium channel.
MitoK_{ATP} channel	: Mitochondrial ATP dependent potassium channel.
KCa channels	: Ca ⁺⁺ activated K ⁺ channels.
Kir 6.x	: Inwardly rectifying K ⁺ channel core.
SUR	: Sulfonylurea receptor.
TMD	: Transmembrane domains.
NBF	: Nucleotide binding fold.
KCO	: ATP dependent potassium channel opener.
SDH	: Succinate dehydrogenase.
ANT	: Adenine nucleotide translocator.
IPC	: Inorganic phosphate carrier.
IMS	: Intermembrane space.
MitoIM	: Mitochondrial inner membrane.
ROS	: Reactive oxygen species.
MPTP	: Mitochondrial permeability transition pore.
PPase	: Peptide prolyl cis trans isomerase.
VDAC	: Voltage dependent anion channel.

PKC	: Protein kinase C.
PDS	: Paroxysmal depolarization shift
GABA	: Gama Amino butyric acid
EPSP	: Excitatory postsynaptic potential
IPSP	: Inhibitory Post synaptic potential
SE	: Status Epilepticus
5HD	: 5 -hydroxydecanoic acid
EEG	: Electroencephelography
ECoG	: Electrocortigography
SRED	: Spontaneous recurrent epileptiform discharges
HNC	: Hippocampal neuronal cultures
CaMK-II	: Calcium-calmodulin protein kinase-2
VMH	: Ventro medial hypothalamus in brain
DZX	: Diazoxide
DEND	: Dysmorphic features and neonatal diabetes
SNR	: Substantia nigra
PTZ	: Pentilentetrazol
PTX	: Picrotoxin
4a-AP	: 4 - aminopyridine
GABA_A	: Gaba A receptor
GABA_B	: Gaba B receptor
mGluR	: Metabotropic glutamate receptors
ACh	: Acetylcholine
BMI	: Bicuculline methioiodide
CAMP	: Cyclic Adenosine Monophosphate

CNS	: Central nervous systems
PDS	: Paroksismal depolarization shift
SE	: Status Epilepticus
PKA	: Protein kinase A

1. INTRODUCTION

Epilepsy is one of the neurological diseases that has the most incidence in the world. It is characterized by excessive activation of neurons that can not be controlled by the central nervous system. The balance between excitation and inhibition shift to the excitation side during an epileptic seizure and during these events a high amount of neurotransmitters are released. While some of these neurotransmitters increases excitation, some of them decreases excitation. It has been proposed that, calcium ions play an important role in the formation of epilepsy. Calcium (Ca^{+2}) entry into the cell leads to the release of excitatory neurotransmitters (1).

Epilepsy is a disorder that can be seen in men and women and in all kinds of races from every region of the world. A specific cause can not be found in about half of the patients but some known causes are; brain developmental problems that occur during pregnancy or birth, meningitis, brain infections, brain tumors, serious head injuries or severe poisoning. The role of the T-type Ca^{+2} channel that is found especially in the thalamic cell has been proved in the formation of epilepsy for some types of seizure. However the view that emphasizing the cause of some types of epileptic seizures became increasingly predominant in cortical and subcortical connection. Most types of epilepsy occurs as a result of a complex genetic etiology containing interaction of one or more genes (2). To understand the molecular mechanisms and genetic basis, new studies are needed.

Seizures caused by simultaneously discharges of neurons are based on the effects Ca^{+2} channels on the cell membrane. While Ca^{+2} ions increases the excitation, outflow of K^{+} ions provides the return of cell to the resting state protecting resting potential.

ATP dependent potassium (K_{ATP}) channel modulation are related with the epilepsy. K_{ATP} channels have been found first in the heart (3). They have wide distribution on many types of tissue and cell types. While K_{ATP} channels are inhibited by intracellular ATP, they are activated by ADP (3). Interior region of the cell is sensitive to changes in adenine nucleotide concentration. K_{ATP} channels is thought to have an important role in various condition, such as hyperglycemia, hypoglycemia, ischemia, reperfusion (4). Different characteristics of K_{ATP} channel in many cell types has been identified in the brain that comprise hippocampal cells, in glia cells, in the dorsal vagal cell, in hypothalamic neurons and in the substantia nigra (SNR) (5). Opening of K_{ATP} channels have been shown to be protective against neuronal damage and neurodegeneration during metabolic stress (6).

K_{ATP} channels are found in pre-and post-synaptic neuron in many regions of the brain. K_{ATP} channels can be opened or closed according to the changes in intracellular ATP / ADP ratio. When ATP level decrease, these channels open and K^{+} leaks out of the cell and hyperpolarization takes place (7-8). K_{ATP} channel activity is regulated by cellular metabolism (9-10). This condition is associated with the electrical activity of cells. Pharmacological studies has proven that K_{ATP} channels play an important role in controlling seizure threshold (3).

In experimental model of epilepsy induced with Pentilentetrazol (PTZ: pentylenetetrazol) and 4 - aminopyridine (4a-AP: Aminopyridine) was determined

that K_{ATP} channel agonists (diazoxide, cromakalim, pinacidil, levcromakalim, nicorandil, minoxidil etc.) decreases seizures (10), while K_{ATP} ion channel antagonists (glibenclamide etc.) improve (9) epileptic seizures. In other words, these agents changes neuronal excitability by modulating the K_{ATP} ion channels. Although, the underlying mechanisms of K_{ATP} ion channel agonist and antagonist on epileptic seizure have not been fully understood, there are few studies investigating the effects of the K_{ATP} ion channel agonist and antagonist in Penicillin G- epilepsy model (9-11). K_{ATP} ion channel agonist cromakalim and antagonist 5-HD were determined to have different effects in rat diabetic epilepsy model induced by PTZ (8-11).

In this study, we aimed to investigate the effect of selective K ATP channel agonists and antagonists on the initiation and severity of epileptic seizures. This study will bring some understanding about the effect of ATP dependent mitochondrial and sarcoplasmic channel agonist and antagonists on the appearance and the duration of seizure activity. The result of this study have also been expected to provide some data to the clinical treatment of epilepsy in human being.

1.1. Epilepsy

Epilepsy is a common and serious neurological disorder that has %1 prevalence in the world. The data from the World Health Organization in 2009 reveals that there are 50 million patients with epilepsy in the world. While the incidence of epilepsy is highest in childhood and older ages, it is lower in early adulthood. Epileptic seizures are caused by a group of neurons which are causing continuous excessive unsynchronous discharge. The factors that responsible for epileptic seizures are; metabolic abnormalities such as hypoglycemia, hyponatremia, hypocalcemia,

meningitis that causing acute neurologic damage, stroke, head trauma, drugs that lowers seizure threshold and alcohol.

Epilepsy is characterized by epileptic seizures and involves neurobiological, cognitive, psychological and social consequences. Definition of epilepsy requires at least one occurrence of epileptic seizures (12). Epileptogenesis refers to process which involves brain damage that result in spontaneous seizures (13). Although the mechanism is not same in all epileptic seizures, common features are increased neuronal excitability and synchronized neural activity. Cellular mechanisms which are responsible for epileptogenesis is still not fully understood. The cells in epileptogenic foci in brain regions show increased excitation and abnormal signaling that is caused by fully unexplained reasons and incorporates with the surrounding normal cells (14). In some epileptic syndromes, the roles of the genetic factors are known. For example; gene mutations can cause abnormality in the function of ion channel and abnormal network connections (15). This effect could be monogenic or poligenic. Complex or poligenic inheritance is concerned for in many epileptic conditions. A large fraction of epilepsy is caused by single gene mutations encoding neuronal ion channels (16). Mutations in ion channels cause change in the activity of excitatory and inhibitory neurotransmission and leading to the increasing excitatory neurotransmission or loss of the function of inhibitory neurotransmission. Besides ionic channels, genetic disorders have been related to GABAergic system. Gamma-aminobutyric acid is the main inhibitor for neuronal excitability in brain. This effect could be seen through the GABA-A and GABA-B receptors (17). Binding of GABA to GABA-A receptor increases the permeability of chloride ions. This provides rapid inhibition of neuronal electrical activity (18). Binding of GABA to GABA-B receptors increases the flow of potassium, reduces intake of calcium ions and inhibits

release of other presynaptic neurotransmitters (19). Various studies have shown that decrease in GABA-A transmission causes epileptiform activity in vitro mammalian neocortex. Also it is found that during the development of epilepsy, GABA-A receptors were overexpressed. The role of GABA-B receptors in epilepsy and the relation with the occurrence of seizures is not clear. These receptors have been associated with the primary generalized epilepsy, but their roles in focal epilepsy is controversial. GABA-B receptors blockade facilitates the formation of seizures during in vivo condition in rats which are sensitive to audiogenic seizures. Glutamatergic system has an important role in secondary epilepsy syndromes. It was suggested that many types of epilepsy are caused due to excessive glutamatergic synaptic transmission disorder (20). Glutamate is the most important excitatory neurotransmitter in brain (21). It's known that there are eight metabotropic glutamate receptors (mGluR). It is reported that glutamate or ionotropic glutamate receptor agonist cause seizures during in vivo and in vitro studies. It was found that epilepsy patients and experimental epileptic animals had high glutamate levels (22).

The temporal lobe areas, especially hippocampus, amygdala and piriform cortex are the most sensitive regions; which forming seizures or brain damage that triggers epileptogenesis (23). Hippocampus takes cholinergic innervation from medial septal areas. Also entorhinal cortex has rich cholinergic innervation coming from basal forebrain. It is shown that the activation of muscarinic acetylcholine receptors (ACh) in hippocampal slices causes synchronized neuronal discharge patterns. It is proposed that activation of nicotinic ACh receptors could affect both excitatory and inhibitory modulators. Neurochemical studies showed that activation of presynaptic ACh receptors increases the release of neurotransmitters such as GABA and glutamate (24). Recently, clinical and experimental data showed that epileptiform

discharges could increase and maintain cholinergic activity in the Entorhinal cortex. Many researchers founded that suppressed cholinergic system results in increased seizure sensitivity or increased hippocampal seizure activity (25-26). How and why the seizures occur, how these seizures affect other brain structures and how and which treatment will be most effective for prevention or treatment of epilepsy are questiones that still wait to be explained. Inventiones and improvement in molecular genetics, pharmacogenomics, imaging techniques and physiological studies in cellular level will provide discovery of new target molecules and enhance further the quality of life of patients with epilepsy.

1.2. Physiopathology of epilepsy

The specific mechanisms which cause the initiation, spread and the end of epileptic discharges in the brain are not fully understood. Discussed topics in this case can be summarized as follows:

1. Changing in intrinsic membrane channels such as voltage-dependent Na^+ channels that can lead to defects in the ionic conductivity.
2. Neurotransmitter synthesis which leads to lack of inhibitory neurotransmitters as like Gamma aminobutyric acid (GABA) or production of excessive excitatory neurotransmitters as like glutamate.
3. Intracellular enzyme deficiency. regulating ionic pump of neurons and glial cells and repolarization.

Epileptogenic focus in the area called "pacemaker" cells exhibit increased excitiment and abnormal signaling property which makes cooperation with surrounding cells for this signaling. It is acknowledged that CA, CA2, CA3 neurons of hippocampal pyramidal cells of patients having epilepsy may have "pacemaker" center (27).

It is probable that some chemicals and neurotransmitters may play a role in supporting cellular membrane excitation and spreading in the synaps. They are also likely to play a role in the epileptogenic activity. It has been determined that acetylcholine (ACh) which is excitatory neurotransmitter is secreted in large amounts during epileptic seizures. Ventricular injection of ACh causes seizures and it has been reported that AChE release is modulated by endogenous NMDA receptors and GABA agonists (28) .

On the other hand, deficiency of GABA which is known to be the most important inhibitory neurotransmitter that is held responsible from epileptic seizures. It has been seen that decrease in 50-60% GABA concentration in the experimentally induced epileptic seizures and loss of function in GABAergic inhibitory synapses cause generation of epileptic foci. GABA is thought to be responsible from two mechanisms which effect seizures. First one is the decrease in neuronal inhibition due to the decreasing concentration of GABA in the synapse. Second one is inability to use GABA although its concentration is in normal levels. In induced experimental status epilepticus (SE) model formed by injection of Lithium and pilocarpine; unexpected increase occurs in GABA concentration especially during epileptic period and excitatory aminoacid concentration level decreases than normal (29). Chapman and friends have found similar results in epileptic model which was created by Bicucilline methiodide (BMI) (28). It has been found that increased GABA levels may be caused by the failure in the uptake of GABA back or decreased metabolism in synaptic regions (30) .

Glycine increases the response of glutamate to the NMDA receptors. Thus, the excitatory effect of glutamate is further increased by increased glycine that is found in the extracellular area. In contrast to this view, in the study of Guilarte and friends

(31) were determined that decreased glutamate level in the cortex and hippocampus increases glycine level in the seizures which was induced by deficiency of pyrodoxine (32-33) .

Biogenic amines are known to be important in the pathogenesis of epilepsy. It is known that increase in Cyclic Adenosine Monophosphate (cAMP) prevents seizures, also adenosine and biogenic amines show inhibitory effect by increasing cAMP level in CNS. Also, ACh creates a depolarized state by activating Guanosine Cyclase or affecting Na⁺ transition (34).

Ischemia and hypoglycemia are also known to be two reasons in the formation of epilepsy. Glucose is necessary for both neurotransmitter construction and formation of Na⁺-K⁺ATPase. As a result of ischemia, metabolism is disrupted and more blood flow is needed to this region, in this case threshold of excitability of that region decreases (32-34).

Whatever the reasons, paroxysmal depolarization shift (PDS) occurs in the epileptic neurons. In this case, neuron groups have abnormal prolongation of the postsynaptic potential that is responsible for membrane depolarization. It is claimed that PDS occurs due to the imbalance between excitatory neurotransmitters glutamate, aspartate and inhibitory neurotransmitter GABA. Apart from this, it is thought to be the ion channels disorders in the membrane could be effective for the occurrence of PDS and PDS are similar to the excitatory postsynaptic potential (EPSP), but it has higher amplitude. A large number of fast-paced action potential occurs because of PDS. High-frequency impulse sequences created by PDS spreads from one neuron to another and thus leads to seizures or epileptic seizure activity. Epileptic seizure activity spreads one hemisphere to other by rich commusural connection. It changes

to tonic chronic seizures due to the spreading of excitation to the diencephalon by the way of corticothalamic pathway (35-36) .

1.3. Experimental models of epilepsy

Most information related with epilepsy has been provided from studies performed in animal models. Large number of experimental models of epilepsy has been developed, because only one model can not simulate a whole clinical epilepsy, so different aspects of seizures require different models. Animal epilepsy models are commonly used for explaining; electrical activity of the brain on the basis of cellular, molecular and systemic levels and testing or developing drugs or methods for the treatment of epilepsy (37,33). Scientific results were obtained inducing convulsion activity due to repeated administration of the electrical and chemical stimuli. It provides information on animal models for epilepsy and epileptogenesis (38).

Pentylentetrazol (PTZ), penicillin, pilocarpine, kainic acid, FG-7142 and picrotoxin can be used as a chemical stimuli. Epilepsy induced by PTZ, penicillin, Pilocarpine, kainic acid, FG-7142 ve picrotoxin may cause different types of epileptic seizures according to dose administered. Single high dose of these chemicals provides SE (status Epilepticus) model (39).

1.4. Penicillin models of epilepsy

It is probable that penicillin causes epileptiform activity by blocking GABA's effect. Penicillin prevents inhibitory postsynaptic potentials that shown in vitro hippocampal slices and it enhances the release of acetylcholine from presynaptic terminal and increase the effect of acetylcholine. It has been reported that penicillin increases the secretion of glutamate (40). Furthermore, it has been determined that penicillin can lead to the burst activity by presynaptic and calcium pathway. It has been found that

penicillin increases the level of extracellular calcium level before the start of epilepsy in the anesthetized cat (40). Despite all these, there are studies showing that inhibition mediated by GABA was not found effective in the cat penicillin model (41).

It was suggested that petitmal epilepsy is caused by subcortical structures of cortex, especially thalamus and brain stem reticular formation (41). It is difficult to say the same thing about models in felines. Because in this model, spike wave were recorded in the cortex before the medial thalamus and reticular formation (42). Penicillin commonly given to the cortex provides appearance of spike wave pattern although it does not reach to the thalamus (43). So, discharges in this model is induced by cortex and increase excitation stress in the circuit between thalamus and cortex (44).

Pharmacological response of this model to the anticonvulsant is very similar to that of clinical petitmal epileptic response. While Ethosuximide and sodium valproate are effective in both experimental and clinical epilepsy, diphenylhydantoin is much less effective. In addition, the effects of amobarbital and pentylenetetrazol which given through carotid vein in cat, spike wave pattern is similar to the effects which observed in humans (45-46).

1.4.1. Focal penicillin model

Focal penicillin model is one of the acute model of simple partial epilepsy. Penicillin that is an antibiotic is mostly used as a topical convulsant agent in the simple partial seizures. When penicillin is given systemically, it constructs generalized (petitmal) epilepsy model with systemic focal epilepsy (47).

If a small piece of blotter paper soaked with 1.7 to 3.4 m M penicillin subjected to opened rat, rabbit or cat cortex surface, similar EcoG is recorded in the acute focal

epilepsy to human being. The discharges began in 2-5 min after application of penicillin and its spike behavior is similar to human interictal spike (48). A single cell response recorded as interictal discharges from acute penicillin focus is called paroxysmal depolarizing shift (PDS). Intracellular recording from the focus of penicillin demonstrates that these are related with increased membrane permeability in PDS focus (49- 50).

Topical penicillin model is a convenient method in terms of researching how epilepsy is flourishing. Marked penicillin studies showed that focus remains limited to a few square millimeters (51). The neurons in this focus show inhibitory activity to prevent the spread of epileptiform activity. It was determined that when low dose of penicillin is given to the anesthetized animal cortex and hippocampus, postsynaptic inhibition is occurred by the inhibition of gamma aminobutyric acid (GABA) (52).

In some studies, the effects of 300-500 IU crystalline penicillin applied to the cortex region on the epileptiform activity in cats, rabbit and rat was investigated. In cats, the 0.1% adrenaline solution in 30 cubic microns given below the pia reduced epileptic activity at 10 to 13 minutes following penicillin application; primidal repetitive stimulation reduced thoroughly in one minute (53).

Etomidate given after 25 minutes from application of 300 IU penicillin significantly blocked epileptiform activity at 10 minutes following application of penicillin in rabbit. In rats sodium nitroprusside (5 μ l. 5 n M ic) given into the cortex after letting the 300 IU penicillin, suppressed discharges at 4-5 minutes following penicillin application (54).

1.4.2. Systemic penicillin model

Systemic penicillin model is one of the most common model created by high-dose systemic penicillin. Especially EEG created by systemic penicillin in cats is very similar to the clinical model (55).

Systemically administered high doses of penicillin (200 000- 400 000 IU/kg I.M.) leads to the appearance of generalized, bilateral, synchronous spike-wave pattern in 30-60 minutes following administration of penicillin in cats and this epileptiform activity continues for 3-5 hours. This model was formed in acutely anesthetized cats and chronically in unanesthetized cats placed electrode (56). Generalized penicillin model created in cats are especially important in terms of searching the answer to the following two questions; 1. What is the cellular basis of spike-wave pattern recorded at EEG? 2. What is the role of the cortex and subcortical structures in the formation of spike-wave pattern?

1.5. Neuronal Ca^{+2} ATPase and epilepsy

Cells contain a large amount of Ca^{+2} , but essential part of these ions is not found in a free form. Intracellular Ca^{+2} attach to the some proteins and is sequestered in organelles like mitochondria, endoplasmic reticulum (57). Ca^{+2} mobilization act on various channels or molecules in some regions in the cells. These are voltage-dependent Ca^{2+} channels, $\text{Na}^{+} / \text{Ca}^{+2}$ exchanger, sarcolemmal Ca^{+2} ATPase, Ca^{+2} binding sites in plasma and mitokondrial membrane (58).

Neuronal Ca^{+2} are involved in regulation of many neuronal functions such that synaptic transmission, plasticity and survival of cells (59). Therefore defects in Ca^{+2} homeostasis can affect the cellular activity in different ways and in varying degrees in neurons (60-61).

Physiological disturbances in calcium homeostasis is associated with aging. With age, oxidative stress, Ca^{+2} homeostasis may lead to neuronal degeneration in association with abnormalities. Neuronal loss was determined as a results of disorder in Ca^{+2} homeostasis in neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's disease. All these chronic pathologies such as mitochondrial and endoplasmic reticulum dysfunction. Glutamate excitotoxicity is observed due to damage in calcium entry into neurons. Similar situations are seen in the group of multifactorial diseases such as epilepsy, schizophrenia, amyotrophic lateral sclerosis and glaucoma. Similarly, HIV infection and sudden events such as traumatic brain injury and stroke can lead to brain death due to impaired Ca^{+2} regulation. There are many reports stating that Ca^{+2} ions have an important role in the formation and continued epileptic activity in the CNS. Carbondioxide content in the extracellular space is reduced during the epileptic activity (62).

Epilepsy is characterized with spontaneous recurrent epileptiform discharges (SRED) in neurons. In acquired formed epilepsy model in hippocampal neuronal cultures (HNC), SRED appearance is observed as a result of reducing calcium-calmodulin protein kinase-2 (CaMK-II) activity with a changing of Ca^{+2} homeostasis (63-64).

Chronic elevation of intracellular Ca^{+2} changes epileptic phenotype of neurons that plays a role in initiation and sustainability of epilepsy (65,66,67).

In normal cells Ca^{+2} concentration is controlled by various homeostatic mechanisms. Studies in epileptic neurons have shown that not only disorders in release and secretion mechanism of Ca^{+2} leads to increase in basal Ca^{+2} but also it decrease the ability of the neuron to return the level of Ca^{+2} to the previous concentrations (68,69,70).

1.6. K^+ Channels types

There are various K^+ channels that open or close in varying conditions of cells. Closure of some of K^+ channels causes synaptic stimulation and decrease EPSP. The studies in sympathetic ganglia and invertebrates have demonstrated that closure of some of K^+ channels that are open at rest can cause synaptic stimulation (71).

In some cells K^+ channels that contribute to the formation of the resting membrane potential are controlled by synaptic action. Transmitters that led to the closure of this channel depolarizes the cell. For example, ACh has two main receptor types. One of them is muscarinic, other one is nicotinic. Both of them bind to the ACh receptor. However, there are agonists and antagonists for these receptors as well. While agonists such as nicotine and muscarine mimic the effects of ACh, antagonists such as curare and hexamethonium blocks this effect. Both types of receptors with different chemistry in the nervous system have a different roles. Sympathetic neurons and receptors in the cortex and hippocampus are muscarinic. Adams and the colleagues found that ACh causes closing of some kinds of potassium channels. This channels are called muscarinic channels and their distinguishing characteristic is that they open during the repolarization (72).

In some synapses, neurotransmitter released from presynaptic neuron not only induce closing of potassium channel in the postsynaptic membrane but also it causes closure of K channel in presynaptic membrane. The binding of transmitter to the receptor starts expression of second messenger in the cell. Second messenger expressions commonly affect the channels. Potassium channels that open at the resting state is called S channel (73). Serotonin leads to the closure of these channel. The transmitter substances attaches to the receptor during the synaptic interaction is not a part of ion channel, but it is the part of the enzyme cascade. Serotonin attaches to a receptor on

the postsynaptic cell. When the receptor is bound with serotonin, a receptor bound protein called Gs protein is activated and then Gs protein activates an enzyme called adenylate cyclase (74). This enzyme produces cyclic AMP from adenosine triphosphate (ATP). When the amount of the cAMP increases, another enzyme called cAMP-dependent protein kinase is activated and it allows activating of phosphorylation of enzyme protein. Here phosphorylated protein is either associated with S channel itself or other regulatory protein, providing closure of the K^+ channel. Nicolle and colleagues claimed that there was a similar mechanism in the effects of norepinephrine in the cells of cerebral cortex. The source of the cells that release norepinephrine is located in locus coeruleus region of the brain stem. These cells send projections to cerebral cortex and hippocampus. Norepinephrine leads to closure of some kinds of K^+ channels by acting through cAMP. This type of K^+ channel is called as Ca^{+2} dependent channel (75,76).

1.7. ATP dependent potassium channels (K_{ATP})

K_{ATP} channels are first found in heart (77). In the later studies, these channels were observed in many cell and tissue types such as; pancreatic β cells, brain, skeletal muscle, smooth muscle and kidneys. K_{ATP} is inhibited by intracellular ATP, whereas it is activated by MgADP (77- 78).

It is thought that K_{ATP} channels play important role in the cellular response of the tissues in different metabolic situations as follows; hyperglycemia, hypoglycemia, ischemia, hypoxia (79).

The physiological role of the K_{ATP} channels is best understood with the studies about the secretion of insulin by pancreatic β cells (80). In pancreatic β cells, K_{ATP} channels are closed according to the elevation of ATP concentration which is related

with the glucose metabolism. As a result of the depolarization of β cell membrane Ca^{+2} channels (VDCC) open and Ca^{+2} ions enter into the cell. The exocytosis of the granules which contains insulin is triggered by the elevation of intracellular Ca^{+2} concentration in β cells (81).

K_{ATP} channels in the cardiovascular system, have an important role in metabolic stress conditions which decreases the intracellular ATP concentration such as; ischemia and hypoxia (82). In heart, action potential duration shortens when the K^{+} leaves the cell (83,84). Both the leakage of K^{+} from the cell and the shortening of the action potential cause electrophysiological disorders and arrhythmias (85). The activation of the K_{ATP} channels in the heart during the ischemia provides ischemic preconditioning and minimize the cardiac damage (86).

The relaxation of the smooth muscles by the K_{ATP} channel openers in vascular system, is related with the activation of K^{+} outflow (87). K_{ATP} channels regulate the tonus of the cardiac smooth muscles and play a role in the regulation of the blood pressure (88).

It is thought that K_{ATP} channels cause vasodilation during the ischemia in coronary arteries. The vasodilation which is caused by ischemia and hypoxia is blocked by glibenclamide that is a K_{ATP} blocker (89,90).

In brain, K_{ATP} channels are determined in many cell types that have different features. For example, in hippocampal neurons (91), Glia cells (92), dorsal vagal neurons (93), hypothalamic neurons (94-95) and in substantia nigra (SNr) (96). During metabolic stress, it is proved that opening of the K_{ATP} channels is protective against neurodegeneration and neuronal damage (97-98).

K_{ATP} channels use K_{ATP} openers and blockers which are pharmacological agents to understand the primary cellular response.

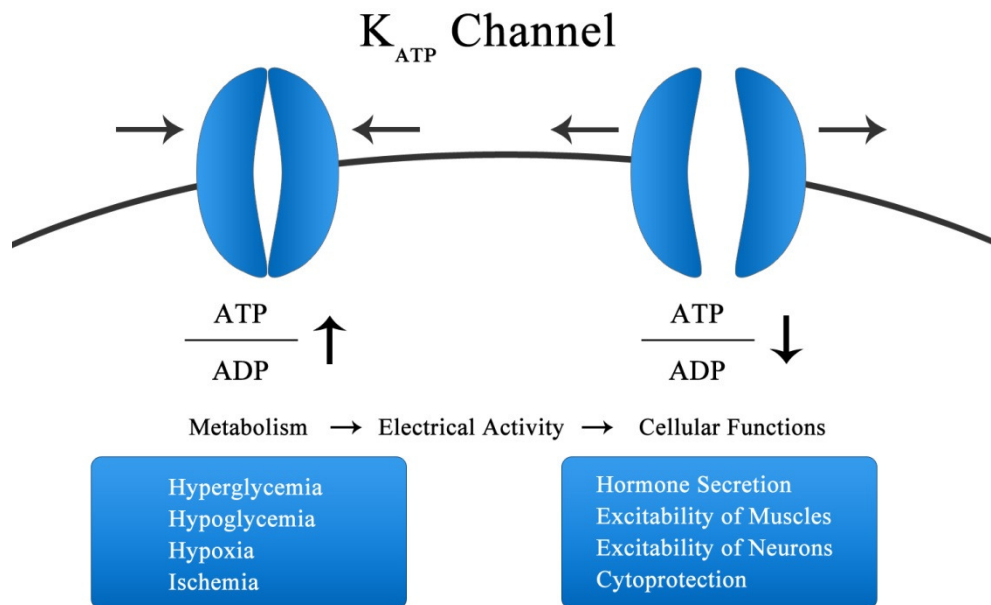


Figure 1.1. The effect of K_{ATP} channels on metabolic activity of the cell

1.7.1. Types of K_{ATP} channels

There are two types of K_{ATP} channels; sarcoplasmic and mitochondrial. Sarcoplasmic K_{ATP} channels are localized on the cytoplasmic membrane whereas mitochondrial K_{ATP} channels are localized in the inner membrane of mitochondria.

1.7.2. Sarcoplasmic K_{ATP} (sarc K_{ATP}) channel

K_{ATP} channel is in a heterooctameric structure and consists of two subunits. One of these two subunits is Kir 6.x (Kir 6.1 or Kir 6.2) which is responsible for the pore formation, and the other one is SUR which is a regulator subunit and sulfonylurea receptor (99-100). Sulfonylurea receptors are a member of protein super family

which can bind to ATP (ABC) (101). These have two isoforms; SUR1 and SUR2 which are derived from two different genes (101).

The C terminal of SUR2B is similar with SUR1. Sulfonylurea has 3 trans membrane domain; TMD0, TMD1, TMD2 and these have 5,5,6 membrane bound parts, this membrane is composed of waterproof biotin melamide (102,103). SUR1 has multi sequence extensions and a protein which is a member of multi drug resistance associated protein family (104).

Sulfonylurea receptors have two nucleotide binding parts; NBF-1 and NBF-2. These parts are at the cytoplasmic side (105). NBF-1 and NBF-2, TMD1 and TMD2 make loops in each other and respectively and they are in C terminal. The affinity of SUR1 protein to glibenclamide which is a sulfonylurea is high.

Therefore, SUR 2A is produced primarily in heart and striated muscle (106). It is determined that SUR 2B has a wide distribution throughout the body by using RT-PCR (107). SUR2 is another type of it and it is determined by Chutkow at 1999 (108). SUR2 is determined by Sakura in 1999 (109) by using RT-PCR.

The distinction of K_{ATP} channels is very hard in native tissues because their features are very similar. K_{ATP} channels which are composed of Kir 6.2 and SUR1 have 1:1 stoichiometric structure and they have to be in this form to produce a functional channel. In contrast to these; triple association proteins, SUR1, Kir 6.2 and Kir 6.1, do not produce functional K_{ATP} channels.

The molecular masses of Kir6.2/SUR1 (Glycosylated form) are determined by biochemical studies, and it is 950 kDa (110). So, likewise K_{ATP} , Kir 6.2 and SUR 1 have 4:4 stoichiometric structure and they are hetero-octameric complexes (111,112,113).

During the synthesis of Kir 6.2/SUR1 complex, a signal is hold in the endoplasmic reticulum, so in the absence of the other subunit, each subunit's activity in the cell membrane is prevented (114). This signal is found in the C terminal side of Kir 6.2 and in the NBF-1 which is found in the loop part of TM11 in SUR1. Expression of the two subunits together prevent the holding of the signals and allow it to go through the cell. The cut off of the C terminal of Kir 6.2 prevent the protection of the signals, and allow the expression of Kir 6.2 in the absence of SUR subunit (115).

C terminals of SUR 1 have parts that comprise anterograde signals. These parts include dileucine and phenylalanine. These provides the K_{ATP} to leave ER/CIS golgi and to be transported to the cell surface (116).

The cut off of only 7 amino acids from the C terminal of SUR1, especially a part including phenylalanine, reduces the surface expression of K_{ATP} markedly (117)

In contrast to this, in the cell surface, the cut off of many residues from the C terminal of SUR1 can be compensated and the expression of channels can be provided (118).

1.7.3. Mitochondrial K_{ATP} (Mito K_{ATP}) channel

Mito K_{ATP} channels have been described initially in isolated mitochondria from liver (119) and subsequently from heart (120), brain (121), kidney (122), striated muscle (123) and human T lymphocyte (124). This channels are modulated by nucleotides (125).

Mitochondria has a primary role to produce energy in cell. In addition. it has a role in many complex mechanisms like apoptosis. Permeability of mitochondrial membrane causes releasing of cytochrom that can induces apoptotic pathways in various ways (126).

Protection of cell is triggered by the transport of potassium through mitochondrial inner membrane have been shown (127-128). This transfer resembles to the activity of ion channels in plasma membrane.

Potassium selective ion channels located in the inner mitochondrial membrane. Potassium ions controls mitochondrial metabolism by changing the volume of matrix (128). Mitochondrial potassium channels classification includes; ATP dependent potassium channels (mito K_{ATP}), large conductance Ca^{+2} channels, Ca^{+2} activated potassium channels (mito Bca) and voltage dependent potassium channels (mito Kv1.3) (128). It is similar to potassium channels in plasma membrane which exists in most cell types (128)

Different pharmacological agents (channel inhibitors or potassium channel openers) help to explain functional role of mitochondrial potassium channels in cell. K uptake is decreased by respiratory chain inhibition and this leads to mitochondrial contraction. When mito K_{ATP} is activated, this process can be reversed and getting back to physiological levels (129). These results show that mito K_{ATP} has an important role during ischemia so that it is preserving mitochondrial volume and protecting intracellular Ca^{+2} concentration at normal levels. Intracellular Ca^{+2} concentration levels increase if cellular energy metabolism is endangered. Such conditions may lead to ischemia. Such incremental changes may leads to the changes especially in nucleus, mitochondria and endoplasmic reticulum. Mitochondria uses electrical stimuli as driving force for taking up Ca^{+2} through the activity of a Ca^{+2} uniporter and can cause accumulation of large quantities of the cation (129,130).

While uptake of Ca^{+2} on a moderate level into the mitochondria leads to the activation of citric acid cycle enzymes and electron transport (130,131), high amount of Ca^{+2} accumulations may harm this organelle. Ca^{+2} induced mitochondrial loss of

function is; increase in permeability of mitochondrial membrane transition pore (MPT). Ca^{+2} release and swelling on a large scale results in membrane tear up.

Proton gradient are generated under ischemic conditions that is produced by non respiratory conditions (131). Obviously small proton gradient is not useful at all as a driving force for production of ATP, but might be sufficient for allowing uptake of Ca^{+2} (132). It has been shown by different authors that Ca^{+2} overload leads to disruption in cytosolic Ca^{+2} homeostasis and this prevents mito K_{ATP} activation (133-134). These findings are harmonious with the hypothesis that post-ischemic MPT formation is prevented by mito K_{ATP} activity (135).

Some studies showed that MPT formation can be prevented by mito K_{ATP} activation during ischemia by inhibiting the increase in intracellular Ca^{+2} stimulation under mitochondrial oxidative stress (136). In addition, another important role of mito K_{ATP} is to prevent Ca^{+2} uptake (137).

ATP synthase generates a gradient of protons as respiration stop in mitochondria under ischemic conditions (138). It has been shown by different authors that Ca^{+2} overload can be prevented by mito K_{ATP} activation (139), but not under normal conditions (139).

It was recently found that MPT can be prevented by mito K_{ATP} activation during ischemia by inhibition of Ca^{+2} which stimulates mitochondrial oxidative stress (140).

A variety of potentially lethal conditions are precluded by influx of K^{+} through mitochondrial Ca^{+2} activated and ATP-sensitive K^{+} channels during ischemia/reperfusion. The physiological function of mito K_{ATP} are; mitochondrial volume arrangement, favoring energy metabolism and arrangement the release of mitochondrial reactive oxygen levels under mild conditions. Intracellular high-energy phosphate levels' maintenance, inhibition of excessive Ca^{+2} uptake, decreased release

of ROS and the prevention of MPT formation may be included in the protective effects of these channels during ischemia (141).

1.7.4. Potassium channel openers (agonist) and inhibitors (antagonist) of mitochondrial ATP-regulated potassium channels

Many of K_{ATP} channel openers, like pinacidil, dizoxide and nicorandil, have been shown to prevent damage against ischemia and reperfusion (142-143). Presently, acceptable view is that the protection against ischemia occur by the activation of potassium channel in the inner membrane of mitochondria. Since diazoxide had been pointed out to be more selective to the mitochondrial membrane than plasma membrane K_{ATP} channels, it is widely used opener in KCO-mediated cytoprotection studies (144). 5-hydroxydecanoic acid (5-HD), a mitoKATP channel inhibitor, is used to study physiological role of the mitochondrial potassium channel. 5HD is conceived to be selective for mitoKATP channels (145). Nevertheless, all of the drugs mentioned earlier have off-target effects, which should not be forgotten while interpreting the experimental results. Diazoxide and pinacidil were shown to uncouple oxidative phosphorylation in mitochondria in a manner that is potassium-independent (146).

Although higher dose of potassium channel agonists are used in the various studies, cytoprotective effect was seen in the lower doses that is especially mentioned in the studies researching the role of potassium channel in ischemic preconditioning.

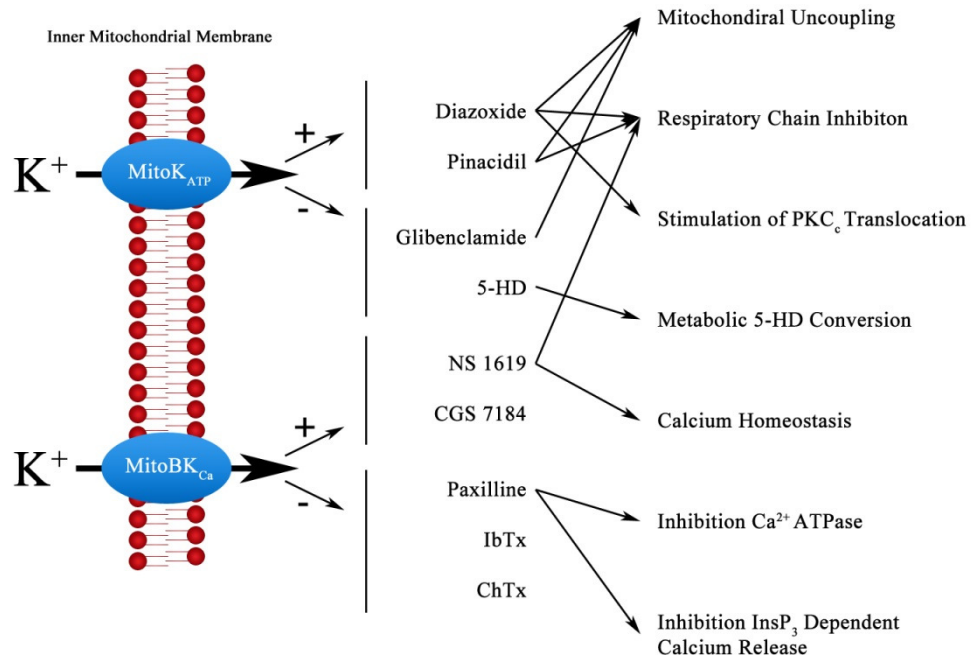


Figure 1.2. Potassium channel openers (agonist) and inhibitors (antagonist) of mitochondrial ATP-regulated potassium channels

Presence of electro neutral K⁺/H⁺ antiporter mechanisms in the efflux of K⁺ from mitochondria and electrophoretic pathways for K⁺ entry into the mitochondria is well established and they play a critical role in mitochondrial function and volume regulation together (147).

The mitochondrial ATP-sensitive K⁺ channel (mitoK_{ATP}) would generate a parallel K⁺ intake pathway when it is open and if it is present. Its V_{max} is thought to be about same as influx of K⁺ through the leak pathway. Exchange of K⁺ with H⁺, which is electrically coupled will alkalinize the matrix, causing inflow of phosphate via electroneutral P-H⁺ symporter. K⁺ salts' net uptake is escorted by osmotically obligated water, resulting in matrix swelling. Volume and pH regulation of the

K^+/H^+ antiporter leads to increased efflux of K^+ by this pathway and achieve to have a new steady state at a slightly higher volume and matrix pH with momentous effects on mitochondrial function (148). It has been proposed that mito K_{ATP} channel activation plays a major role in ischemic preconditioning (149-150).

1.7.5. Sulfonylureas binding to sur subunits

Sulfonylurea and analogous drugs like tolazamide, tolbutamide, glibenclimide and glimepirid reduce blood sugar level by stimulating insulin secretion. These drugs bind sulfonylurea binding site located at K_{ATP} channel (151).

Sulfonylureas bind to an ATP-dependent $K^+(K_{ATP})$ channel on the cell membrane of pancreatic beta cells. It inhibits a tonic, hyperpolarizing efflux of potassium, thus causing the electric potential over the membrane to become more positive. This depolarization opens voltage-gated Ca^{2+} channels. The rise in intracellular calcium leads to increased fusion of insulin granulae with the cell membrane, and therefore increased secretion of (pro)insulin (152).

There is some evidence that sulfonylureas also sensitize β -cells to glucose, that they limit glucose production in the liver, that they decrease lipolysis (breakdown and release of fatty acids by adipose tissue) and decrease clearance of insulin by the liver (153).

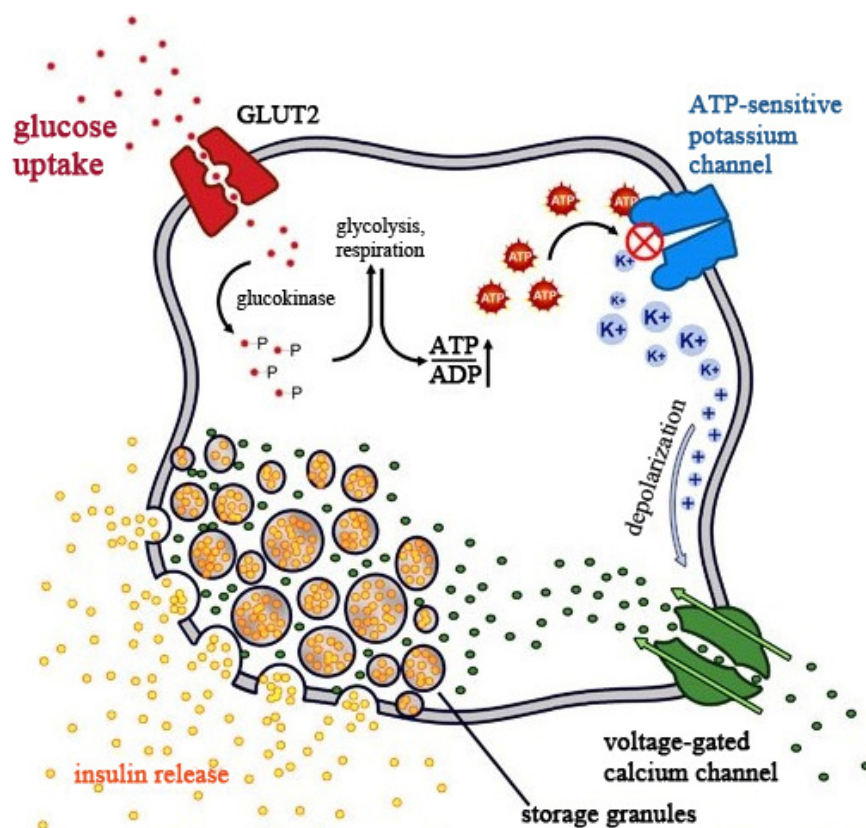


Figure 1.3. The insulin regulation to response to opening of K_{ATP} channels

Although there were many studies about the sulfonylurea binding sites of SUR1 and SUR2A, the location could not be determined (151). TMD2 that is especially the area between TM15 and TM16 is a critical binding site for sulfonylurea (152). This site has a great affinity for Tolbutamide, Glibenclamide. Therefore, it has both sulfonylurea and benzamide moieties. Glibenclamide binds these two sites of SUR1 and it is known that there is one site for tolbutamide. In contrast to these, only one sulfonylurea for tolbutamide binds to one site of SUR1 (153). Therefore, SUR1 has binding sites for meglitinide which is a derivative of tolbutamide and benzamide (154). Both SUR1 and SUR2 have binding sites for benzamide. SUR 2 does not contain any binding sites for sulfonylurea. SUR2B containing channels are blocked

by tolbutamide (155). Forty two aminoacids localized at the C terminal of SUR1 and SUR2B contain sulfonylurea binding site (156).

1.7.6. Binding of potassium channel opener to sur subunit

The ability for opening of K_{ATP} channels varies according to the cell type. Despite potassium channel openers varies in their structures, generally they cause plasma membrane hyperpolarization and decrease electrical activity (157). Different SUR types show different sensitivities to KOCs. For example; Kir 6.2 /SUR 1 channels are activated by diazoxide whereas pinacidil does not effect Kir 6.2 / SUR2A channels. This channels are activated by pinacidil and kromakalim whereas diazoxide has less effect. Kir 6.2 / SUR2B channels are activated by diazoxide, pinacidil and kromakalim (158). However, Kir6.2/SUR 2A channels become sensitive as like Kir6.2/SUR1 channels in the presence of MgADP.

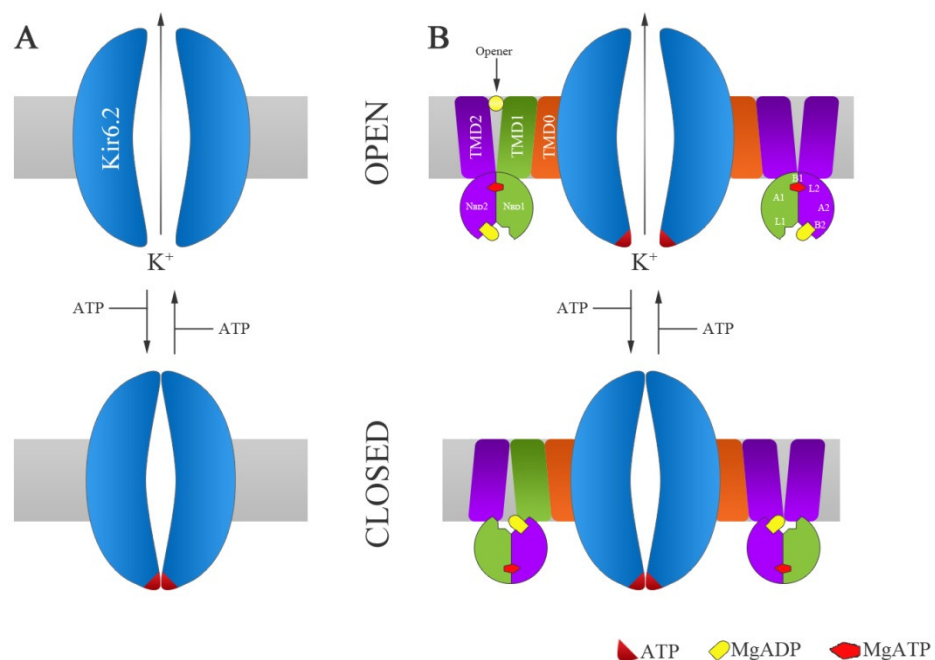


Figure 1.4. Opening of the K_{ATP} channels

In addition potassium channel openers (KCOs) such as; pinacidil and NBF2 provides channel opening by stabilizing of Mg-nucleotide compound by the stimulation of ATP hydrolyses (159).

As a result of the interaction between nucleotides and KOCs, complex formation occur on the K_{ATP} channels. It has been shown that KOCs have specific sensitivity for SUR1, SUR2A, SUR2B and SUR2. For example; pinacidil has high affinity for TMD2 site of SUR2A, sites between TM13 – TM14 in intracellular loop and sites between TM16 – TM17 (160). Therefore two residues of SUR2A which are TM17 and Lys 1249, 1253 are especially critical (161).

However, the localization of the binding site of diazoxide is not certain. Diazoxide can bind to all SUR1, SUR2A and SUR2B subunits. It can activate 6.2/SUR1, Kir 6.2/SUR 2A and Kir 6.2/SUR 2B in the presence of Mg ADP. Mg ADP is necessary for the binding of diazoxide to NBF-2 (nucleotide binding fold).

1.7.7. Regulation of K_{ATP} channels by various factors

K_{ATP} channels are regulated by numerous cytosolic factors. Adenine nucleotides ATP and ADP are very important two factors, which interact with 2 sites on the channel, one inhibitory and the other stimulatory (162,163).

Their distinguishing character is based on difference in nucleotide binding to the stimulatory, but not the inhibitory site that requires Mg^{+2} (164). Thus, in the absence of Mg^{+2} only the inhibitory effect is observed. However within the cell, Mg^{+2} is always present and channel activity is determined by nucleotides (165). As a result, reciprocal changes in the intracellular concentrations of ATP and MgADP are suggested to effect metabolic regulation of the K_{ATP} channel (166).

The activation of K_{ATP} channels are also regulated by various intracellular signals. Protein kinase A (PKA) stimulates K_{ATP} channel activity and it phosphorylates K_{ATP} channels in β cell (167). Phosphorylation of Kir 6.2 increase channel activity. There are studies about PKA is responsible for the stimulation of these channels but they are arguable (168).

It has been shown that PIP2 and PIP3 membrane phospholipids modulate ATP sensitive K_{ATP} channels (169). PIP2 decrease the ATP sensitivity of K_{ATP} channels dramatically. Tolbutamide blocks the opening of the channels (170). The breakdown of PIP2 by phospholipase C increase the ATP sensitivity of K_{ATP} channels (171). It has been proved that the effects of PIP2 is carried out by the subunits of Kir6.2. It has been shown that K_{ATP} channels modulate trimeric GTP binding proteins.

G α i protein stimulates Kir6.2/SUR1 and Kir6.2/SUR2A channels. G α i2 only stimulates Kir6.2/SUR2A (172). G $\beta\gamma$ subunits does not have any effects on Kir6.2/SUR1 (173).

1.7.8. Physiological roles of K_{ATP} channels

Electrical activity of the plasma membrane and cell metabolism are bound by ATP-sensitive potassium (K_{ATP}) channels which regulates membrane K^+ fluxes (174). A reduction in metabolism opens K_{ATP} channels which promotes K^+ efflux and membrane hyperpolarization. On the other hand, increased metabolic activity results in closure of K_{ATP} channels. Metabolic stimulus generated by the depolarization of membrane may trigger cellular responses such as the release of hormones and neurotransmitters.

In ventromedial hypothalamic neurons, K_{ATP} channels mediate the counter-regulatory response to glucose (175) and in arcuate nucleus neurons they may be

involved in appetite regulation (176). Fluctuation in blood glucose concentration triggers a response in glucose-sensing cells by K_{ATP} channels. But in many other tissues, K_{ATP} channels are largely in closed state under resting conditions. Opening of K_{ATP} channels are induced in response to ischemia, hormones or neurotransmitters. In cardiac muscle and central neurons, the resulting reduction in electrical activity helps the protection against cardiac stress and brain seizures (177,178).

K_{ATP} channels also modulate electrical activity and neurotransmitter release at synapses in many brain regions including the hippocampus, substantia nigra and hypothalamus (179,180). Disruption of K_{ATP} channel function can lead to disease since their role is critical in regulation of electrical excitability in many cells. Various studies enlighten the path that; mutations in K_{ATP} channel genes results in neonatal diabetes (181), hyperinsulinemia and dilated cardiomyopathy (182) in humans. Some studies on genetically modified mice have also showed impaired K_{ATP} channel function in angina (183).

K_{ATP} channels have an important role in insulin secretion that had been first discovered (184,185). Increased glucose concentration in plasma stimulates glucose uptake and its metabolism which produces a changes in cytosolic nucleotide concentrations that result in closure of K_{ATP} channels. This leads to a membrane depolarization that opens voltage-gated Ca^{+2} channels, initiating cell electrical activity, Ca^{+2} intake and a rise in intracellular calcium concentration ($[Ca^{+2}]_i$) and thereby exocytosis of insulin granules. Glucose metabolism has additional effects on insulin release (186,187), but under physiological conditions K_{ATP} channel closure is an essential step in stimulus-secretion coupling in cells. Effectiveness of sulfonylurea drugs which are widely used to treat type 2 diabetes, like tolbutamide and

glibenclamide can be explained by their direct effect on closure of K_{ATP} channels (188). They bypass cell metabolism by binding directly to the K_{ATP} channel and effects insulin secretion. Conversely, the K channel opener diazoxide opens K_{ATP} channels and inhibits insulin secretion, independently of blood glucose levels (189).

1.7.9. Neuronal K_{ATP} channels

Like most of the β cells mentioned above, neuronal population does not directly effect the glucose sensing. Neuronal K_{ATP} channels are the control element of metabolism. Neuronal ATP consuming acts in the setting of metabolic activity of neuron are very sensitive to the changes in the electrical activity. Increased electrical activity causes accumulation of internal Na^+ and this is performed by the stimulation of Na^+/K^+ ATP ase activity. It is the place where the neuronal ATP consumption is maximum 40-70 % of ATP consumed by this way (190).

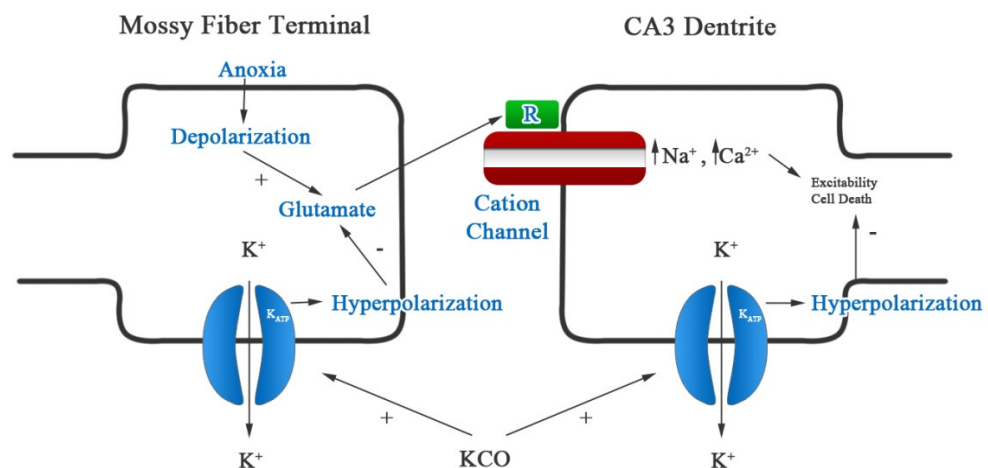


Figure 1.5. The role of K_{ATP} chanelns in CA3 neurons

As a result of K_{ATP} channels activation, cell hyperpolarise and excitability decreases.

K_{ATP} is controlled by the negative feed back mechanism which pair with electrical signals and energy consuming. Some K_{ATP} channels are activated in brain in physiologic conditions (191).

Activity of K_{ATP} channels have two feedback loop: it controls exitability of individual neurons and synapses and also controls local electrical activity and local blood stream by utilizing the local K^+ stream.

K_{ATP} channels have an extra role on dopaminergic neurons. Dopaminergic terminals directly innervate brain arterioles. Not only neuronal activity is controlled in dopaminergic neurons but also perfussion of axonal target region is provided (192).

Neuronal K_{ATP} channels are not only metabolic sensors. It is an effector in other biochemical pathways and secondary messenger system. Like the G-proteins and PIP and phosphorylation mediated by proteinkinase, neuronal K_{ATP} channels modulates metabotropic receptors, cytoskeletal changes and other cellular mechanisms (193).

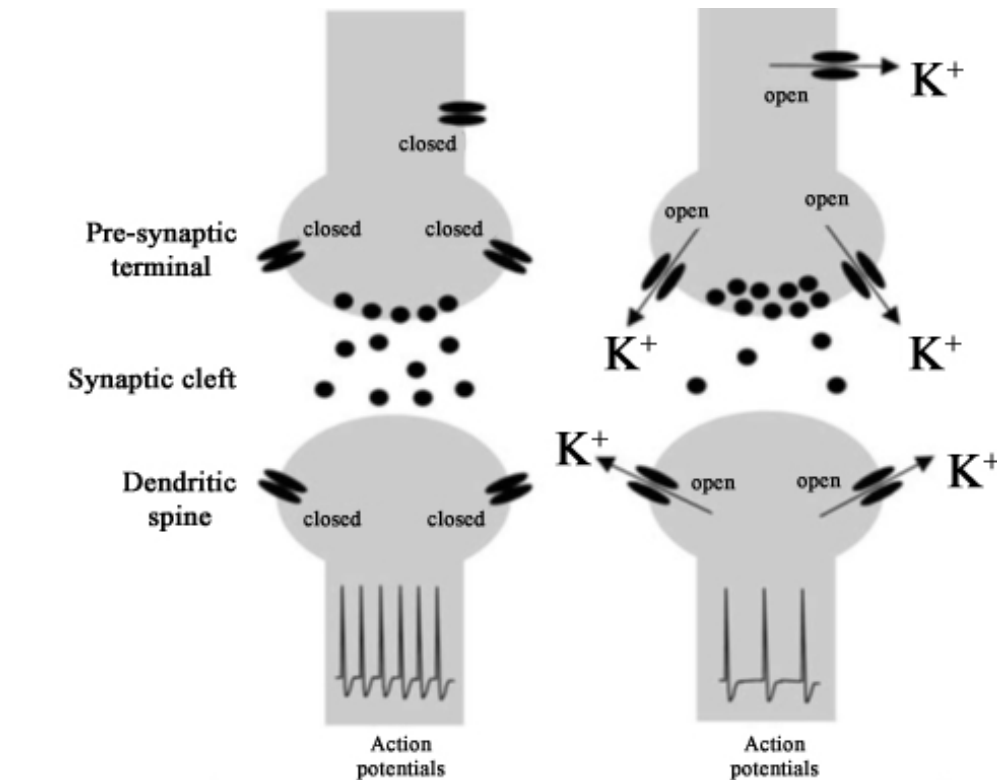


Figure 1.6. Neuronal K_{ATP} channels play an important role in the regulation of neuronal excitability (191)

1.7.10. Involvement of K_{ATP} channels in seizure propagation

Amoroso and colleagues showed that opening of K_{ATP} channels reduces GABA release in the SNR and they were first to estimate the control sequence of seizure propagation. They also estimated involvement of K_{ATP} channels in the substantia nigra (194). An incisive study supplied direct experimental proof for the concept of K_{ATP} -channel-mediated seizure control (195). K_{ATP} channel knockout mouse where the gene encoding Kir 6.2 was inactivated (196) to ask the key question of if K_{ATP} channels are related in hypoxia-induced seizure. When they combined their behavioral data with electroencephalogram (EEG) and electromyogram (EMG)

recordings, they clearly showed that K_{ATP} knockout mice have impressively reduce the level of threshold for hypoxia-induced seizure generation.

A recent supplementary study gives additional support for a role of neuronal K_{ATP} channels in the dynamic control of the seizure threshold (197). These authors procreated transgenic mice that selective overexpressed K_{ATP} channel SUR1 in forebrain structures and controlled by a Ca⁺²calmodulin kinase promoter, and discovered that not only threshold of kainate induced seizure increase significantly, but also shows resistance to excitotoxic neuronal harm in these animals that overexpresses SUR1. These studies investigate both the ends of a spectrum of expression of K_{ATP} channel- complete loss and decuple overexpression and provide strong support that the figure of active neuronal K_{ATP} channels controls the seizure threshold in brain dynamically.

It will be convenient in this context to understand mechanisms of regulation like ischemic preconditioning which might tune the level of expression of neuronal K_{ATP} channels in vivo and therefore determine the protection level (198).

Electrophysiological proof at the cellular level that postsynaptic K_{ATP} channels alone are enough to decrease the activity of the GABA-containing SN neurones as an answer to hypoxia. In SNr neurons from knockout mice, the decrease of indigenous discharge in response to hypoxia is not completely lost but is transformed into a hypoxia mediated excitation, which indicates K_{ATP} channel activation is a substantial mechanism of counterbalance that offsets increased excitability stimulated by impaired metabolism. This suggests that K_{ATP} channels in the pancreatic β -cell and in metabolically responsive neurones all share the same molecular makeup of Kir6.2 and SUR1 subunits (198). However, studies focusing the selective pharmacological targeting of the SNr K_{ATP} channels suggested by Yamada and coworkers might be

difficult to construct. A special role of K_{ATP} channels in the SNr as a major seizure gate have been demonstrated. Nevertheless, to provide direct evidence, study may need a new generation of transgenic mouse models with K_{ATP} channel expression in SNr neurones altered specifically (198) .

1.8. ECoG (Electrocorticography) and EEG (Electroencephalography)

EEG (Electroencephalogram) and ECoG (Electrocorticogram) are the most used method in studies about epilepsy. Brain waves recorded over scalp is named EEG (Electroencephalogram) and waves recorded with directly from brain cortex with macroelectrodes are named ECoG (Electrocorticogram).

Brain waves occur with the synchronic synaptic activity that is algebraic summation of excitatory and inhibitory post synaptic potentials (EPSP and IPSP) and are recorded by electrodes put on the surface of neural structure. EPSP's of neuronal structures close to the surface of cortex creates the positive part of EEG waves.

Epileptic discharges refer to excessive synchronization of EEG. EEG is considered to be the sign of epileptic seizure. In the absence of seizures, 3-4 rhythmic spike complexes are observable on EEG. In generalized tonic-clonic seizures (grand mal) no spike complex can be detected. When going into a seizure, first change on EEG can be low amplitude desynchronized spikes.

In tonic-clonic seizure, sharp spikes with 15-25 per second can be seen after seizure. EEG flattens and is followed by spikes slower than control. Also ictus is used for seizures. Time after seizure is called postictal period and time between seizures is called interictal period. In interictal period, very short-term discharges may be detected on EEG.

Interictal discharges gives information about sources of epilepsy in brain. Records obtained from experimental epilepsy models usually resemble interictal epilepsy. If these behaviors do not support it, is not possible to say spike-like waves on EEG shows epilepsy. On the other hand, no spikes on EEG in interictal period does not mean there is no epilepsy (199).

Micro or macro electrodes are used to observe and record behaviors of neuronal communities. Single cell response is recorded with microelectrodes. This method which is harder and more time consuming is used more likely on experimental animals. Total activity of crowded cell communities is recorded with macro electrodes. In 19th century it has been understood that brain has continuous and spontaneous electrical activity which they are recorded by electrodes placed on brain or scalp. We owe first important information about human EEG from H. Berger's studies. In between 1929-1938, Berger printed spontaneous activity of brain from hairy scalp by using sensitive galvanometers and argued that EEG changes in some diseases. Brain waves vary with age, sensory stimulation, brain diseases and chemical condition of body. As like physiological studies on sleep-awakeness or dreams. EEG can also be used to diagnose and localize neurologic diseases like tumor, infarcts or epileptic lesions. Flat EEG record means absence of electrical activity in brain and used as a clinical sign of death. EEG records can be taken bipolar or unipolar. In bipolar records EEG activity between two points is recorded. In unipolar record, a location like ear lobe where potential is zero used as an inactive electrode, an electrode put on anywhere on the scalp is used as active electrode. In clinical studies, standard electrode locations is used for EEG recording.

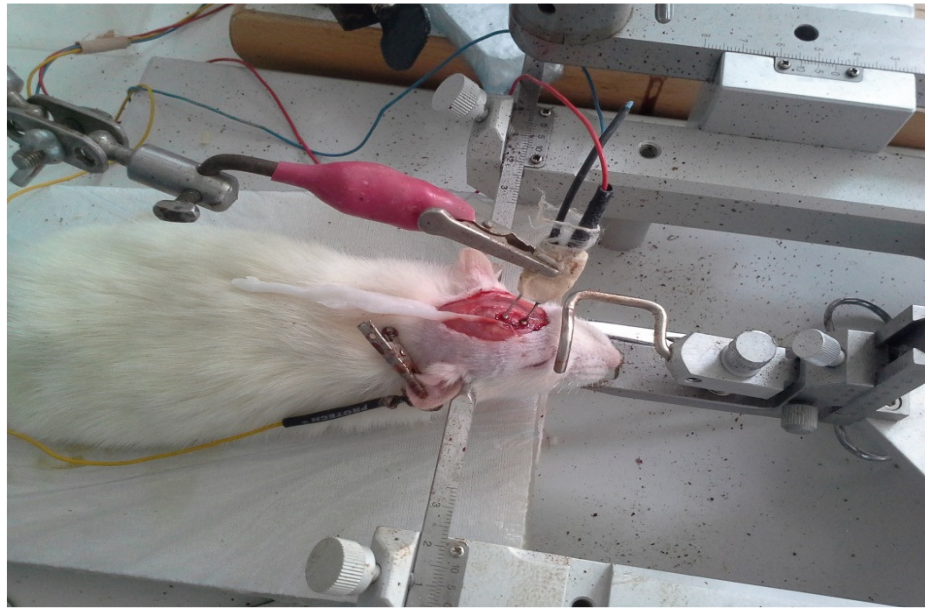


Figure 1.7. Locations of electrodes in EEG recording

1.8.1. Physiological basis of ECoG

In order to record an electrical potential as an ECoG wave, electrical currents must spread large sections of brain tissue and reach up to somatomotor cortex. Potential changes from brain cortex recorded as ECoG, are generated by thousands of cells below recording electrodes. We can see the obtained potentials as algebraic summation of ion currency belonging to thousands of cells. Most of the activity recorded on ECoG belongs to surface layers of cortical gray matter. It is believed that there are more than 10 billion nerve cells on brain cortex. Glia cells are not included in this number. Cells of brain cortex are distributed to constitute layers from surface to deep. These layers consists very few cell soma and largely dendrites. Various cells are found in brain cortex accordingly their structure and shape. Length and distribution of dendrites, branching and termination of axons. But it is possible to

separate them into two big classes as satellite cells and pyramidal cells. Satellite cells are neurons with short axons and round or oval cell bodies. Their axons do not leave cortex, ends at neurons found nearby. Satellite cells, which are intermediate neurons, provide the establishing of required communication inside cortex colons. Satellite cells have an important type called basket cells with dendrites extended vertically. These cells distribute information obtained directly from neurons in thalamus to other intermediate neurons or pyramidal cells. While some of satellite cells are excitatory and secreting glutamate, some have inhibitory properties and secretes GABA (200,201).

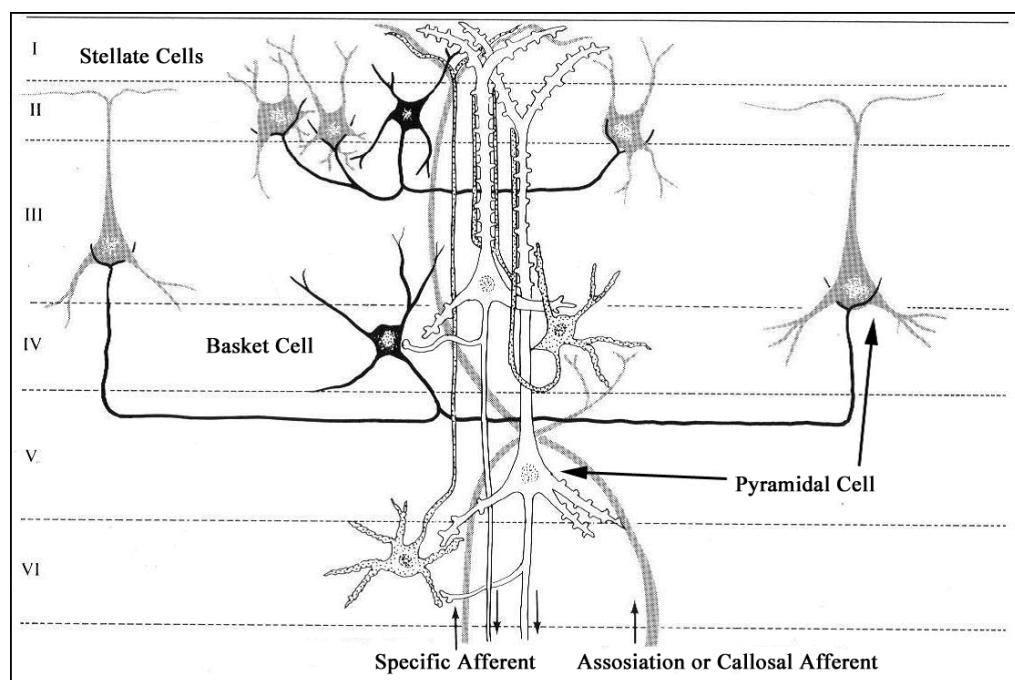


Figure 1.8. Main cell types found in brain cortex and intercellular connections.

Dark colored cells are inhibitory basket cells (211).

In pyramidal cells, cell body is in shape of pyramid. Top of the pyramid is situated on cortex surface, its bottom is downwards. Long dendrites coming out of the top of the pyramid reaches up to the surface of cortex. Axons, on the other hand, extend to downside and reaches variety of brain and spinal cord. Pyramidal neurons are stimulating cells and secrete mainly glutamate and aspartate (202). (Figure 2.9)

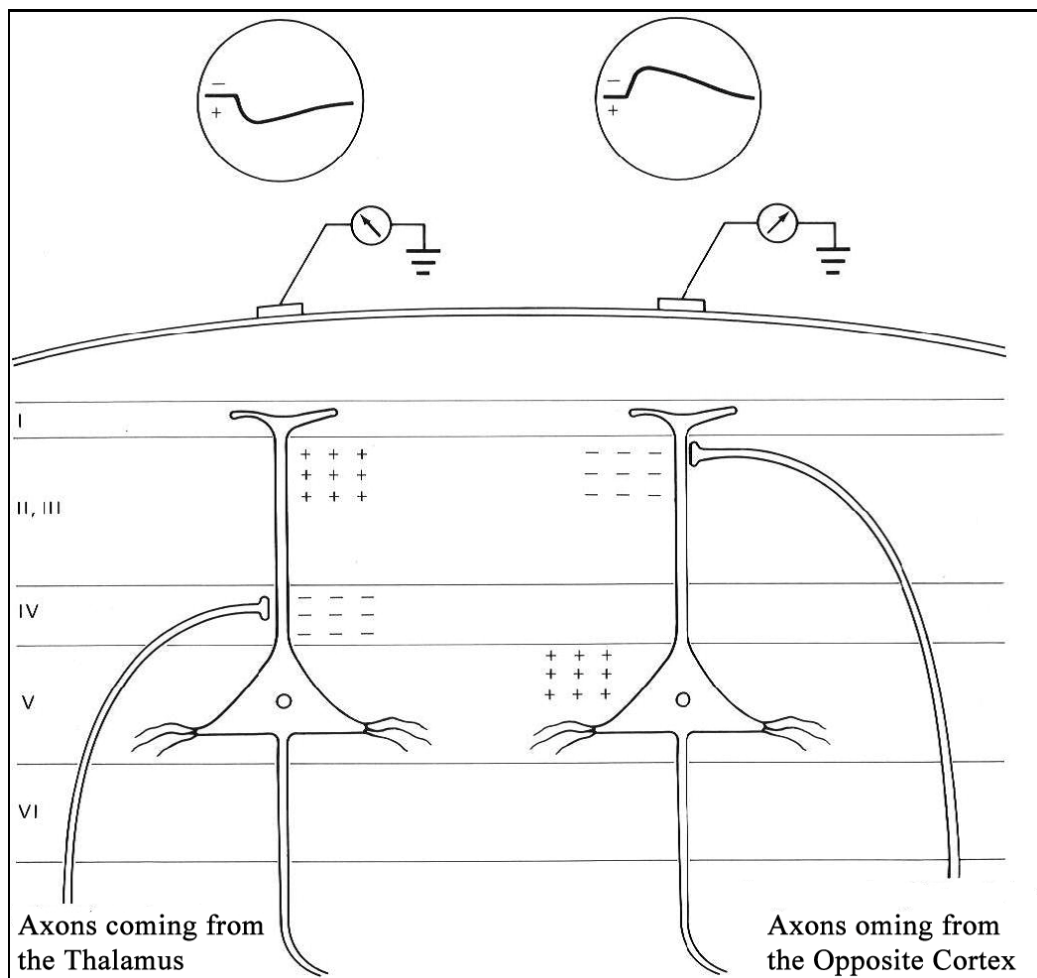


Figure 1.9. Records obtained from scalp and synaptic mechanisms generating basis of them (211).

On the left side of the figure, potential recorded from thalamus that axon reach to IV layer. On the right side, potential consisted of activation of upper layers by entries from opposing cortex. Most of specific sensory fibers pass from thalamus and ends at IV layer of cortex. On the other hand axons of pyramidal cells found on V and VI layer of cortex reaches to brainstem and spinal cord. Axons of pyramidal neurons are found on II and III layers of cortex are connected with other region of cortex (203).

A potential difference between cell bodies and dendrites occurs with hyperpolarization or hypopolarization in dendrites of brain cortex. Stimulation of pyramidal cell dendrites with excitatory signals from II layer which cortical neurons have connections that creates negative (over bottom line) waves because surface layers being more negative and deeper layers staying positive (204).

1.8.2. Brain waves on EEG

Frequency of potentials recorded from scalp of a normal human usually 1 to 30 Hz while amplitude is about 0-300 microvolts. Measurement model and intensity of electrical activity is largely determined by excitation level in the result of RAS function. Skull and scalp shows an effect of decreasing amplitude of EEG waves. Both frequency and amplitude of EEG waves shows a highly complicated structure and may vary on different conditions. Rhythm of dominant EEG frequency varies with age in resting state. Alpha type in adults is seen especially in adolescence. EEG waves are separated into four major groups (205,206).

1.8.2.1. Alpha rhythm

Waves with 20-50 microvolts of amplitude and 8-13 per seconds of frequency are dominant. Alpha waves are also called Berger rhythm due to work of Hans BERGER showing EEG changes in diseases. It is recorded from a normal individual, in a quiet

room and calm state with eyes closed, while mentally and physically resting. It is clearer in parietal and especially occipital zone. It disappears in sleep. Wave amplitude is more in dominant hemisphere. When eyes are opened, sensational stimulations are taken or when mind is busy with a problem, alpha rhythm disappears. Instead, a lower voltage and high frequency activity is observed. This event is called alpha blockage or desynchronization. During alpha blockage, corresponding neurons cannot discharge. Factors blocking or decreasing alpha rhythm are decrease in glucose level in blood, decrease in both body heat and glucocorticoid hormones, increases in PCO_2 in arterial blood (207).

1.8.2.2. Beta rhythm

It is recorded more in frontal zone. It is more intense in the presence of stimulants and when there is excessive mental activity. Beta rhythms are smallest (5-10 microvolts) but highest frequency (13-30 Hz) waves of EEG. Its resource is the cortex. It decreases or completely disappears in damaged zones of brain. It arises in condition with intensive activation of CNS (208).

1.8.2.3. Teta rhythm

Slow waves with the frequency of 4-7 Hz and amplitude of 10-100 microvolts are dominant. It is not seen on healthy adults in awake situation. In children, it is normal to see teta rhythm in recordings from parietal or temporal zones. Teta rhythm might be observed in existence of sub-focal cortex lesions, metabolic encephalopathy and in the presence of lesion in depths of mid-plane of brain and often in hydrosephaly (209).

1.8.2.4. Delta rhythm

They are waves of EEG with lowest frequency (0.5-4 Hz) and with highest amplitude (20-200 microvolts). It is the dominant rhythm in infants (up to one year old) and in 3rd and 4th phases of sleep. It is observed when there are widespread lesions, metabolic encephalopathy and in hydrocephaly in subcortical areas. It is more prominent in frontal zone in adults and in occipital zone in children (210).

Average frequency of rhythm in EEG depends on the activity of brain. Usually frequency increases as the activity increase. Highest frequency β waves occur with mental activity. However these waves are more likely to be desynchronized instead of being synchronized. Therefore although cortical activity is increased, voltage is determined to be significantly decreased (211).

2. MATERIAL AND METHOD

2.1. Animals

123 Male Wistar-Albino rats with weights ranging from 300-350 grams have been used. Animals were grown in 12 L / 12 D light – dark cycles and water ad libitum, in rooms with temperature of 22-25°C and 50% humidity. All animals were treated in adherence to all of the guiding principles in the care and use of animals approved by animal ethical committee of Abant Izzet Baysal University together with the recommendation from the Declaration of Helsinki.

2.2. Surgical operation

All rats were anesthetized with 1.2 gr/kg urethane applied intraperitoneally before surgical operation. After controlling the depth of anesthesia that was checked with the eye and claw reflexes; rats were taken to the operation table. After shaving the hair on upper part of rat head, an incision is made on rostrocaudal axis of about 2-4 cm long with help of a scalpel. Skull bones were lifted carefully after lambda and bregma points and dura was exposed and a part to the left of bregma line thinned with a handdrill. Then, dura mater is removed carefully after skull bone has been removed completely. ECoG record is taken by two Ag/AgCl top electrodes and earth connection was made by an Ag/AgCl clamp electrode for grounding. In this process of electrophysiological recording, positive electrodes placed in front of bregma,

negative one is to a few millimeters behind of bregma and grounding electrode is placed on left ear. Activity taken from electrodes is amplified by BioAmp (ADInstruments, Australia) interface and transferred to PowerLab 8/SP (ADInstruments, Australia) data recording system. PowerLab brain activity is viewed by Chart 5.1.1 (ADInstruments, Australia) software, and deposited in computer for post-experiment analysis.

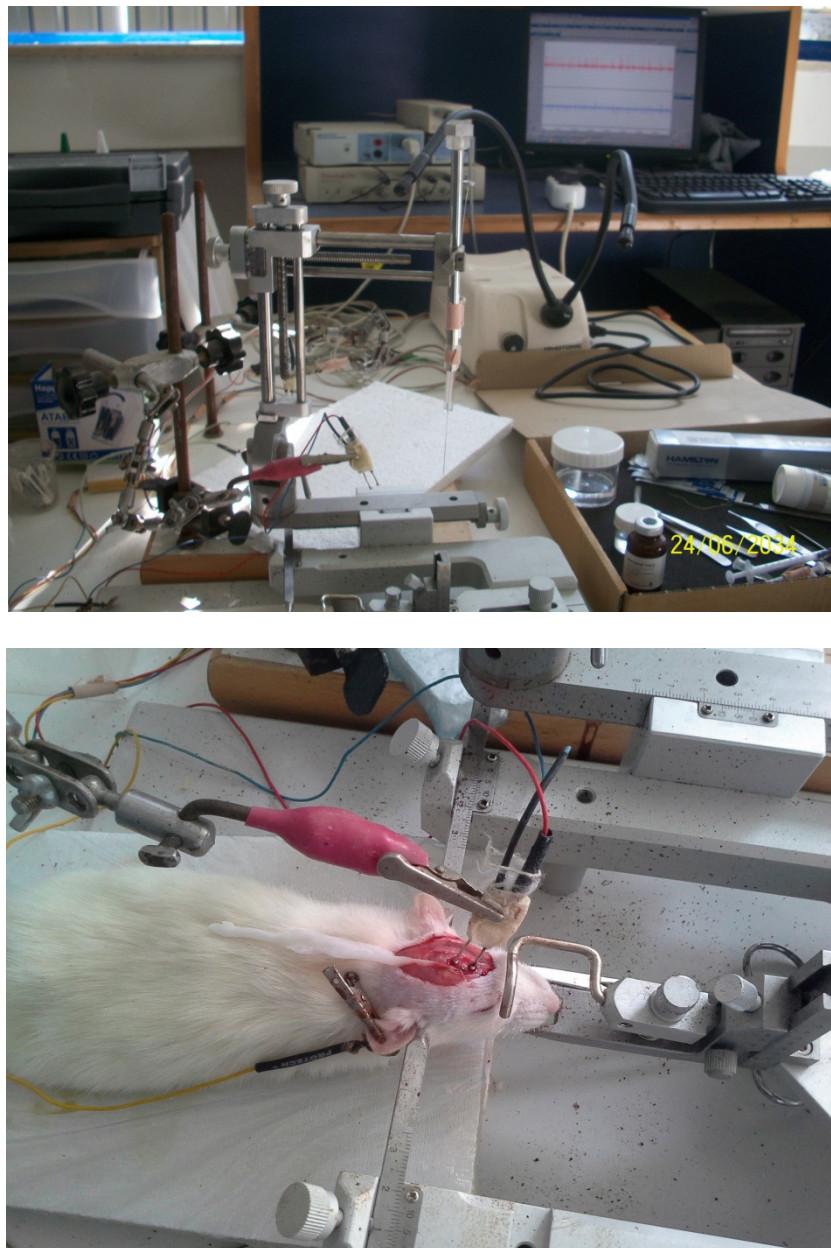


Figure 2.1. Experimental setup; Recording of ECoG from operated animals

2.3. Preparation of drugs

All drugs including mitochondrial KATP channel openers (agonist) Bepridil, mitochondrial blocker (antagonist) 5HD, and sarcolemmal opener (antagonist) HMR 1098 used in this study were prepared daily.

Doses of HMR 1098 and 5HD were determined and given in the same dose as like in previous studies. Since dose of Bepridil and P1075 were not known previously, the effective dose of these drug in the epilepsy were determined by the preliminary studies.

Chemical name of Bepridil (Sigma Aldrich) is “1-Isobutoxy-2-pyrrolidino-3-(N-benzylanilino) propane hydrochloride” and its molecular weight is 403

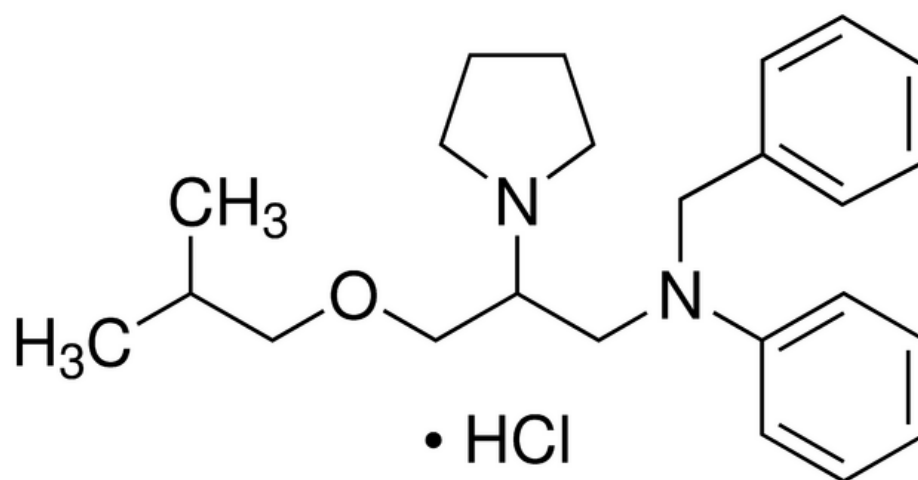


Figure 2.2. Chemical structure of Bepridil

As a result of preliminary studies, the most effective dose of bepridil was determined as 1 mg / kg. Bepridil was dissolved first in ethyl alcohol and then mixed with the

saline in 1/1. Bepridil has been applied intravenously before and during seizure in a dose of 1mg/kg / 100μl.

Chemical name of 5HD (Sigma Aldrich) is “**5-hydroxydecanoate sodium salt**” and **its chemical formula is “C₁₀H₁₉NaO₃”** with molecular weight of 210.25. It is a selective mitochondrial KATP blocker (antagonist).

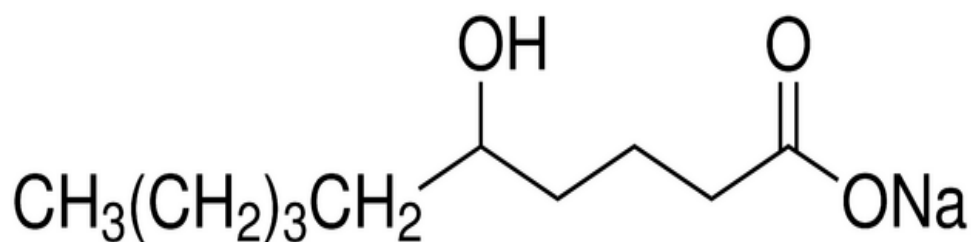


Figure 2.3. Chemical structure of 5HD

5HD dissolved in physiological saline and applied intravenously before and during seizure in a dose of 10 mg / kg / 100μl.

Chemical name of P1075 is “N-cyano-N'-(1,1-dimethylpropyl)-N''-3—pyridylguanidine” with chemical formula of C₁₂H₁₇N₅ with molecular weight of 231.30. It is a selective sarcolemmal K_{ATP} channel opener (agonist).

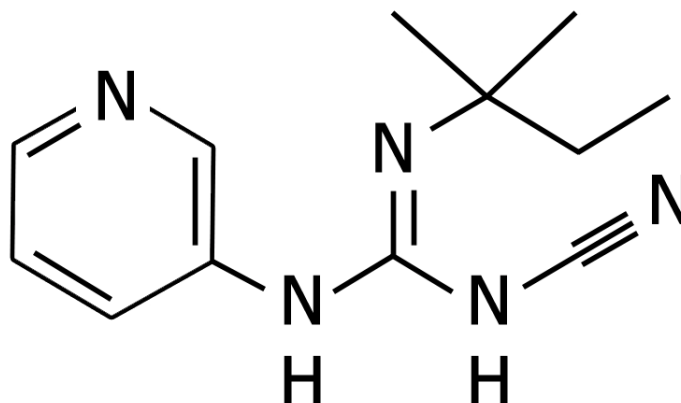


Figure 2.4. Chemical structure of P1075

As a result of dose study performed for P1075, 0.5 mg/kg was determined as a most effective dose, P1075 was prepared by dissolving in DMSO then mixing with saline with a ratio of 1/1. P1075 has been applied intravenously before and during seizure in a dose of 0.5 mg/kg /100 μ l.

Chemical name of HMR 1098 is “1-[5-[2-(5-chloro-o-anisomido) ethyl]-2-methoxyphenyl] sulfonyl-3-methylthiourea” and its chemical formula is “C₁₉H₂₁ClN₃NaO₅S₂” with molecular weight of 493.94. It is an selective sarcK_{ATP} channel blocker that was given as a gift from Sanofi Aventis, Deutschland.

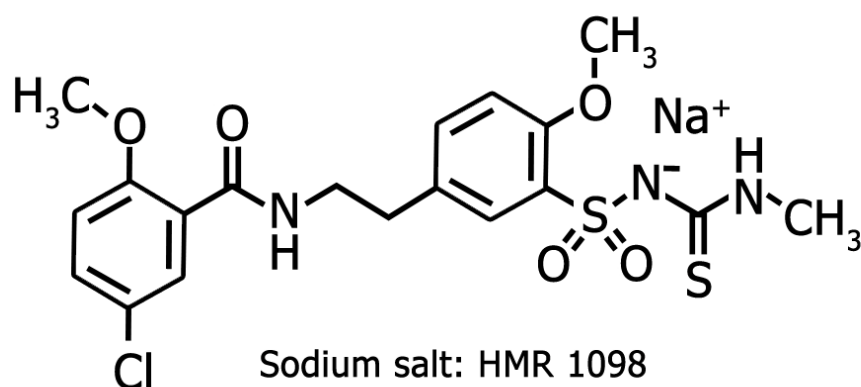


Figure 2.5. Chemical structure of HMR 1098

HMR 1098 was dissolved in saline and was applied intravenously before and during seizure in a dose of 3mg/kg /100 μ l.

2.4. Drug application

After observation of basal activity in the first five minutes, penicillin-G with 500 I.U of dose and 2.5 μ l in volume has been injected on to the zone that was 3 mm lateral, 2 mm posterior and 2 mm ventral region of bregma point in the left cortex via an Hamilton microinjector to create epileptiform activity.

Three doses of bepridil 0.1mg / kg, 1mg / kg, 10mg/kg and P1075; 0.1mg / kg, 0.5mg / kg, 1mg/kg were applied intravenously before and during seizure to determine the effective doses. Effective doses were determined with the least spike formation in animals having seizure in respect to control group. At least six animals were used in the treatment of each doses of drug. The ECoG activity was recorded during period of 180 minutes following penicillin-G injection in animals getting to the experiment.

In control groups, no drug but its solvent was given in the same way before and during seizure. In pre-seizure group, drugs were given 5 minutes before application of penicillin G.

All drugs prepared daily before administration and given intravenously from tail vein. Drugs were given 5 minutes before seizure in pre-seizure group and at 30 minutes following penicillin G application in during seizure group.

2.5. Statistical analysis

By the help of macro which were included in Chart 5.1.1 (ADInstruments, Australia) program, the electrophysiological recordings were analysed after transformation of electrophysiological recordings into numeric recording in 5 minute intervals in terms of total spike waves number and mean amplitude in values. These analyses were conducted in 5 minute intervals along the 180 minutes recording. One way ANOVA was used for statistical evaluations to compare the differences within groups in terms of periodic variations. Significant results were tested by LSD post hoc test. Differences having p values lower than 0.05 were accepted as statistically significant. PASW 18.0 program was used for statistical calculations. Descriptive statistics were given with standard variation in tables and figures.

3. RESULTS

Data comprising mean spike frequency and mean amplitude of spikes, start of spike from all groups during 180 minutes record following penicillin injection were presented as tables and figures. First of all, figures and tables for each group was given and spike frequency and amplitude was shown in both tables and figures. Initially whole record along 180 minutes was shown for each group.

3.1. Basal activity of brain in animals having no drug or penicillin treatment

ECoG records that are taken before the application of penicilline is demonstrated below. No epileptic occasions and spike waves were observed in this case.



Figure 3.1. A typical basal EcoG activity of left hemispheric somatomotor area of Wistar rat which was under urethane anesthesia (LabChart 6 Pro, AD Instruments) recording programme were used.

3.2. Epileptic activities induced by penicillin

Penicillin caused epileptic discharges in the cortex and this occasion is recorded via electrocardiogramme. The spike wave formations was seen around 15 minutes, following injection of penicillin one - two mm below brain cortex. Epileptic discharges continued for certain amount of time depending on dose injected and vanishes after certain time latter.

Just after the injection of penicilline a latent period in which having lower amplitude waves indicating return of basal activity and it last for three to eight minutes. After this period, an indistinct transition has come and then irregular spike wave starts and led to epileptic seizure.

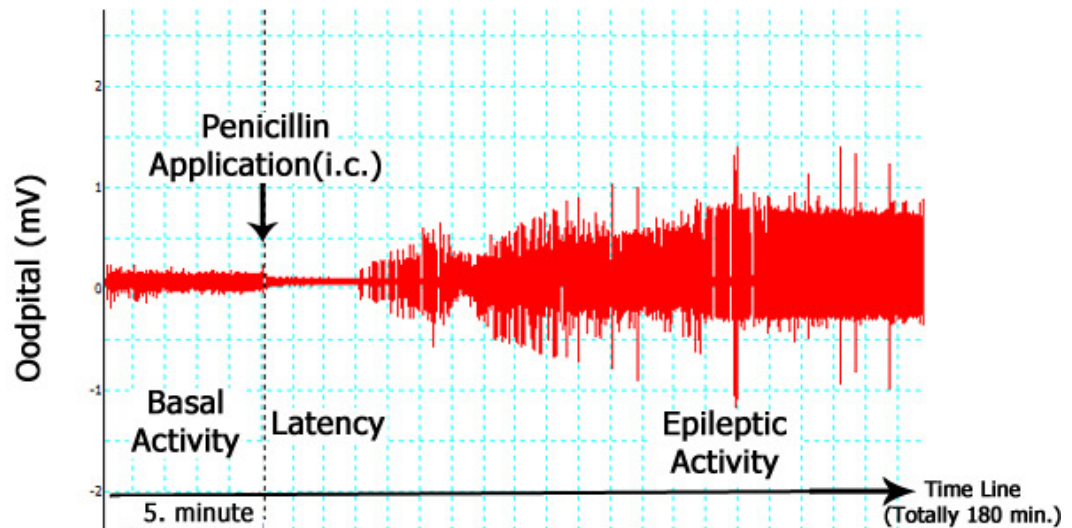


Figure 3.2. Observed changes of ECoG waves after Penicillin-G injection.

The first arrow in figure 3.2. shows the time that penicillin (500 IU/2,5 μ l) injection was made. Three to eight minutes after the injection of penicillin, a significant decrease in wave amplitude considered as basal activity can be observed. After this period, there is an epileptic period in which significant increase in the wave amplitudes is observed.

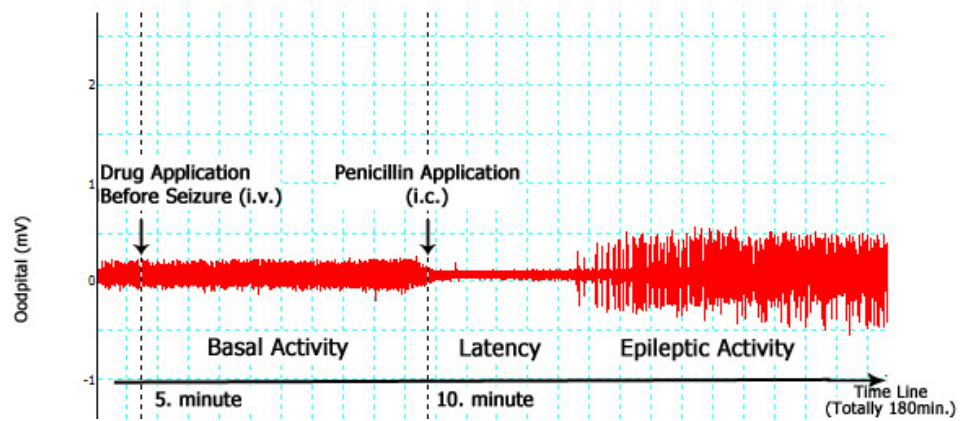


Figure 3.3. ECoG recording before seizure groups .The first arrow shows the time that drug (0,1 mg / kg, 1 mg / kg, 10mg/kg Bepridil and 0,1mg / kg, 0,5mg/kg ,1 mg/kg P1075, 3mg/kg HMR 1098, 10 mg/kg 5HD) injection were applied intravenously. Second arrow shows the time of intracortical penicillin (500 IU / 2,5 μ l) injection

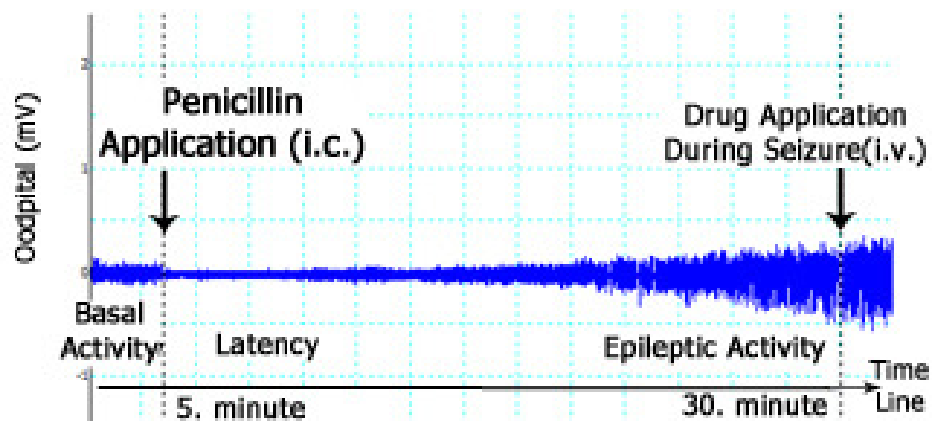


Figure 3.4. ECoG recording during seizure groups. The first arrow shows the time that penicillin (500 IU / 2,5 μ l) injection intracortically. Second shows the time of drug (0,1 mg / kg, 1 mg / kg, 10 mg/kg Bepridil and 0,1 mg / kg, 0,5 mg/kg ,1 mg/kg P1075, 3mg/ HMR 1098, 10 mg/kg 5HD) injection intravenously.

3.3. The latency of epileptic activity formation

Spike waves related to epileptic activity were observed after application of penicillin that usually started at 3 to 8 minutes. However when the drugs were injected before the application of penicillin, spike waves were observed starting from 9 to 27 minutes. P1075 in 0.1mg/kg dose applied before seizure (BS group) was found to be significantly higher than the control group in terms of latency ($p < 0,05$). The seizure initiation times was also significantly higher in this group (Table 3.1. and Fig 3.5. ($p < 0,05$).

There was no significant difference between control group and Bepridil BS (0,1, 1, 10 mg / kg), Bepridil DS (0,1,1,10 mg / kg), p1075 BS (0,5, 1 mg / kg), HMR 1098 BS, HMR 1098 DS, 5HD BS and 5HD DS groups in terms of latency and seizure initiation time ($p > 0,05$).

Table 3.1. The initiation time of epileptic seizure following penicilin application in all groups in second (Data are means $\pm$ SE *P < 0.05: Compared control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	726,67	$\pm$	147,12	
0,1mg BEP BS	6	720,00	$\pm$	183,30	0,98
1mg BEP BS	6	530,00	$\pm$	84,02	0,77
10 mg BEP BS	8	1626,67	$\pm$	1057,00	0,16
0,1mg BEP DS	6	645,71	$\pm$	179,30	0,90
1 mg BEP DS	6	440,00	$\pm$	95,08	0,68
10 mg BEP DS	8	750,00	$\pm$	213,04	0,98
0,1 mg P1075 BS	6	2460,00	$\pm$	1550,82*	0,02
0,5 mg P1075 BS	6	770,00	$\pm$	299,77	0,96
1 mg P1075 BS	6	1530,00	$\pm$	600,35	0,26
0,1 mg P1075 DS	8	637,50	$\pm$	63,07	0,88
0,5mg P1075 DS	6	600,00	$\pm$	147,78	0,85
1 mg P1075 DS	8	622,50	$\pm$	125,21	0,86
5HD BS	8	592,50	$\pm$	45,97	0,83
5HD DS	10	516,00	$\pm$	96,42	0,72
HMR 1098 DS	8	323,00	$\pm$	25,00	0,77
HMR 1098 BS	8	570,00	$\pm$	174,56	0,80

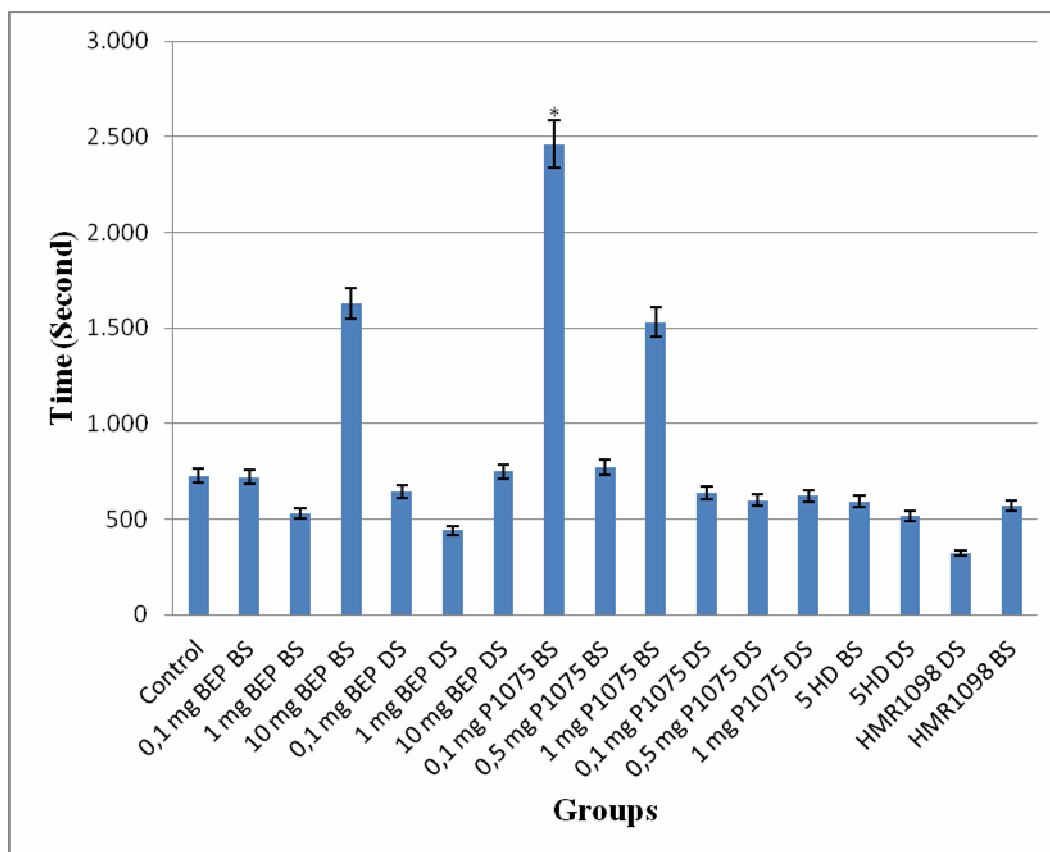


Figure 3.5. The latency of first epileptic activity (Data are means $\pm$ SE *P<0.05: Compared to control)

3.4. The effect of bepridil on spike wave frequency in the epileptic activity

The effect of 0,1 mg/kg bepridil which was applied within five minutes before penisilin application was seen at the fourth period (15 minute) and lasted for 3 periods ($p<0,01$). Between 13 and 17 periods the spike wave frequency was found significantly decreased compared to control group and bepridil reduced total seizure time ($p<0,05$).

While the dose of 1 mg/kg bepridil which was applied before seizure increased the spike wave frequency till the fifth period, it decreased the frequency starting from 14. period to the end of the recording ($p<0,05$).

The application of 10 mg/kg dose of bepridil before seizure group, significantly decreased spike wave frequency compared to control group in between 8 and 26 period ($p<0,05$) (Table 3.1.2 and Fig.3.1.2). Bepridil which was applied at the dose of 0,1 mg/kg and 1 mg/kg during seizure decreased total spike wave number in between 13. and 28. periods significantly. The most effective time period was with in 13. and 28. periods ($p<0,05$). 10 mg/kg dose of bepridil during seizure had no significant effect ($p>0,05$).

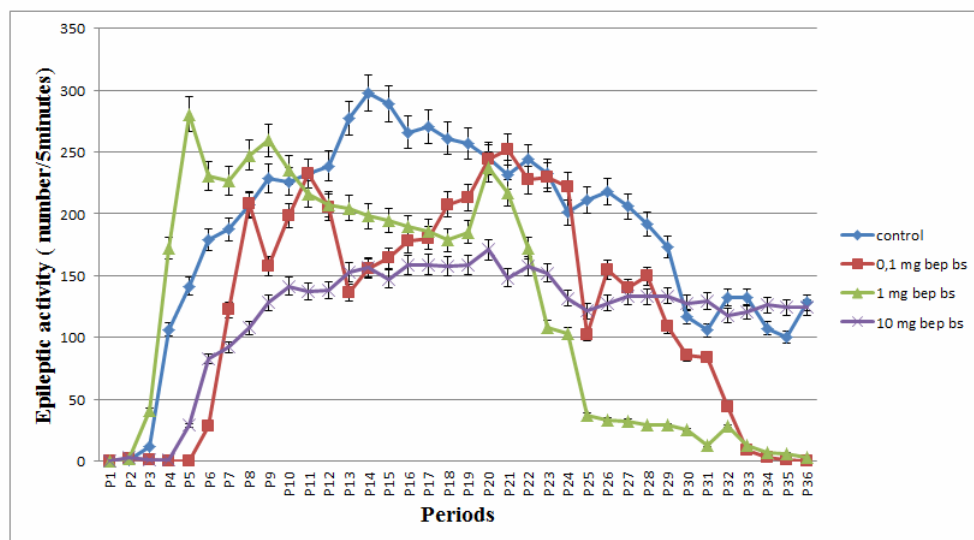


Figure 3.6. The number of spike wave during 180 minutes ECoG records in bepridil groups before seizure.

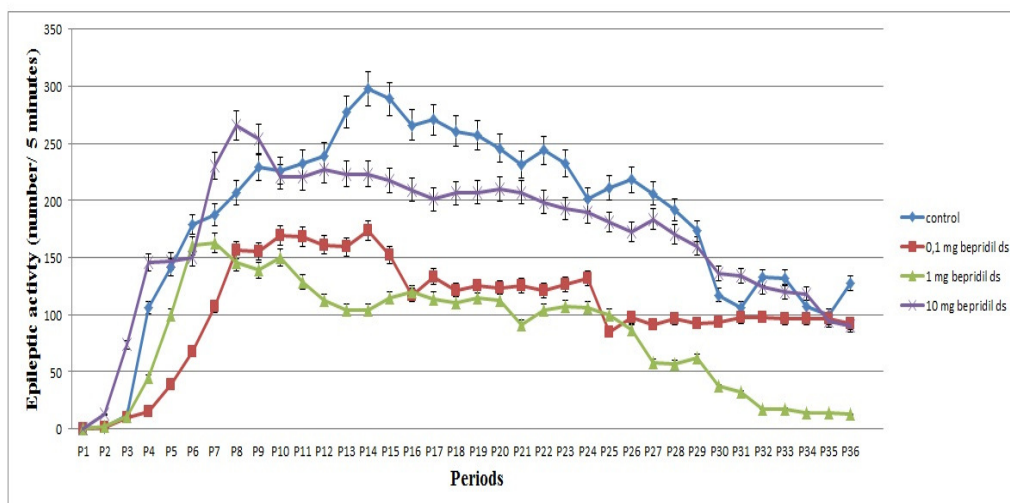


Figure 3.7. The number of spike wave during 180 minutes ECoG records in bepridil groups during seizure.

3.5. The effect of P1075 on spike wave frequency in the epileptic activity

P1075 applied before seizure significantly decreased spike wave frequency just after the 4. period compared to control group in all three different doses ($p < 0,05$). The dose of 0,1 mg/kg of P1075 was effective between 4. and 36. period and shortened the seizure time ($p < 0,05$). While the dose of 0,5 mg/kg of P 1075 decreased total spike wave frequency between 4 and 15 period ($p < 0,05$), the dose of 1 mg/kg decreased total spike wave frequency between 4. and 16. period compared to control group ($p < 0,05$).

P1075 applied during seizure significantly decreased total spike wave frequency between 8. and 36. periods compared to control in all three different doses ($p < 0,05$). P1075 in 0,1 mg/kg dose applied during seizure decreased total spike wave count much more than other groups just after the 17. Period ($p < 0,05$).

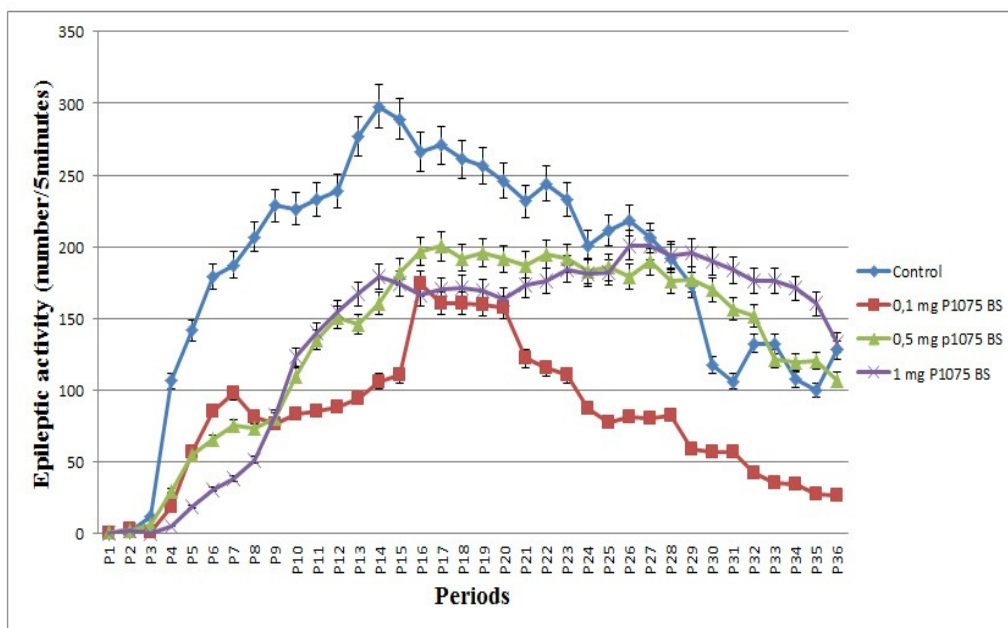


Figure 3.8. The number of spike wave during 180 minutes ECoG records in P1075 before seizure

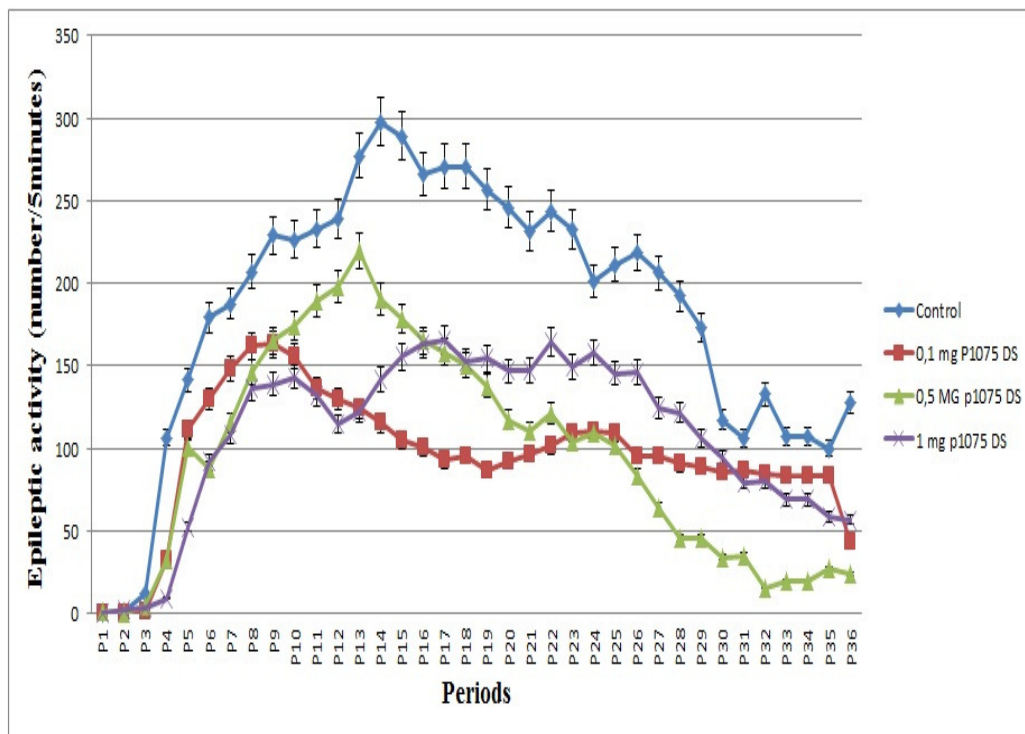


Figure 3.9. The number of spike wave during 180 minutes ECoG records in P1075 during seizure

3.6. The effect of HMR 1098 on spike wave frequency in the epileptic activity

HMR 1098 application before seizure significantly decreased spike wave amplitude just after the 3. period compared to control group whereas HMR 1098 application during seizure significantly decreased spike wave amplitude just after the 9. period compared to control group ($p<0,05$). HMR 1098 applied during seizure decreased the spike frequency between 9-17 periods of epileptic seizure in respect to control. However in 34. period frequency was greater than the control group ($p<0,05$).

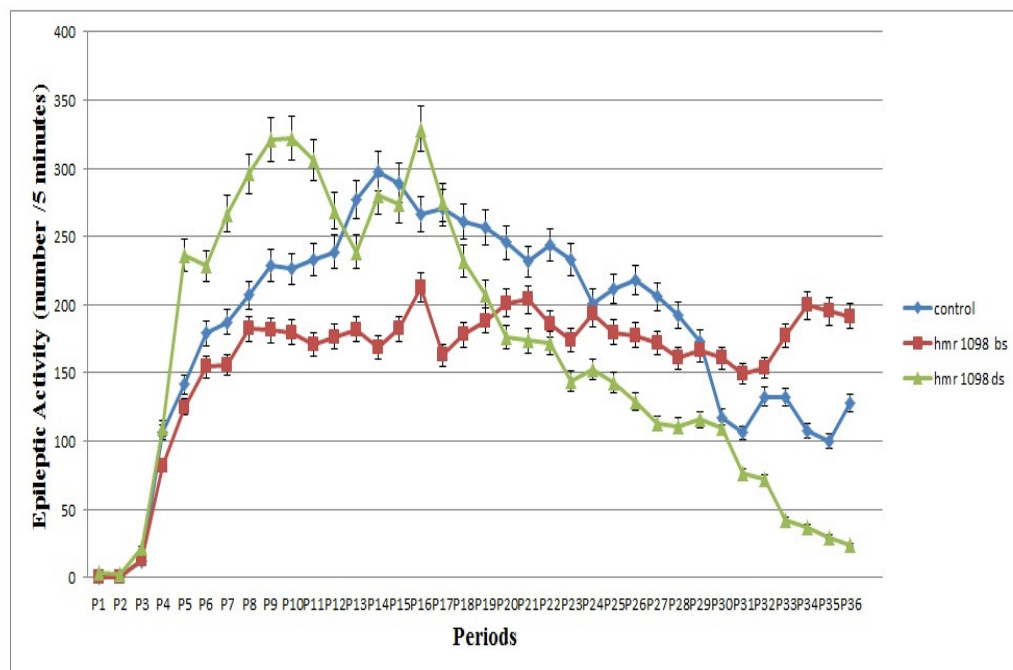


Figure 3.10. The number of spike wave during 180 minutes ECoG records in HMR 1098 before and after seizure.

3.7. The effect of 5HD on spike wave frequency in the epileptic activity

The spike wave frequency in 5HD applied during seizure and before seizure were lower than control in between 1– 15 periods. Epileptic activity of 5HD applied during seizure was ended in the 34 period ($p<0,05$).

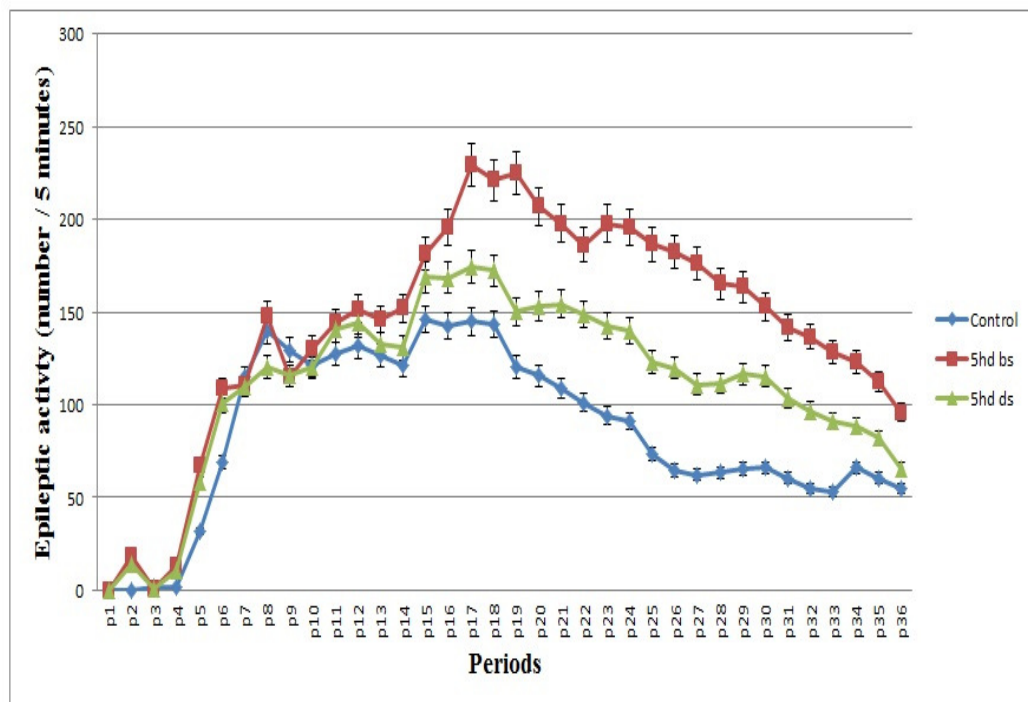


Figure 3.11. The number of spike wave during 180 minutes ECoG records in 5HD before and after seizure groups.

3.8. Spike wave frequency in the 5 minutes interval between 0-180 minutes ECoG recording following penicillin application.

The spike wave frequency were determined and compared with the control in every 5 minutes interval along the 180 minutes ECoG recording following penicilline application.

3.8.1. Epileptic activity between 0 – 5 minutes in terms of spike wave frequency in all groups (Period 1)

The spike wave frequency in groups 0,5mg P1075 BS and 0,5mg P1075 DS between 0 – 5 Minutes time interval is significantly higher than control group (Table 3.2, Fig 3.12.) ($p < 0,05$).

Table 3.2. Spike wave frequency (count/minute) obtained from 0 to 5 minute (Period 1) recordings in all groups. BS: Before seizure, DS: During seizure.

(Data are means $\pm$ SE * $P < 0.05$: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	0,00	$\pm$	0,00	
0,1mg BEP BS	6	0,00	$\pm$	0,00	1,00
1mg BEP BS	6	0,00	$\pm$	0,00	1,00
10 mg BEP BS	8	0,00	$\pm$	0,00	1,00
0,1mg BEP DS	6	0,00	$\pm$	0,00	1,00
1 mg BEP DS	6	0,00	$\pm$	0,00	1,00
10 mg BEP DS	8	0,00	$\pm$	0,00	1,00
0,1 mg P1075 BS	6	0,00	$\pm$	0,00	1,00
0,5 mg P1075 BS	6	0,83	$\pm$	0,54*	0,01
1 mg P1075 BS	6	0,00	$\pm$	0,00	1,00
0,1 mg P1075 DS	8	0,13	$\pm$	0,13	0,64
0,5mg P1075 DS	6	0,67	$\pm$	0,67*	0,02
1 mg P1075 DS	8	0,13	$\pm$	0,13	0,64
5HD BS	8	0,25	$\pm$	0,25*	0,35
5HD DS	10	0,20	$\pm$	0,20*	0,43
HMR 1098 DS	8	0,13	$\pm$	0,13	0,64
HMR 1098 BS	8	0,13	$\pm$	0,13	0,64

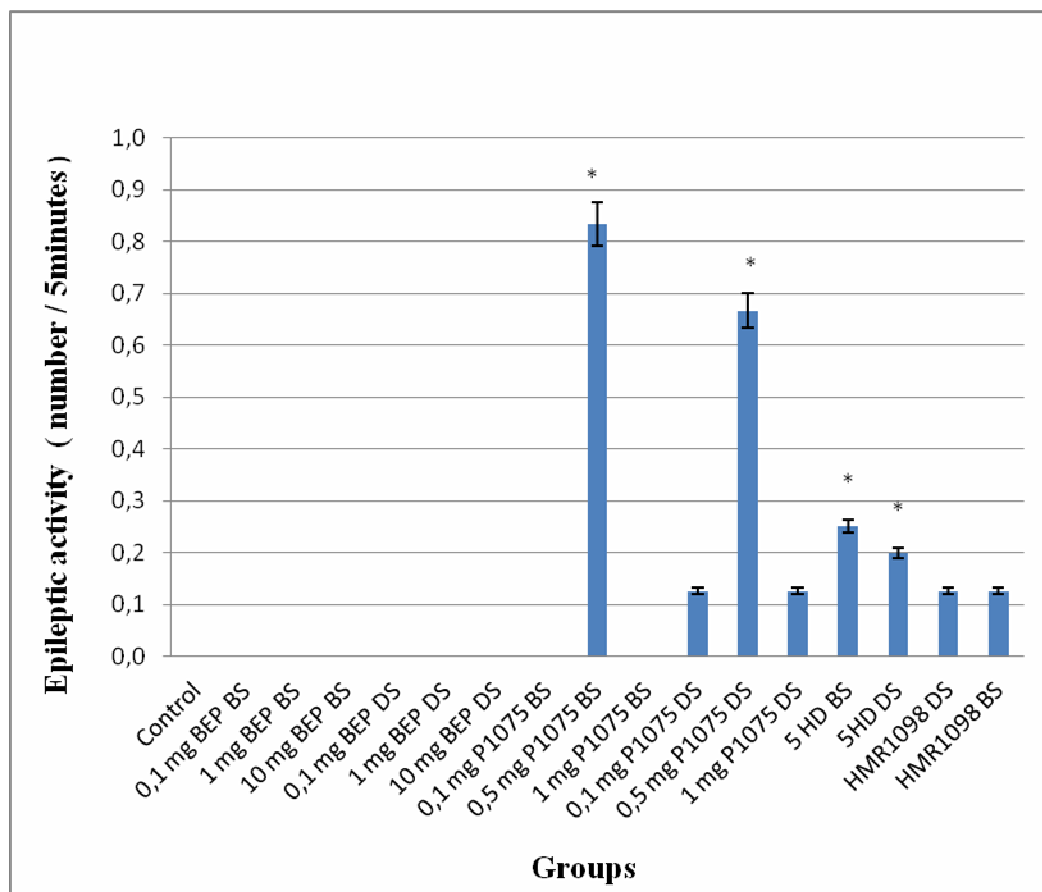


Figure 3.12. Spike wave frequency obtained from 0 to 5 minutes recordings (Period 1). (Data are means $\pm$ SE *P<0.05: Compared to control)

3.8.2. Epileptic activity between 5 to 10 minutes in terms of spike wave frequency in all groups (Period 2)

There was no significant difference between groups and control in terms of spike wave frequency in 5 to 10 minute (Period 2) time interval (Table 3.3, Fig 3.13.) ($p>0,05$).

Table 3.3. Number of spike obtained from 5 to 10 minute recordings in all groups. (Data are means $\pm$ SE *P < 0.05: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	1,33	$\pm$	1,11	
0,1mg BEP BS	6	1,83	$\pm$	0,54	0,98
1mg BEP BS	6	2,33	$\pm$	0,84	0,94
10 mg BEP BS	8	3,11	$\pm$	2,31	0,87
0,1mg BEP DS	6	1,14	$\pm$	0,99	0,97
1 mg BEP DS	6	2,00	$\pm$	1,00	0,96
10 mg BEP DS	8	12,62	$\pm$	8,03	0,26
0,1 mg P1075 BS	6	3,16	$\pm$	1,62	0,88
0,5 mg P1075 BS	6	1,83	$\pm$	1,83	0,98
1 mg P1075 BS	6	2,00	$\pm$	1,00	0,96
0,1 mg P1075 DS	8	0,12	$\pm$	0,13	0,89
0,5mg P1075 DS	6	0,50	$\pm$	0,22	0,93
1 mg P1075 DS	8	2,12	$\pm$	1,86	0,95
5HD BS	8	18,25	$\pm$	17,55	0,09
5HD DS	10	14,10	$\pm$	14,10	0,18
HMR 1098 DS	8	9,37	$\pm$	6,00	0,43
HMR 1098 BS	8	0,37	$\pm$	0,26	0,91

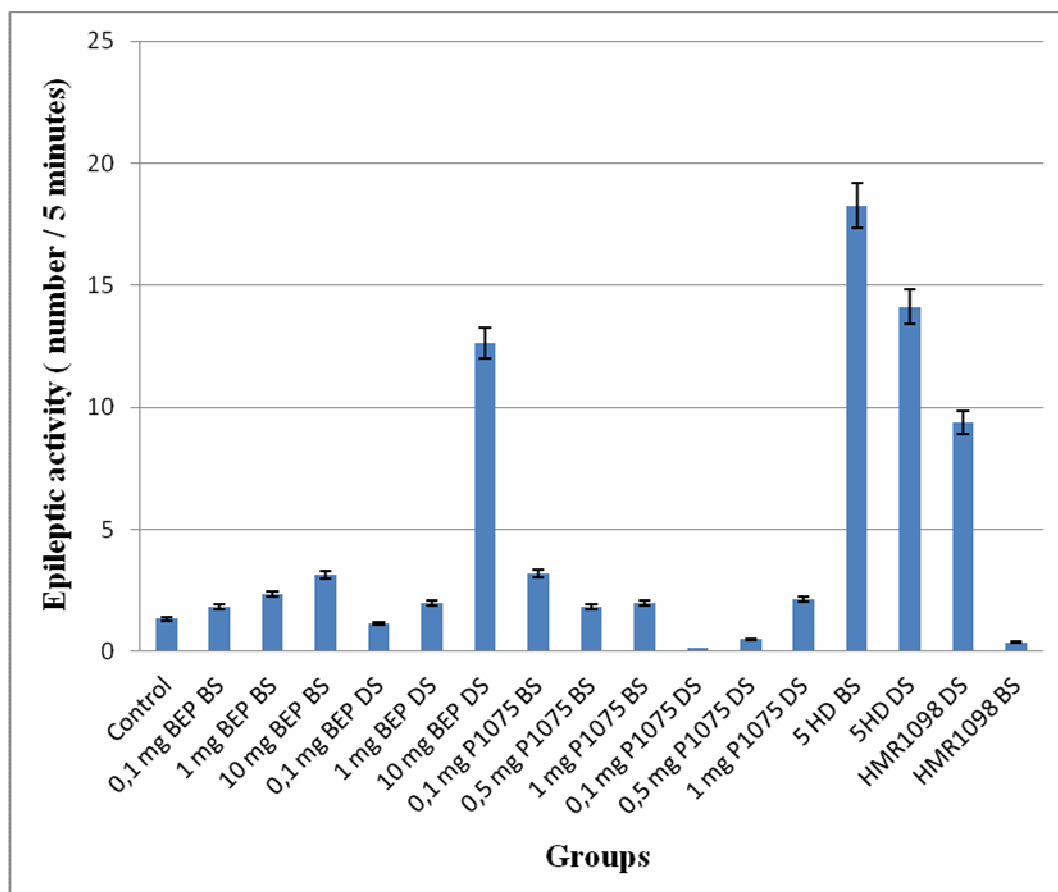


Figure.3.13. Spike wave frequency obtained from 5-10 minutes recordings (Period 2). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.3. Epileptic activity between 10 to 15 minutes in terms of Spike wave frequency (Period 3)

The spike wave frequency in groups 10 mg Bepridil DS and 1 mg Bepridil BS between 10 – 15 minutes time interval were significantly higher than control group (Table 3.4., Fig.3.14.) ($p < 0,05$).

Table 3.4. Spike wave frequency (count/minute) obtained from 10 to 15 minute recordings in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	12,11	$\pm$	5,87	
0,1mg BEP BS	6	1,00	$\pm$	0,45	0,58
1mg BEP BS	6	40,67	$\pm$	24,90*	0,22
10 mg BEP BS	8	1,00	$\pm$	0,65	0,53
0,1mg BEP DS	6	9,57	$\pm$	9,41	0,86
1 mg BEP DS	6	11,17	$\pm$	7,48	0,92
10 mg BEP DS	8	73,50	$\pm$	50,24*	0,00
0,1 mg P1075 BS	6	1,00	$\pm$	0,82	0,58
0,5 mg P1075 BS	6	6,00	$\pm$	5,41	0,74
1 mg P1075 BS	6	0,33	$\pm$	0,21	0,56
0,1 mg P1075 DS	8	0,88	$\pm$	0,88	0,54
0,5mg P1075 DS	6	4,00	$\pm$	3,80	0,67
1 mg P1075 DS	8	3,00	$\pm$	2,37	0,61
5HD BS	8	0,75	$\pm$	0,41	0,54
5HD DS	10	0,90	$\pm$	0,41	0,52
HMR 1098 DS	8	4,75	$\pm$	4,20	0,67
HMR 1098 BS	8	13,38	$\pm$	11,31	1,00

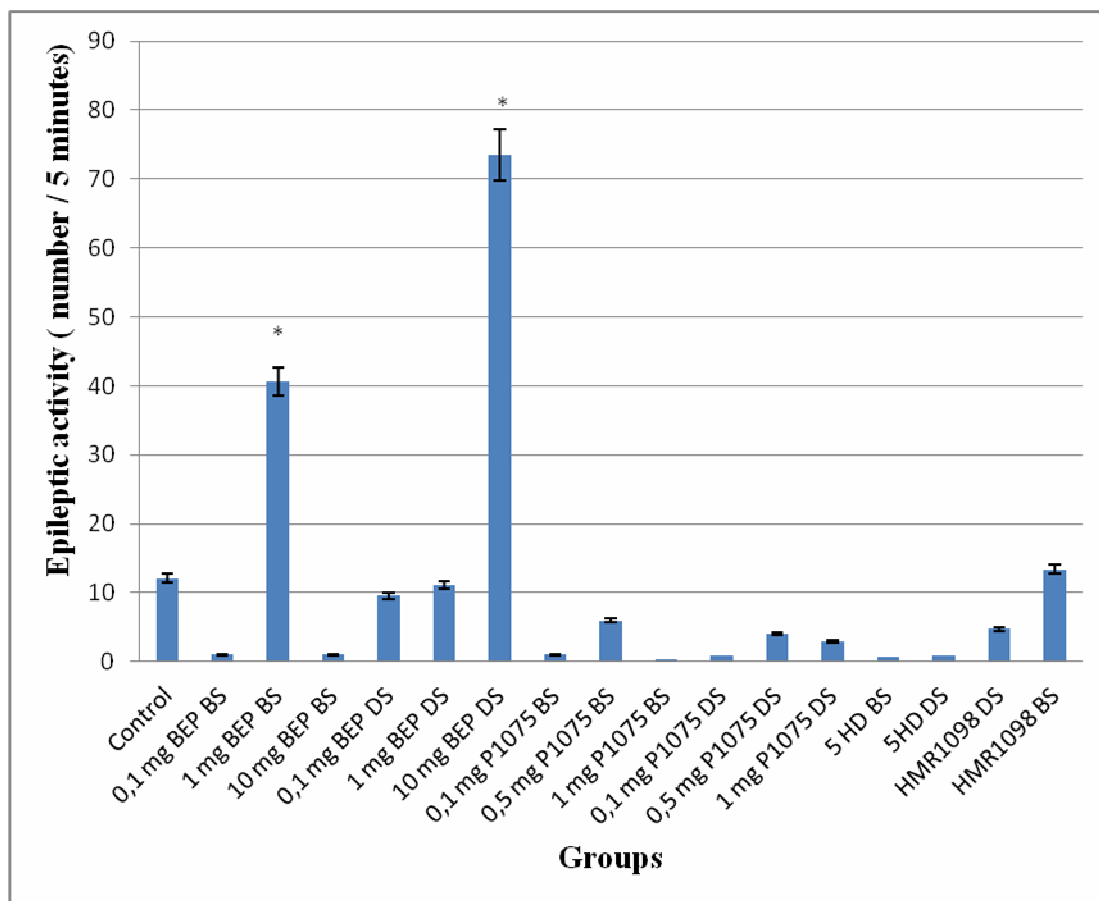


Figure 3.14. Spike wave frequency obtained from 10 to 15 minutes recordings (Period 3). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.4. Epileptic activity between 15 – 20 minutes in terms of spike wave frequency (Period 4)

The spike wave frequency in groups 10 mg BEP BS; 0,1 mg BEP BS; 0,1 mg BEP DS; 1 mg BEP DS; 1 mg P1075 BS; 1 mg P1075 DS; 5 HD BS; 5HD DS; HMR1098 DS between 15 – 20 minutes time interval were significantly smaller than the control group (Table3.5., Fig.3.15.) ($p < 0,05$).

Table 3.5. Spike wave frequency (count/minute) obtained from 15 to 20 minute recordings for all groups. (Data are means $\pm$ SE *P < 0.05: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	106,44	$\pm$	38,27	
0,1mg BEP BS	6	0,00	$\pm$	0,00*	0,02
1mg BEP BS	6	172,50	$\pm$	82,79	0,13
10 mg BEP BS	8	1,22	$\pm$	1,00*	0,01
0,1mg BEP DS	6	15,43	$\pm$	4,73*	0,04
1 mg BEP DS	6	45,33	$\pm$	18,30*	0,19
10 mg BEP DS	8	146,00	$\pm$	71,61	0,31
0,1 mg P1075 BS	6	18,83	$\pm$	14,99	0,06
0,5 mg P1075 BS	6	29,50	$\pm$	17,96	0,10
1 mg P1075 BS	6	5,00	$\pm$	4,61*	0,03
0,1 mg P1075 DS	8	32,00	$\pm$	16,13	0,08
0,5mg P1075 DS	6	32,50	$\pm$	14,67	0,11
1 mg P1075 DS	8	8,88	$\pm$	5,81*	0,02
5HD BS	8	13,13	$\pm$	11,45*	0,03
5HD DS	10	10,60	$\pm$	9,18*	0,02
HMR 1098 DS	8	1,25	$\pm$	0,75*	0,01
HMR 1098 BS	8	81,38	$\pm$	34,34	0,58

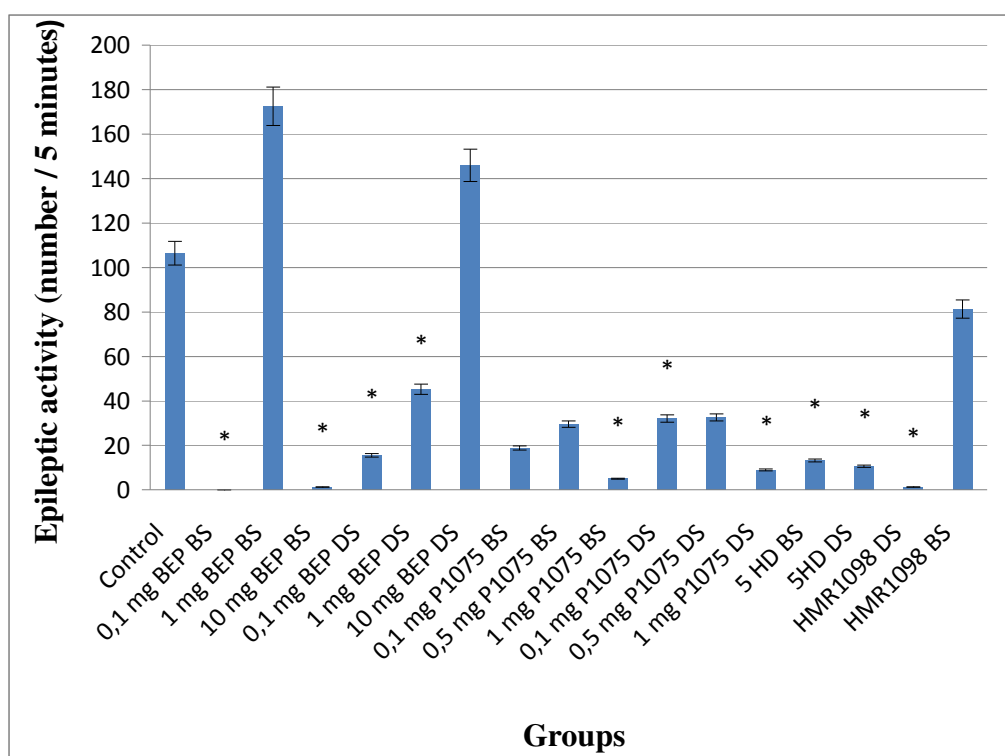


Figure 3.15. Spike wave frequency obtained from 15 to 20 minutes recordings (Period 4). (Data are means $\pm$ SE *P<0.05: Compared to control).

3.8.5. Epileptic activity between 20 to 25 minutes in terms of spike wave frequency (Period 5)

The spike wave frequency in groups 0,1 mg BEP BS; 1 mg BEP BS between 20 – 25 minutes time interval are significantly smaller than control group (Table3.6., Fig.3.16.) ($p < 0,05$).

Table 3.6. Spike wave frequency (count/minute) obtained from 20 to 25 minute recordings in all groups. (Data are means $\pm$ SE *P < 0.05 Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	141,44	$\pm$	37,79	
0,1mg BEP BS	6	0,00	$\pm$	0,00*	0,04
1mg BEP BS	6	280,67	$\pm$	86,81*	0,02
10 mg BEP BS	8	29,00	$\pm$	16,47	0,08
0,1mg BEP DS	6	38,86	$\pm$	14,23	0,13
1 mg BEP DS	6	100,00	$\pm$	28,37	0,64
10 mg BEP DS	8	147,00	$\pm$	74,88	0,77
0,1 mg P1075 BS	6	56,50	$\pm$	26,55	0,25
0,5 mg P1075 BS	6	54,33	$\pm$	37,79	0,23
1 mg P1075 BS	6	18,67	$\pm$	18,27	0,08
0,1 mg P1075 DS	8	111,63	$\pm$	61,06	0,75
0,5mg P1075 DS	6	100,33	$\pm$	44,14	0,64
1 mg P1075 DS	8	52,13	$\pm$	37,38	0,18
5HD BS	8	67,00	$\pm$	33,25	0,28
5HD DS	10	58,50	$\pm$	24,35	0,20
HMR 1098 DS	8	40,50	$\pm$	26,99	0,13
HMR 1098 BS	8	125,00	$\pm$	57,33	0,93

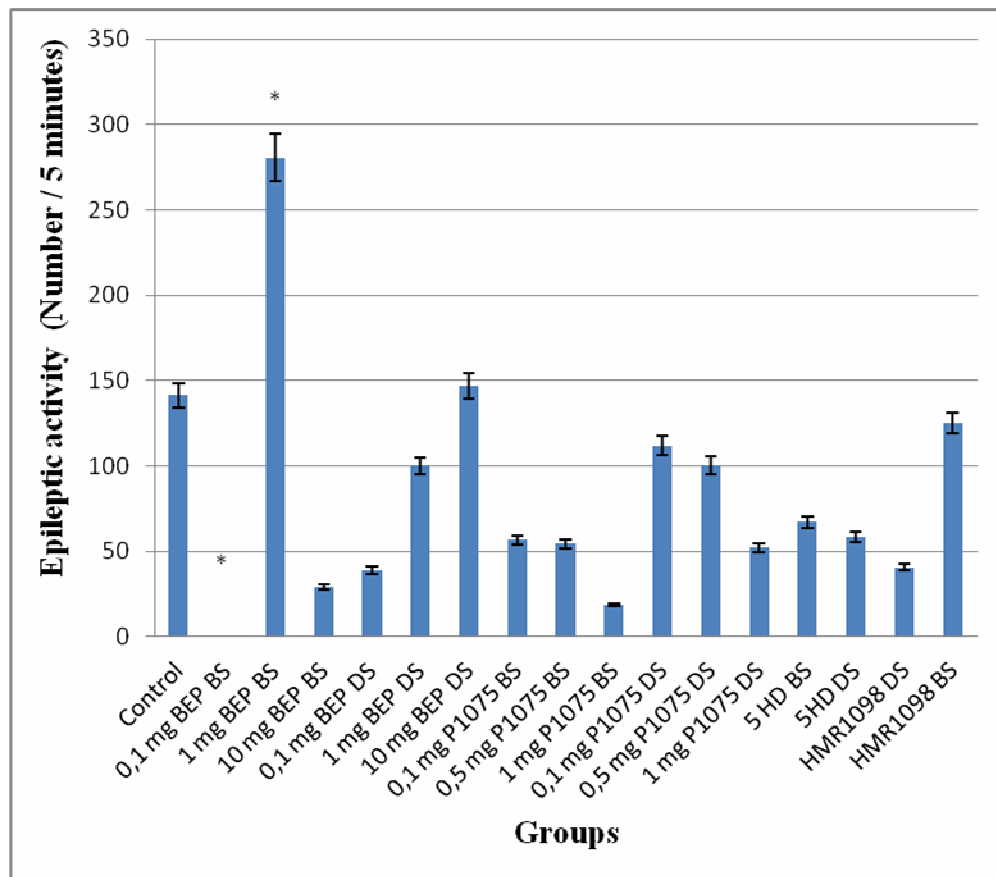


Figure 3.16. Spike wave frequency (obtained from 20 to 25 inutes recordings (Period 5). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.6. Epileptic activity between 25 to 30 minutes in terms of spike wave frequency (Period 6)

There is no significant difference between groups and control in terms of spike wave frequency in 25 to 30 minute (Period 2) time interval (Table3.7, Fig.3.17) ($p > 0,05$).

Table 3.7. Spike wave frequency (count/minute) obtained from 25 to 30 minute recordings in all groups. (Data are means $\pm$ SE *P<0.05: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	179,11	$\pm$	45,76	
0,1mg BEP BS	6	28,33	$\pm$	12,01	0,07
1mg BEP BS	6	230,67	$\pm$	67,56	0,33
10 mg BEP BS	8	82,78	$\pm$	34,35	0,23
0,1mg BEP DS	6	68,00	$\pm$	16,24	0,18
1 mg BEP DS	6	160,67	$\pm$	43,12	1,00
10 mg BEP DS	8	150,00	$\pm$	55,99	0,88
0,1 mg P1075 BS	6	85,50	$\pm$	45,34	0,30
0,5 mg P1075 BS	6	65,33	$\pm$	40,07	0,19
1 mg P1075 BS	6	30,50	$\pm$	27,37	0,07
0,1 mg P1075 DS	8	129,75	$\pm$	63,30	0,65
0,5mg P1075 DS	6	87,33	$\pm$	28,43	0,31
1 mg P1075 DS	8	91,38	$\pm$	49,00	0,30
5HD BS	8	108,88	$\pm$	62,55	0,44
5HD DS	10	100,60	$\pm$	44,19	0,34
HMR 1098 DS	8	70,75	$\pm$	46,34	0,18
HMR 1098 BS	8	154,25	$\pm$	65,54	0,93

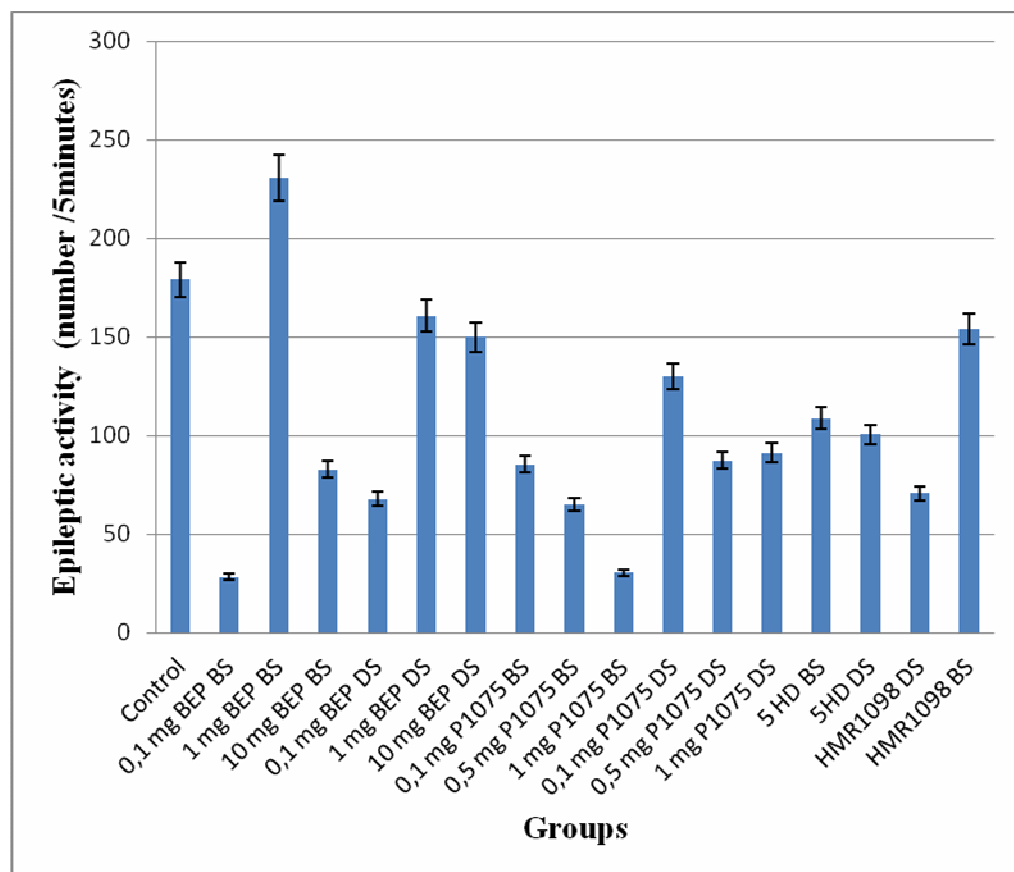


Figure 3.17. Spike wave frequency obtained from 25 to 30 minutes recordings (Period 6). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.7. Epileptic activity between 30 to 35 minutes in terms of spike wave frequency (Period 7)

The spike wave frequency in group 1 mg P1075 BS between 30 – 35 minutes time interval is significantly smaller than the control group (Table3.8., Fig.3.18.) ($p < 0,05$).

Table 3.8. Spike wave frequency (count/minute) obtained from 30 to 35 minute recordings in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	187,33	$\pm$	46,71	
0,1mg BEP BS	6	122,33	$\pm$	35,72	0,54
1mg BEP BS	6	226,67	$\pm$	60,32	0,32
10 mg BEP BS	8	92,11	$\pm$	35,51	0,23
0,1mg BEP DS	6	107,29	$\pm$	29,53	0,38
1 mg BEP DS	6	162,83	$\pm$	41,93	0,99
10 mg BEP DS	8	230,50	$\pm$	42,52	0,25
0,1 mg P1075 BS	6	98,17	$\pm$	39,56	0,33
0,5 mg P1075 BS	6	75,67	$\pm$	39,37	0,18
1 mg P1075 BS	6	38,17	$\pm$	23,09*	0,05
0,1 mg P1075 DS	8	148,25	$\pm$	54,22	0,82
0,5mg P1075 DS	6	115,33	$\pm$	28,92	0,47
1 mg P1075 DS	8	108,63	$\pm$	42,48	0,37
5HD BS	8	110,50	$\pm$	55,95	0,39
5HD DS	10	109,50	$\pm$	36,19	0,36
HMR 1098 DS	8	72,38	$\pm$	44,58	0,14
HMR 1098 BS	8	155,63	$\pm$	57,22	0,92

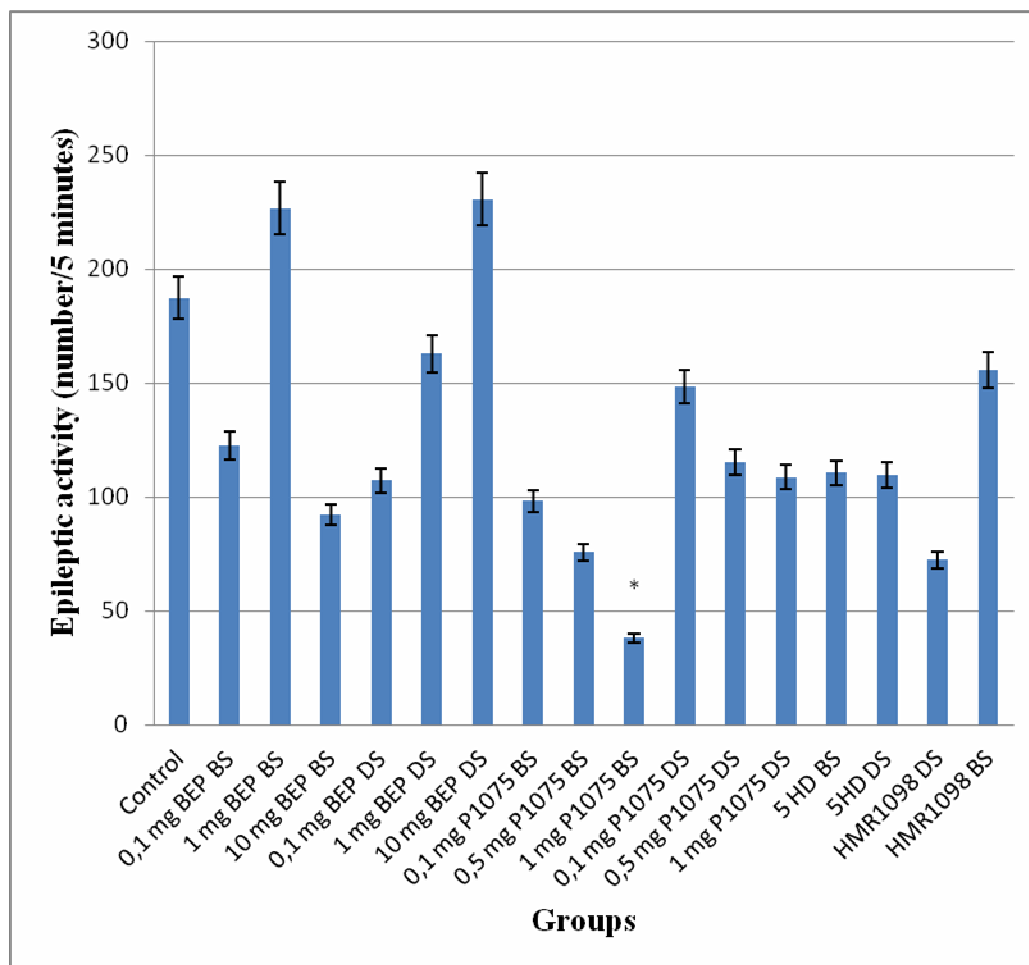


Figure 3.18. Spike wave frequency obtained from 30 to 35 minutes recordings (Period 7). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.8. Epileptic activity between 35 to 40 minutes in terms of spike wave frequency (Period 8)

The spike wave frequency in group 1 mg P1075 BS between 35 – 40 minutes time interval is significantly smaller than the control group (Table3.9., Fig.3.19.) ($p < 0,05$).

Table 3.9. Spike wave frequency (count / minute) obtained from 35 to 40 minute recordings in all groups (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	206,89	$\pm$	36,31	
0,1mg BEP BS	6	208,00	$\pm$	17,80	0,73
1mg BEP BS	6	247,50	$\pm$	55,05	0,33
10 mg BEP BS	8	107,56	$\pm$	29,48	0,16
0,1mg BEP DS	6	156,57	$\pm$	49,28	0,62
1 mg BEP DS	6	145,67	$\pm$	49,00	0,52
10 mg BEP DS	8	265,63	$\pm$	44,04	0,17
0,1 mg P1075 BS	6	80,83	$\pm$	29,83	0,10
0,5 mg P1075 BS	6	73,17	$\pm$	35,44	0,07
1 mg P1075 BS	6	51,17	$\pm$	25,48*	0,03
0,1 mg P1075 DS	8	161,88	$\pm$	44,36	0,67
0,5mg P1075 DS	6	146,00	$\pm$	40,72	0,52
1 mg P1075 DS	8	136,00	$\pm$	36,72	0,39
5HD BS	8	148,25	$\pm$	59,28	0,51
5HD DS	10	120,50	$\pm$	36,64	0,23
HMR 1098 DS	8	108,13	$\pm$	49,62	0,18
HMR 1098 BS	8	182,25	$\pm$	51,36	0,95

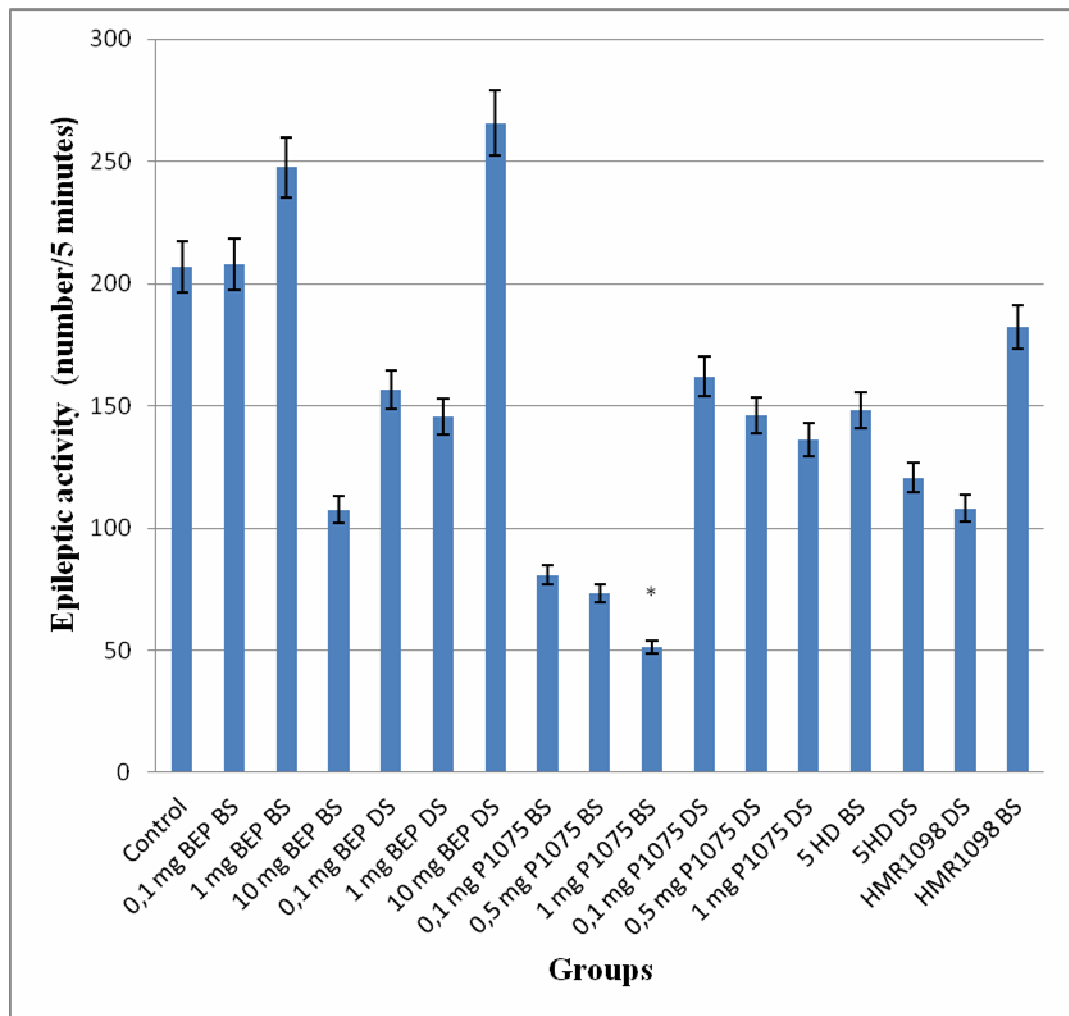


Figure 3.19. Spike wave frequency obtained from 35 to 40 minutes recordings (Period 8). (Data are means $\pm$ SE *P < 0.05: Compared to control)

3.8.9. Epileptic activity between 40 to 45 minutes in terms of spike wave frequency (Period 9)

The spike wave frequency in groups 0,1 mg P1075 BS; 0,5 mg P1075 BS; 1 mg P1075 BS; HMR1098 DS between 40 – 45 minutes time interval were significantly smaller than the control group (Table 3.10, Fig.3.20.) ($p < 0,05$).

Table 3.10. Spike wave frequency (count/minute) obtained from 40 to 45 minute recordings in all groups. (Data are means $\pm$ SE *P < 0.05: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	228,78	$\pm$	38,80	
0,1mg BEP BS	6	158,00	$\pm$	43,65	0,36
1mg BEP BS	6	259,50	$\pm$	68,04	0,42
10 mg BEP BS	8	128,22	$\pm$	26,69	0,11
0,1mg BEP DS	6	155,29	$\pm$	50,15	0,31
1 mg BEP DS	6	138,83	$\pm$	49,11	0,21
10 mg BEP DS	8	253,88	$\pm$	42,02	0,45
0,1 mg P1075 BS	6	76,67	$\pm$	28,15*	0,02
0,5 mg P1075 BS	6	80,50	$\pm$	35,75*	0,03
1 mg P1075 BS	6	82,33	$\pm$	35,11*	0,03
0,1 mg P1075 DS	8	162,75	$\pm$	39,63	0,36
0,5mg P1075 DS	6	165,17	$\pm$	43,75	0,42
1 mg P1075 DS	8	138,63	$\pm$	30,43	0,18
5HD BS	8	115,38	$\pm$	42,87	0,08
5HD DS	10	115,70	$\pm$	31,49	0,06
HMR 1098 DS	8	91,88	$\pm$	33,51*	0,03
HMR 1098 BS	8	181,13	$\pm$	42,45	0,57

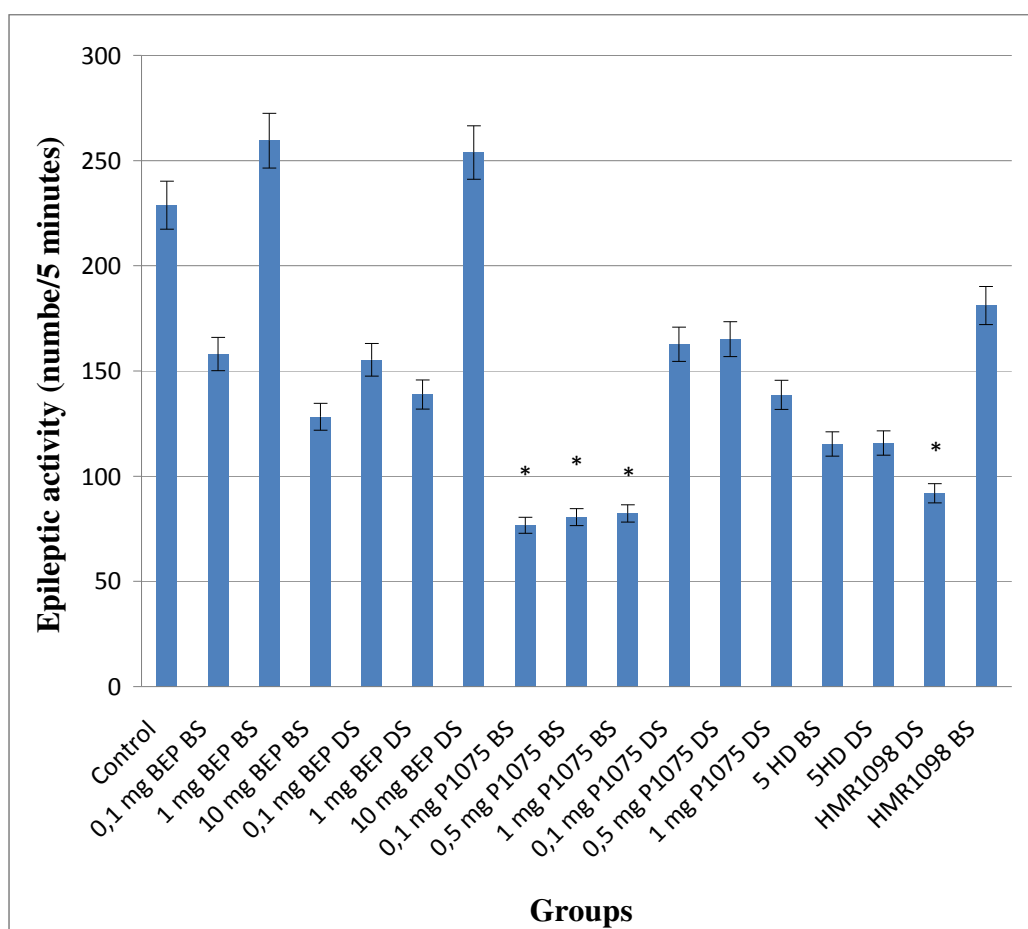


Figure 3.20. Spike wave frequency obtained from 40 to 45 minutes recordings (Period 9). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.10. Epileptic activity between 45 to 50 minutes in terms of spike wave frequency (Period 10)

The spike wave frequency in groups 0,1 mg P1075 BS; HMR 1098 DS between 45 – 50 minutes time interval are significantly smaller than the control group (Table 3.11, Fig. 3.21) ($p < 0,05$).

Table 3.11. Spike wave frequency (count/minute) obtained from 45 to 50 minute recordings in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	226,11	$\pm$	34,34	
0,1mg BEP BS	6	198,67	$\pm$	21,27	0,81
1mg BEP BS	6	235,50	$\pm$	60,42	0,68
10 mg BEP BS	8	141,44	$\pm$	29,26	0,16
0,1mg BEP DS	6	169,57	$\pm$	50,09	0,43
1 mg BEP DS	6	150,00	$\pm$	54,17	0,27
10 mg BEP DS	8	220,88	$\pm$	35,80	0,87
0,1 mg P1075 BS	6	83,33	$\pm$	34,80*	0,02
0,5 mg P1075 BS	6	109,83	$\pm$	35,04	0,07
1 mg P1075 BS	6	122,83	$\pm$	39,91	0,11
0,1 mg P1075 DS	8	155,38	$\pm$	34,09	0,27
0,5mg P1075 DS	6	173,83	$\pm$	50,46	0,49
1 mg P1075 DS	8	143,13	$\pm$	25,71	0,18
5HD BS	8	130,38	$\pm$	35,91	0,12
5HD DS	10	120,00	$\pm$	30,39	0,06
HMR 1098 DS	8	88,25	$\pm$	31,10*	0,02
HMR 1098 BS	8	179,63	$\pm$	46,33	0,53

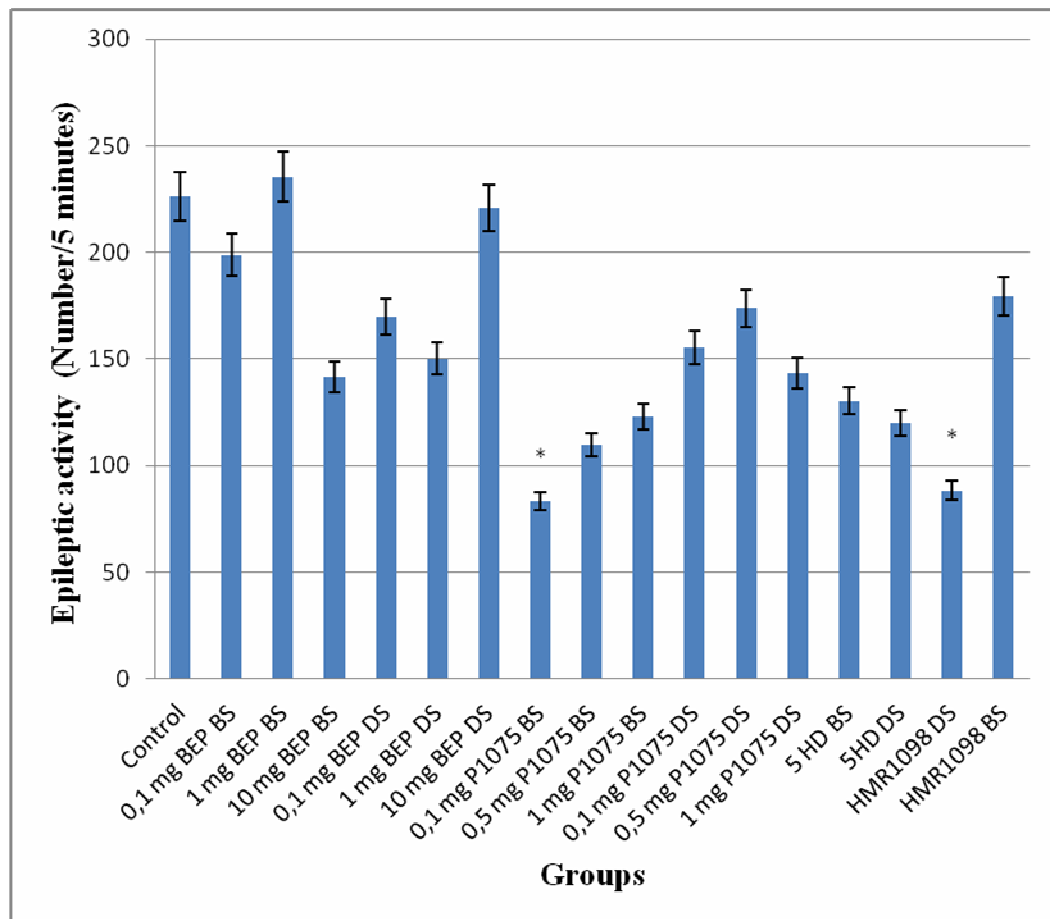


Figure 3.21. Spike wave frequency obtained from 45 to 50 minutes recordings (Period 10). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.11. Epileptic activity between 50 to 55 minutes in terms of spike wave frequency (Period 11)

The spike wave frequency in groups 0,1 mg P1075 BS; HMR 1098 DS between 50 – 55 minutes time interval are significantly smaller than the control group (Table3.12, Fig.3.22) ($p < 0,05$).

Table 3.12. Spike wave frequency (count/minute) obtained from 50 to 55 minute recordings for all groups. (Data are means $\pm$ SE *P < 0.05: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	232,78	$\pm$	34,87	
0,1mg BEP BS	6	232,83	$\pm$	15,20	0,88
1mg BEP BS	6	215,67	$\pm$	51,43	0,87
10 mg BEP BS	8	136,78	$\pm$	32,30	0,08
0,1mg BEP DS	6	168,14	$\pm$	48,88	0,28
1 mg BEP DS	6	128,33	$\pm$	50,82	0,08
10 mg BEP DS	8	220,50	$\pm$	28,36	0,93
0,1 mg P1075 BS	6	85,17	$\pm$	36,66*	0,01
0,5 mg P1075 BS	6	135,00	$\pm$	35,64	0,11
1 mg P1075 BS	6	139,83	$\pm$	37,58	0,13
0,1 mg P1075 DS	8	136,38	$\pm$	23,40	0,09
0,5mg P1075 DS	6	189,00	$\pm$	57,49	0,52
1 mg P1075 DS	8	132,00	$\pm$	23,18	0,07
5HD BS	8	144,38	$\pm$	39,03	0,12
5HD DS	10	140,50	$\pm$	32,84	0,08
HMR 1098 DS	8	64,00	$\pm$	24,95*	0,00
HMR 1098 BS	8	170,88	$\pm$	50,08	0,29

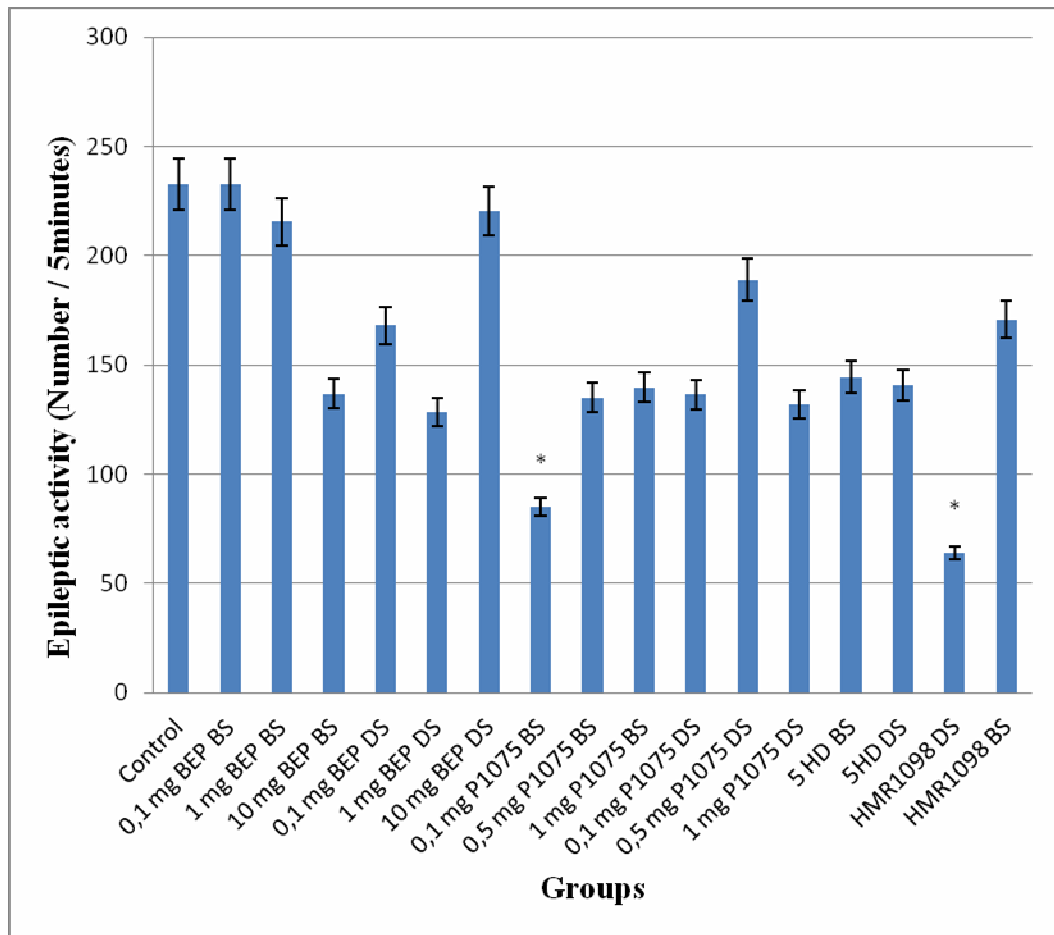


Figure 3.22. Spike wave frequency obtained from 50 to 55 minutes recordings (Period 11). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.12. Epileptic activity between 55 to 60 minutes in terms of spike wave frequency (Period 12)

The spike wave frequency in groups 10 mg BEP BS; 1 mg BEP DS; 0,1 mg P1075 BS ; 0,1 mg P1075 DS ; 1 mg P1075 DS; HMR1098 DS between 55 – 60 minutes time interval were significantly smaller than the control group (Table3.13, Fig.3.23) ($p < 0,05$).

Table 3.13. Spike wave frequency (count/minute) obtained from 55 to 60 minute recordings for all groups. (Data are means $\pm$ SE *P < 0.05: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	238,78	$\pm$	33,86	
0,1mg BEP BS	6	205,33	$\pm$	5,10	0,59
1mg BEP BS	6	207,50	$\pm$	45,74	0,62
10 mg BEP BS	8	137,78	$\pm$	33,52*	0,05
0,1mg BEP DS	6	160,86	$\pm$	34,32	0,16
1 mg BEP DS	6	112,67	$\pm$	42,63*	0,03
10 mg BEP DS	8	226,75	$\pm$	21,58	0,88
0,1 mg P1075 BS	6	88,33	$\pm$	38,02*	0,01
0,5 mg P1075 BS	6	150,67	$\pm$	37,17	0,12
1 mg P1075 BS	6	154,67	$\pm$	36,15	0,14
0,1 mg P1075 DS	8	129,38	$\pm$	24,63*	0,04
0,5mg P1075 DS	6	198,17	$\pm$	66,28	0,51
1 mg P1075 DS	8	114,75	$\pm$	21,28*	0,02
5HD BS	8	151,63	$\pm$	34,35	0,10
5HD DS	10	143,90	$\pm$	32,89	0,06
HMR 1098 DS	8	77,25	$\pm$	20,14*	0,00
HMR 1098 BS	8	176,63	$\pm$	61,50	0,25

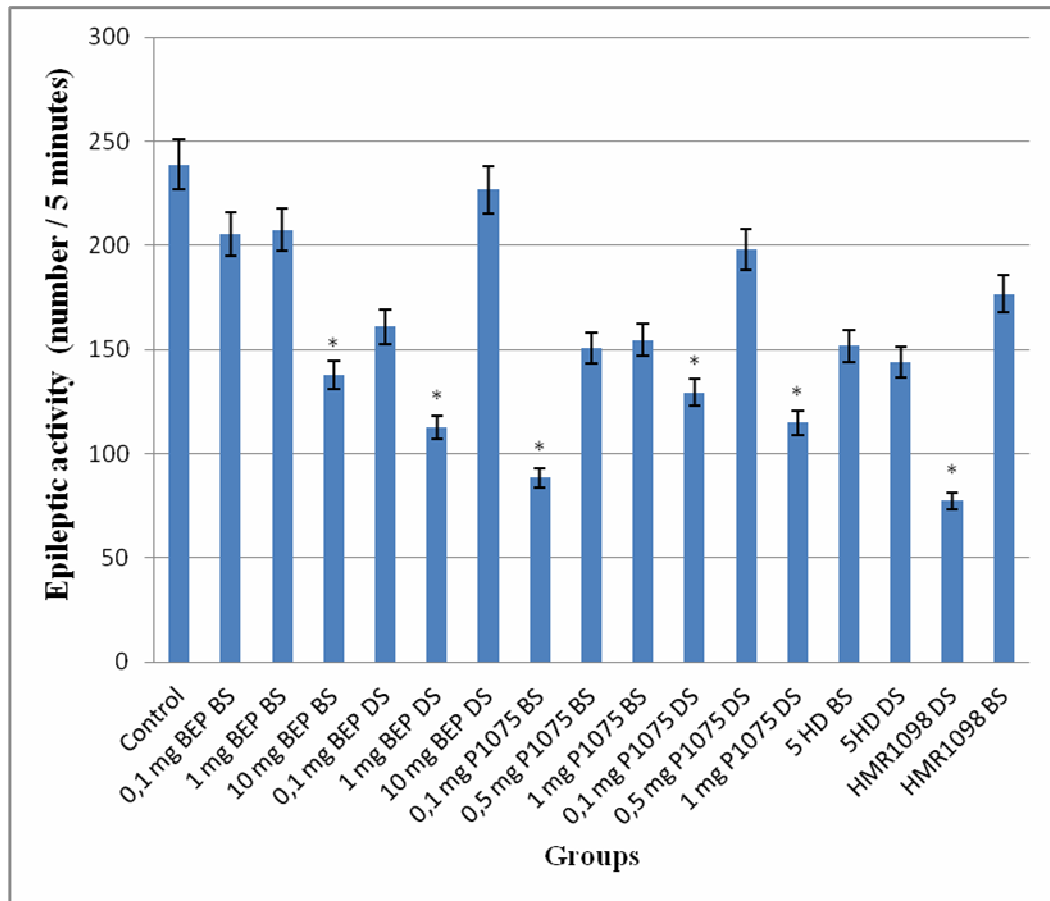


Figure 3.23. Spike wave frequency obtained from 55 to 60 minutes recordings (Period 12). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.13. Epileptic activity between 60 to 65 minutes in terms of spike wave frequency (Period 13)

The spike wave frequency in groups 0,1 mg BEP BS; 10 mg BEP BS ; 0,1 mg BEP DS; 1 mg BEP DS; 0,1 mg P1075 BS ; 0,5 mg P1075 BS; 1 mg P1075 BS ; 0,1 mg P1075 DS; 1 mg P1075 DS ; 5 HD BS ; 5HD DS ; HMR1098 BS between 60 – 65 minutes time interval are significantly smaller than control group (Table 3.14., Fig.3.24) ($p < 0,05$).

Table 3.14. Spike wave frequency (count / minute) obtained from 60 to 65 minute recordings for all groups. (Data are means $\pm$ SE *P < 0.05 Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	277,22	$\pm$	22,72	
0,1mg BEP BS	6	136,17	$\pm$	32,73*	0,01
1mg BEP BS	6	204,50	$\pm$	43,12	0,20
10 mg BEP BS	8	152,78	$\pm$	31,90*	0,01
0,1mg BEP DS	6	159,29	$\pm$	28,48*	0,03
1 mg BEP DS	6	104,50	$\pm$	32,81*	0,00
10 mg BEP DS	8	223,00	$\pm$	18,50	0,31
0,1 mg P1075 BS	6	94,33	$\pm$	42,66*	0,00
0,5 mg P1075 BS	6	145,83	$\pm$	36,03*	0,02
1 mg P1075 BS	6	166,83	$\pm$	39,32*	0,05
0,1 mg P1075 DS	8	123,88	$\pm$	26,29*	0,00
0,5mg P1075 DS	6	219,50	$\pm$	80,61	0,31
1 mg P1075 DS	8	122,13	$\pm$	16,74*	0,00
5HD BS	8	145,88	$\pm$	30,67*	0,01
5HD DS	10	132,50	$\pm$	29,96*	0,00
HMR 1098 DS	8	98,88	$\pm$	18,33*	0,00
HMR 1098 BS	8	181,75	$\pm$	67,65	0,07

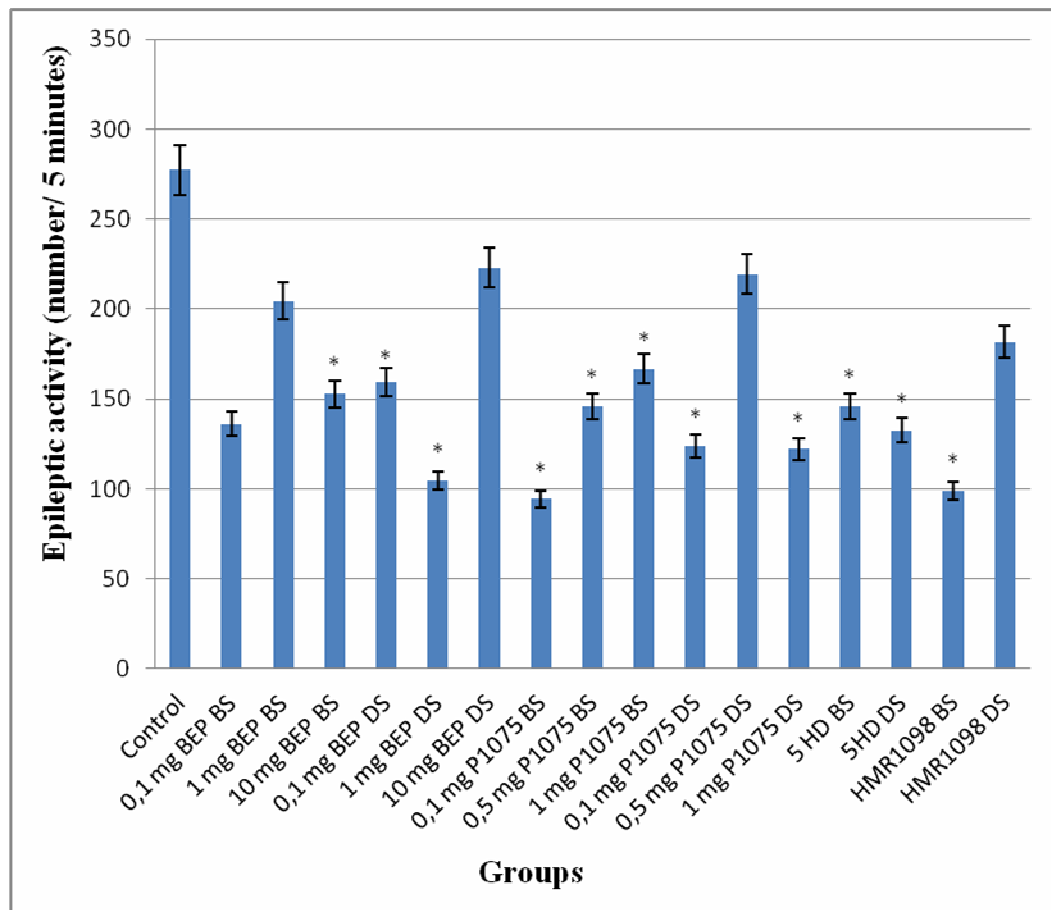


Figure 3.24. Spike wave frequency obtained from 60 to 65 minutes recordings (Period 13). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.14. Epileptic activity between 65 to 70 minutes in terms of spike wave frequency (Period 14)

The spike wave frequency in groups 0,1 mg BEP BS ;1 mg BEP BS; 10 mg BEP BS; 0,1 mg BEP DS; 1 mg BEP DS; 0,1 mg P1075 BS; 0,5 mg P1075 BS; 1 mg P1075 BS; 0,1 mg P1075 DS; 0,5 mg P1075 DS;1 mg P1075 DS; 5 HD BS; 5HD DS; HMR1098 DS; HMR1098 BS between 65–70 minutes time interval are significantly smaller than the control group (Table.3.15, Fig.3.25.) ($p<0,05$).

Table 3.15. Spike wave frequency (count/minute) obtained from 65 to 70 minute recordings for all groups. (Data are means $\pm$ SE * $P<0.05$: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	297,78	$\pm$	27,96	
0,1mg BEP BS	6	156,00	$\pm$	24,48*	0,01
1mg BEP BS	6	198,17	$\pm$	41,01*	0,05
10 mg BEP BS	8	156,67	$\pm$	20,79*	0,00
0,1mg BEP DS	6	173,86	$\pm$	39,34*	0,01
1 mg BEP DS	6	103,83	$\pm$	31,64*	0,00
10 mg BEP DS	8	223,13	$\pm$	18,78	0,11
0,1 mg P1075 BS	6	106,00	$\pm$	52,75*	0,00
0,5 mg P1075 BS	6	160,33	$\pm$	40,10*	0,01
1 mg P1075 BS	6	179,17	$\pm$	43,86*	0,02
0,1 mg P1075 DS	8	115,50	$\pm$	25,52*	0,00
0,5mg P1075 DS	6	190,00	$\pm$	54,23*	0,04
1 mg P1075 DS	8	141,63	$\pm$	29,47*	0,00
5HD BS	8	152,13	$\pm$	30,73*	0,00
5HD DS	10	130,70	$\pm$	25,36*	0,00
HMR 1098 DS	8	98,25	$\pm$	28,73*	0,00
HMR 1098 BS	8	168,38	$\pm$	56,69*	0,01

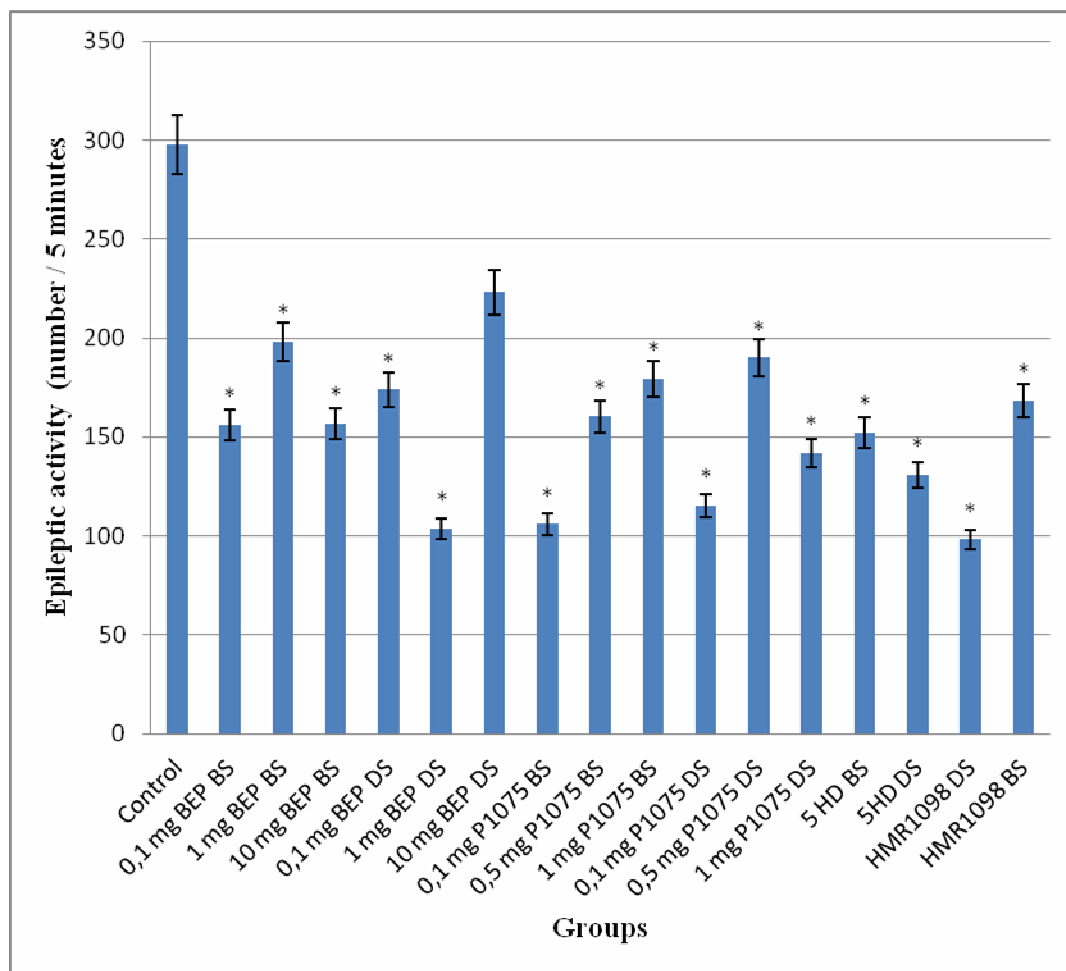


Figure 3.25. Spike wave frequency obtained from 65 to 70 minutes recordings (Period 14). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.15. Epileptic activity between 70 to 75 minutes in terms of spike wave frequency (Period 15)

The spike wave frequency in groups 0,1 mg BEP BS ;10 mg BEP BS;0,1 mg BEP DS;0,1 mg P1075 BS;0,5 mg P1075 BS;1 mg P1075 BS;0,1 mg P1075 DS;0,5 mg P1075 DS;1 mg P1075 DS;5 HD BS;5HD DS;HMR1098 DS,HMR1098 BS;1 mg BEP DS between 70 – 75 minutes time interval were significantly smaller than the control group (Table 3.16, Fig.3.26.) ($p<0,05$).

Table 3.16. Spike wave frequency (count / minute) obtained from 70 to 75 minute recordings in all groups (Data are means $\pm$ SE * $P<0.05$: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	289,11	$\pm$	29,11	
0,1mg BEP BS	6	164,00	$\pm$	11,82*	0,02
1mg BEP BS	6	195,00	$\pm$	40,13	0,07
10 mg BEP BS	8	147,11	$\pm$	22,62*	0,00
0,1mg BEP DS	6	152,43	$\pm$	23,06*	0,01
1 mg BEP DS	6	114,67	$\pm$	33,32*	0,00
10 mg BEP DS	8	217,50	$\pm$	19,26	0,13
0,1 mg P1075 BS	6	110,17	$\pm$	51,11*	0,00
0,5 mg P1075 BS	6	182,33	$\pm$	45,50*	0,04
1 mg P1075 BS	6	174,33	$\pm$	41,40*	0,03
0,1 mg P1075 DS	8	105,13	$\pm$	25,86*	0,00
0,5mg P1075 DS	6	178,33	$\pm$	34,53*	0,03
1 mg P1075 DS	8	155,25	$\pm$	27,29*	0,01
5HD BS	8	181,50	$\pm$	36,28*	0,02
5HD DS	10	168,90	$\pm$	39,10*	0,01
HMR 1098 DS	8	134,63	$\pm$	32,80*	0,00
HMR 1098 BS	8	182,50	$\pm$	56,35*	0,03

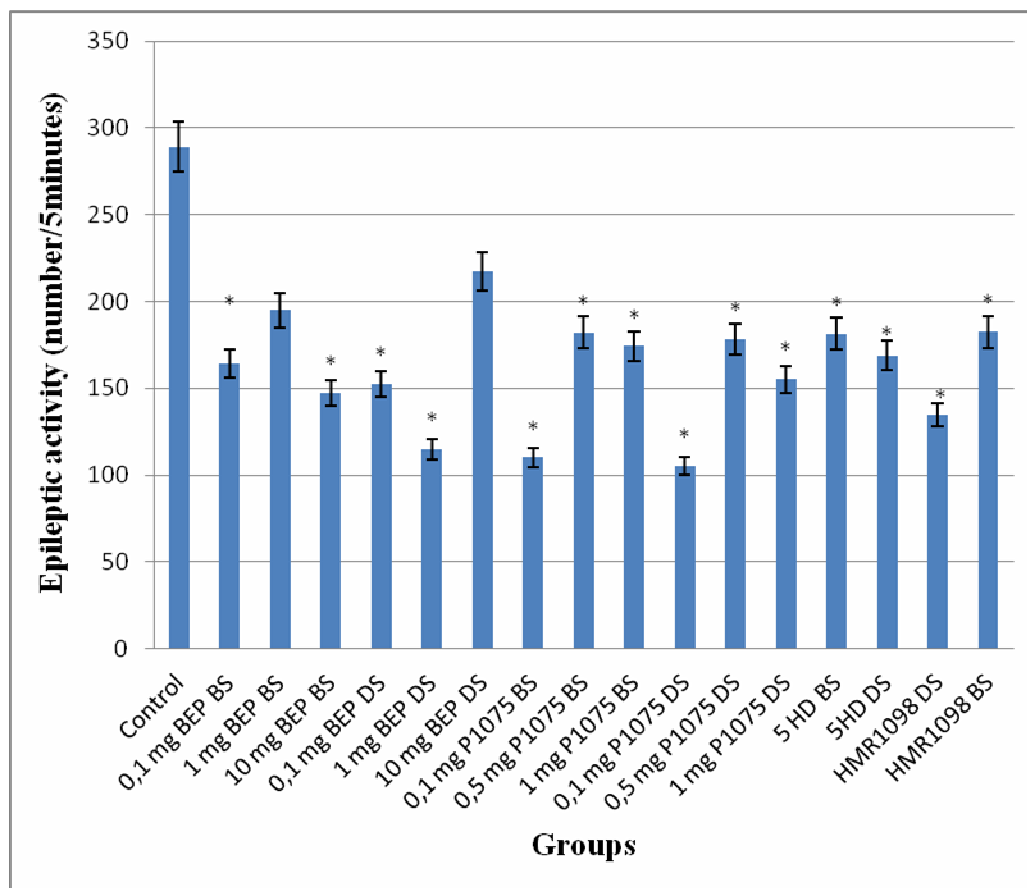


Figure 3.26. Spike wave frequency obtained from 70 to 75 minutes recordings (Period 15). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.16. Epileptic activity between 75 to 80 minutes in terms of spike wave frequency (Period 16)

The spike wave frequency in groups 10 mg BEP BS; 0,1 mg BEP DS; 1 mg BEP DS; 1 mg P1075 BS; 0,1 mg P1075 DS; 0,5 mg P1075 DS; 1 mg P1075 DS; 5HD DS between 75 – 80 minutes time interval were significantly smaller than the control group (Table.3.17., Fig.3.27.) ($p<0,05$).

Table 3.17. Spike wave frequency (count/minute) obtained from 75 to 80 minute recordings in all groups. (Data are means $\pm$ SE * $P<0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	266,11	$\pm$	33,19	
0,1mg BEP BS	6	177,67	$\pm$	16,50	0,07
1mg BEP BS	6	189,33	$\pm$	36,54	0,11
10 mg BEP BS	8	158,78	$\pm$	21,36*	0,02
0,1mg BEP DS	6	117,00	$\pm$	20,75*	0,00
1 mg BEP DS	6	119,67	$\pm$	36,64*	0,00
10 mg BEP DS	8	209,50	$\pm$	20,80	0,20
0,1 mg P1075 BS	6	174,00	$\pm$	49,56	0,06
0,5 mg P1075 BS	6	196,50	$\pm$	41,61	0,15
1 mg P1075 BS	6	166,50	$\pm$	40,57*	0,04
0,1 mg P1075 DS	8	100,25	$\pm$	26,84*	0,00
0,5mg P1075 DS	6	165,17	$\pm$	32,60*	0,04
1 mg P1075 DS	8	163,13	$\pm$	27,36*	0,02
5HD BS	8	195,38	$\pm$	31,91	0,11
5HD DS	10	168,50	$\pm$	38,59*	0,02
HMR 1098 DS	8	202,63	$\pm$	29,13	0,15
HMR 1098 BS	8	212,75	$\pm$	50,18	0,22

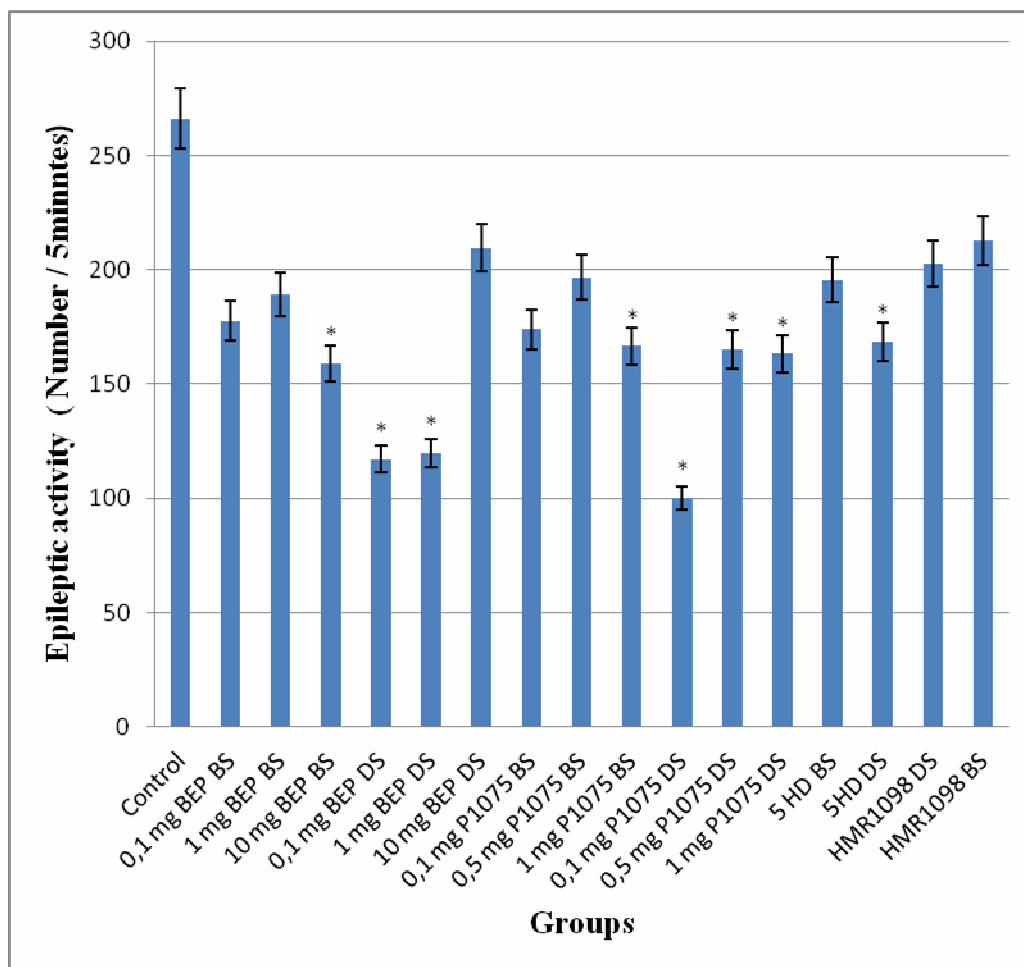


Figure 3.27. Spike wave frequency (results mean $\pm$ SE) obtained from 75 to 80 minutes recordings (Period 16). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.17. Epileptic activity between 80 to 85 minutes in terms of spike wave frequency (Period 17)

The spike wave frequency in groups 0,1 mg BEP BS; 10 mg BEP BS; 0,1 mg BEP DS; 1 mg BEP DS; 0,1 mg P1075 BS; 5HD DS ; HMR1098 BS between 75 – 80 minutes time interval were significantly smaller than the control group (Table 3.18., Fig. 3.28.) ($p < 0,05$).

Table 3.18. Spike wave frequency (count/minute) obtained from 80 to 85 minute recordings for all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	270,67	$\pm$	36,07	
0,1mg BEP BS	6	180,33	$\pm$	38,57*	0,06
1mg BEP BS	6	185,83	$\pm$	38,69	0,01
10 mg BEP BS	8	159,00	$\pm$	18,61*	0,00
0,1mg BEP DS	6	133,29	$\pm$	16,19*	0,00
1 mg BEP DS	6	114,00	$\pm$	33,85*	0,09
10 mg BEP DS	8	201,13	$\pm$	26,16	0,02
0,1 mg P1075 BS	6	160,67	$\pm$	52,42*	0,11
0,5 mg P1075 BS	6	200,17	$\pm$	37,69	0,03
1 mg P1075 BS	6	169,83	$\pm$	39,76*	0,00
0,1 mg P1075 DS	8	92,50	$\pm$	26,25*	0,02
0,5mg P1075 DS	6	158,17	$\pm$	31,39*	0,02
1 mg P1075 DS	8	165,50	$\pm$	28,85*	0,27
5HD BS	8	229,63	$\pm$	41,02	0,02
5HD DS	10	174,40	$\pm$	35,80*	0,26
HMR 1098 DS	8	228,38	$\pm$	33,58	0,01
HMR 1098 BS	8	163,00	$\pm$	44,28*	0,02

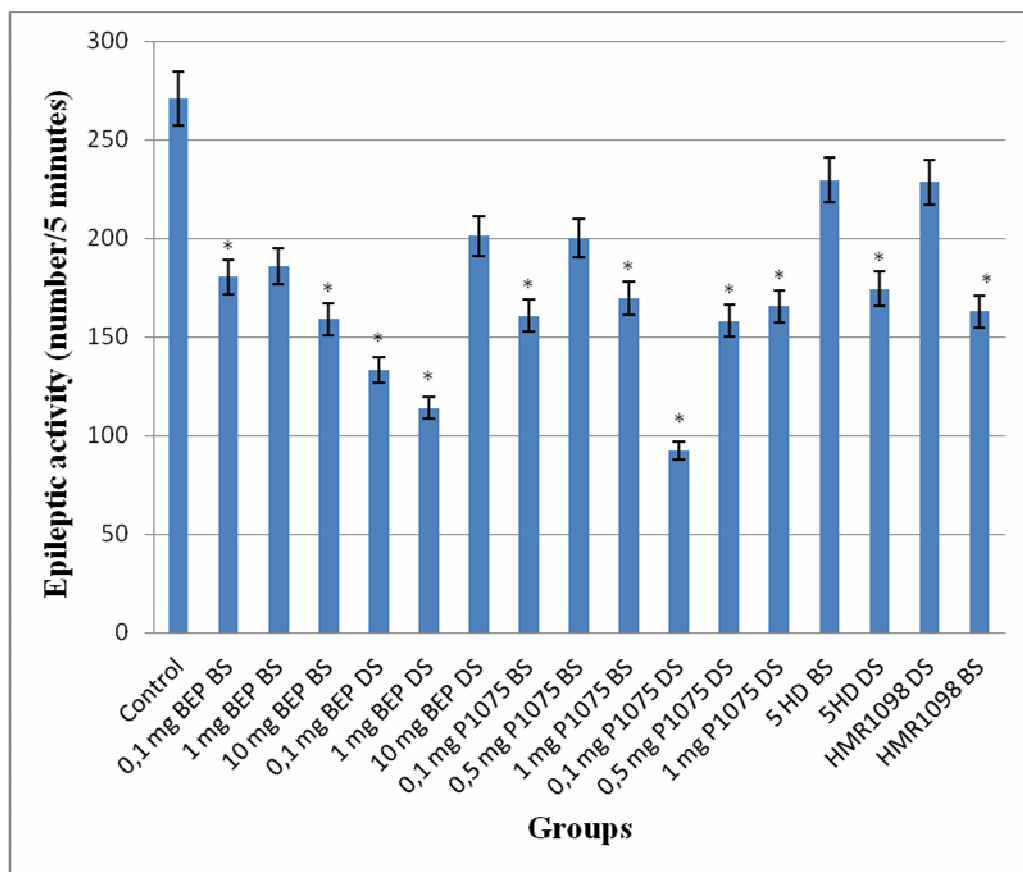


Figure 3.28. Spike wave frequency obtained from 80 to 85 minutes recordings (Period 17). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.18. Epileptic activity between 85 to 90 minutes in terms of spike wave frequency (Period 18)

The spike wave frequency in groups 10 mg BEP BS; 0,1 mg BEP DS; 1 mg BEP DS; 0,1 mg P1075 BS; 0,1 mg P1075 DS; 0,5 mg P1075 DS; 1 mg P1075 DS; 5HD DS between 85 – 90 minutes time interval were significantly smaller than the control group (Table 3.19, Fig.3.29.) ($p < 0,05$).

Table 3.19. Spike wave frequency (count/minute) obtained from 85 to 90 minute recordings in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	260,89	$\pm$	37,97	
0,1mg BEP BS	6	207,67	$\pm$	58,36	0,23
1mg BEP BS	6	178,67	$\pm$	39,85	0,08
10 mg BEP BS	8	157,67	$\pm$	18,82*	0,02
0,1mg BEP DS	6	121,43	$\pm$	13,72*	0,00
1 mg BEP DS	6	110,67	$\pm$	33,00*	0,00
10 mg BEP DS	8	206,63	$\pm$	27,72	0,19
0,1 mg P1075 BS	6	160,67	$\pm$	57,28*	0,04
0,5 mg P1075 BS	6	192,17	$\pm$	37,89	0,14
1 mg P1075 BS	6	171,50	$\pm$	40,72	0,06
0,1 mg P1075 DS	8	91,13	$\pm$	28,46*	0,00
0,5mg P1075 DS	6	162,17	$\pm$	41,71*	0,04
1 mg P1075 DS	8	165,88	$\pm$	28,10*	0,03
5HD BS	8	221,13	$\pm$	39,46	0,30
5HD DS	10	172,30	$\pm$	37,31*	0,04
HMR 1098 DS	8	230,50	$\pm$	36,91	0,40
HMR 1098 BS	8	178,00	$\pm$	40,86	0,06

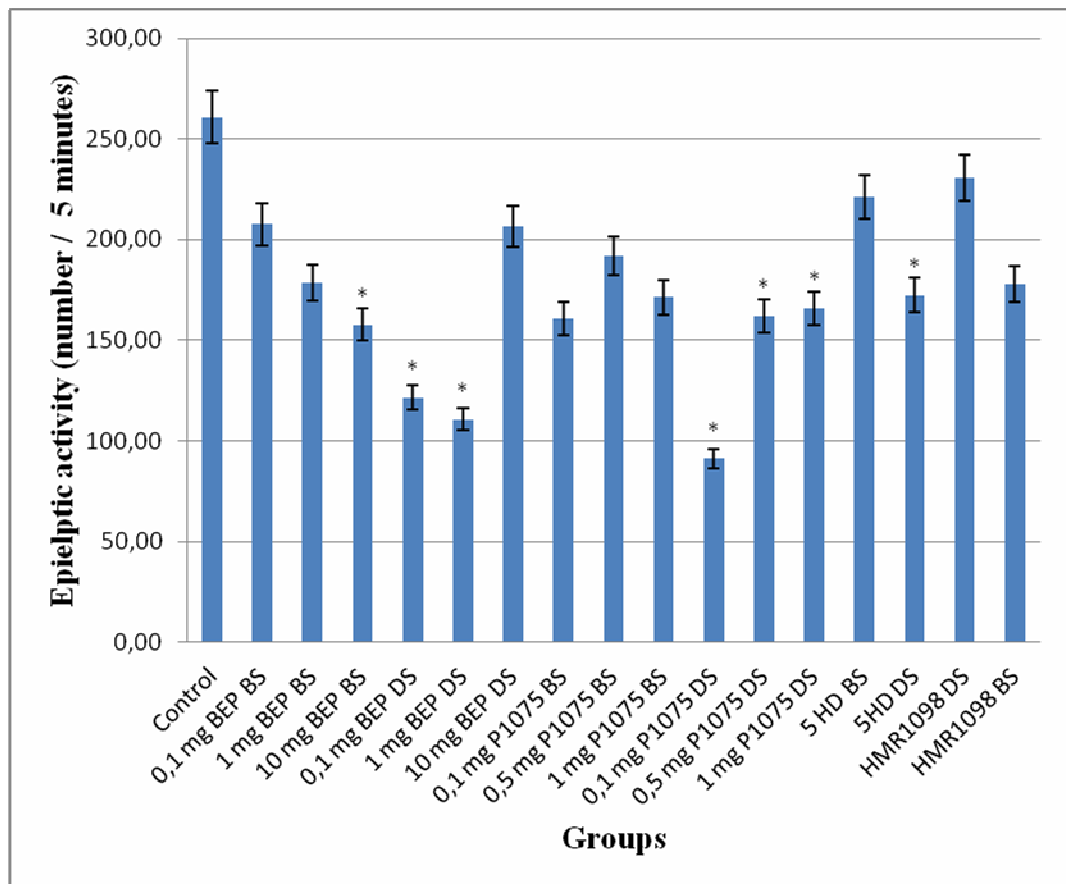


Figure.3.29. Spike wave frequency obtained from 85 to 90 minutes recordings (Period 18). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.19. Epileptic activity between 90 to 95 minutes in terms of spike wave frequency (Period 19)

The spike wave frequency in groups 10 mg BEP BS; 0,1 mg BEP DS; 1 mg BEP DS; 0,1 mg P1075 BS; 0,1 mg P1075 DS; 0,5 mg P1075 DS; 1 mg P1075 DS; 5HD DS between 90 – 95 minutes time interval were significantly smaller than the control group (Table.3.20, Fig.3.30.) ($p < 0,05$).

Table 3.20. Spike wave frequency (count/minute) obtained from 90 to 95 minute recordings for all groups. (Data are means $\pm$ SE *P < 0.05: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	256,67	$\pm$	36,05	
0,1mg BEP BS	6	213,00	$\pm$	60,30	0,31
1mg BEP BS	6	185,17	$\pm$	47,20	0,13
10 mg BEP BS	8	158,33	$\pm$	16,73*	0,03
0,1mg BEP DS	6	125,00	$\pm$	13,44*	0,01
1 mg BEP DS	6	115,17	$\pm$	31,30*	0,01
10 mg BEP DS	8	207,13	$\pm$	27,31	0,23
0,1 mg P1075 BS	6	159,83	$\pm$	57,83*	0,05
0,5 mg P1075 BS	6	195,67	$\pm$	45,76	0,19
1 mg P1075 BS	6	168,83	$\pm$	36,92	0,07
0,1 mg P1075 DS	8	86,00	$\pm$	25,77*	0,00
0,5mg P1075 DS	6	137,50	$\pm$	33,65*	0,02
1 mg P1075 DS	8	154,13	$\pm$	32,94*	0,03
5HD BS	8	225,00	$\pm$	48,22	0,39
5HD DS	10	150,20	$\pm$	30,24*	0,02
HMR 1098 DS	8	225,00	$\pm$	46,56	0,39
HMR 1098 BS	8	188,25	$\pm$	39,99	0,12

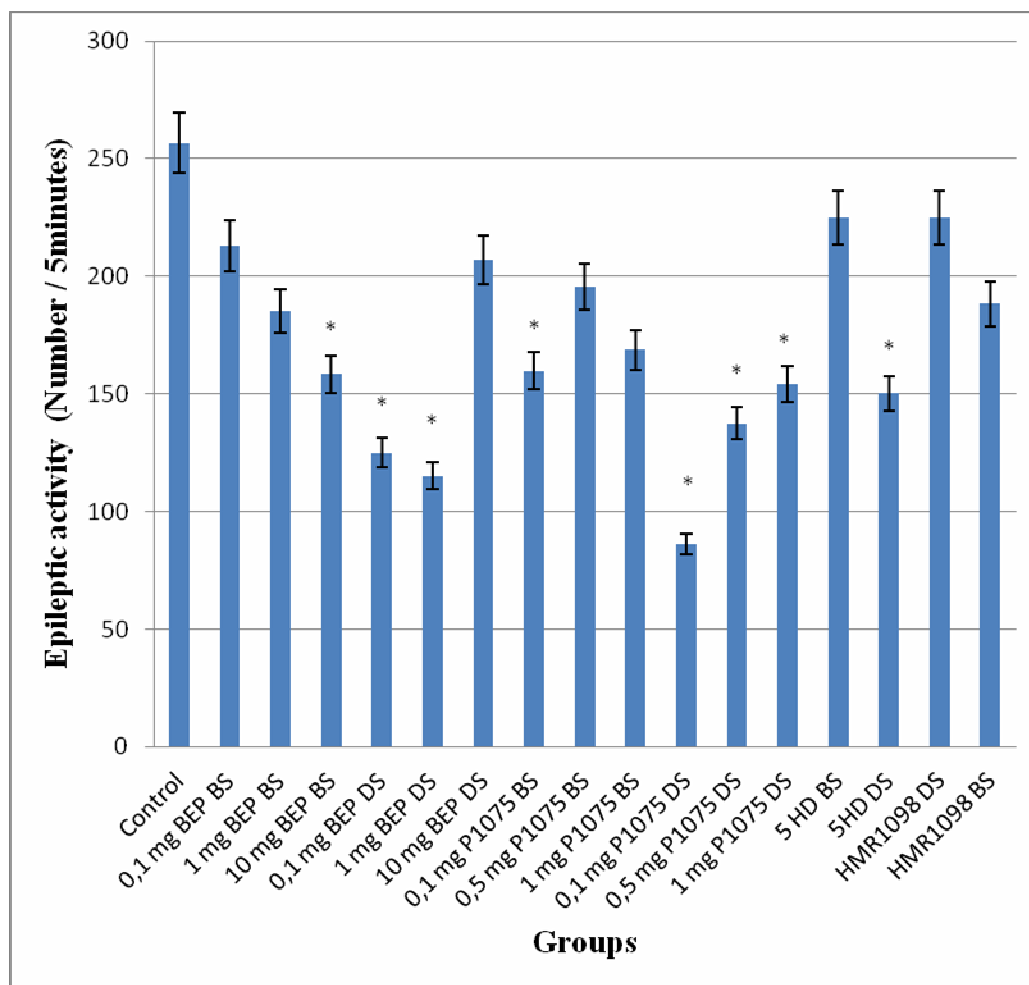


Figure 3.30. Spike wave frequency obtained from 90 to 95 minutes recordings (Period 19). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.20. Epileptic activity between 95 to 100 minutes in terms of spike wave frequency (Period 20)

The spike wave frequency in groups 0,1 mg BEP DS, 1 mg BEP DS; 0,1 mg P1075 DS; 0,5 mg P1075 DS; 1 mg P1075 DS; 5HD DS between 95 – 100 minutes time interval were significantly smaller than the control group (Table.3.21., Fig.3.31.) ($p<0,05$).

Table 3.21. Spike wave frequency (count/minute) obtained from 95 to 100 minute recordings in all groups. (Data are means $\pm$ SE * $P<0.05$: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	245,67	$\pm$	41,04	
0,1mg BEP BS	6	244,17	$\pm$	59,06	0,77
1mg BEP BS	6	237,83	$\pm$	93,42	0,68
10 mg BEP BS	8	170,89	$\pm$	14,10	0,09
0,1mg BEP DS	6	123,71	$\pm$	15,47*	0,02
1 mg BEP DS	6	112,50	$\pm$	29,32*	0,01
10 mg BEP DS	8	210,25	$\pm$	27,53	0,35
0,1 mg P1075 BS	6	157,67	$\pm$	55,79	0,08
0,5 mg P1075 BS	6	191,50	$\pm$	44,95	0,23
1 mg P1075 BS	6	163,17	$\pm$	34,06	0,10
0,1 mg P1075 DS	8	91,63	$\pm$	26,55*	0,00
0,5mg P1075 DS	6	117,17	$\pm$	25,94*	0,02
1 mg P1075 DS	8	146,63	$\pm$	33,90*	0,04
5HD BS	8	206,88	$\pm$	39,89	0,31
5HD DS	10	153,30	$\pm$	27,19*	0,04
HMR 1098 DS	8	207,50	$\pm$	42,38	0,32
HMR 1098 BS	8	201,25	$\pm$	47,91	0,27

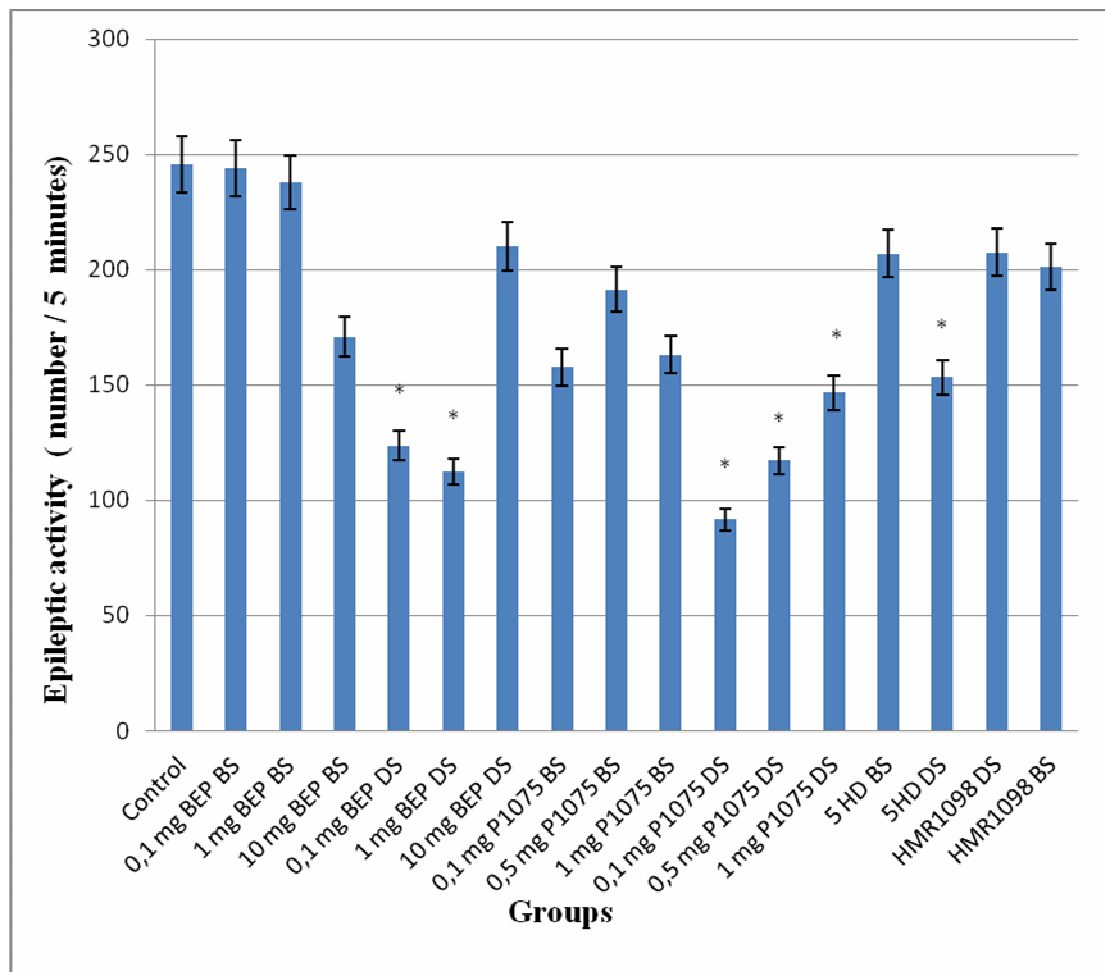


Figure 3.30. Spike wave frequency obtained from 95 to 100 minutes recordings (Period 20). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.21. Epileptic activity between 100 to 105 minutes in terms of spike wave frequency (Period 21)

The spike wave frequency in groups 10 mg BEP BS ; 0,1 mg BEP DS; 1 mg BEP DS; 0,1 mg P1075 BS; 0,1 mg P1075 DS; 0,5 mg P1075 DS; 1 mg P1075 DS; 5HD DS between 100 – 105 minutes time interval were significantly smaller than the control group (Table.3.21, Fig.3.31) ($p < 0,05$).

Table 3.21. Spike wave frequency (number of spike) obtained from 100 to 105 minute recordings in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	231,44	$\pm$	42,91	
0,1mg BEP BS	6	251,67	$\pm$	48,50	0,97
1mg BEP BS	6	217,17	$\pm$	78,74	0,55
10 mg BEP BS	8	148,33	$\pm$	16,71*	0,04
0,1mg BEP DS	6	125,57	$\pm$	18,73*	0,02
1 mg BEP DS	6	91,33	$\pm$	29,32*	0,00
10 mg BEP DS	8	207,25	$\pm$	25,75	0,40
0,1 mg P1075 BS	6	122,00	$\pm$	38,99*	0,02
0,5 mg P1075 BS	6	187,17	$\pm$	43,13	0,25
1 mg P1075 BS	6	173,33	$\pm$	31,33	0,16
0,1 mg P1075 DS	8	96,63	$\pm$	26,52*	0,00
0,5mg P1075 DS	6	110,17	$\pm$	29,64*	0,01
1 mg P1075 DS	8	146,88	$\pm$	34,07*	0,04
5HD BS	8	197,88	$\pm$	35,28	0,31
5HD DS	10	154,40	$\pm$	26,52*	0,05
HMR 1098 DS	8	192,88	$\pm$	37,03	0,26
HMR 1098 BS	8	203,63	$\pm$	48,88	0,36

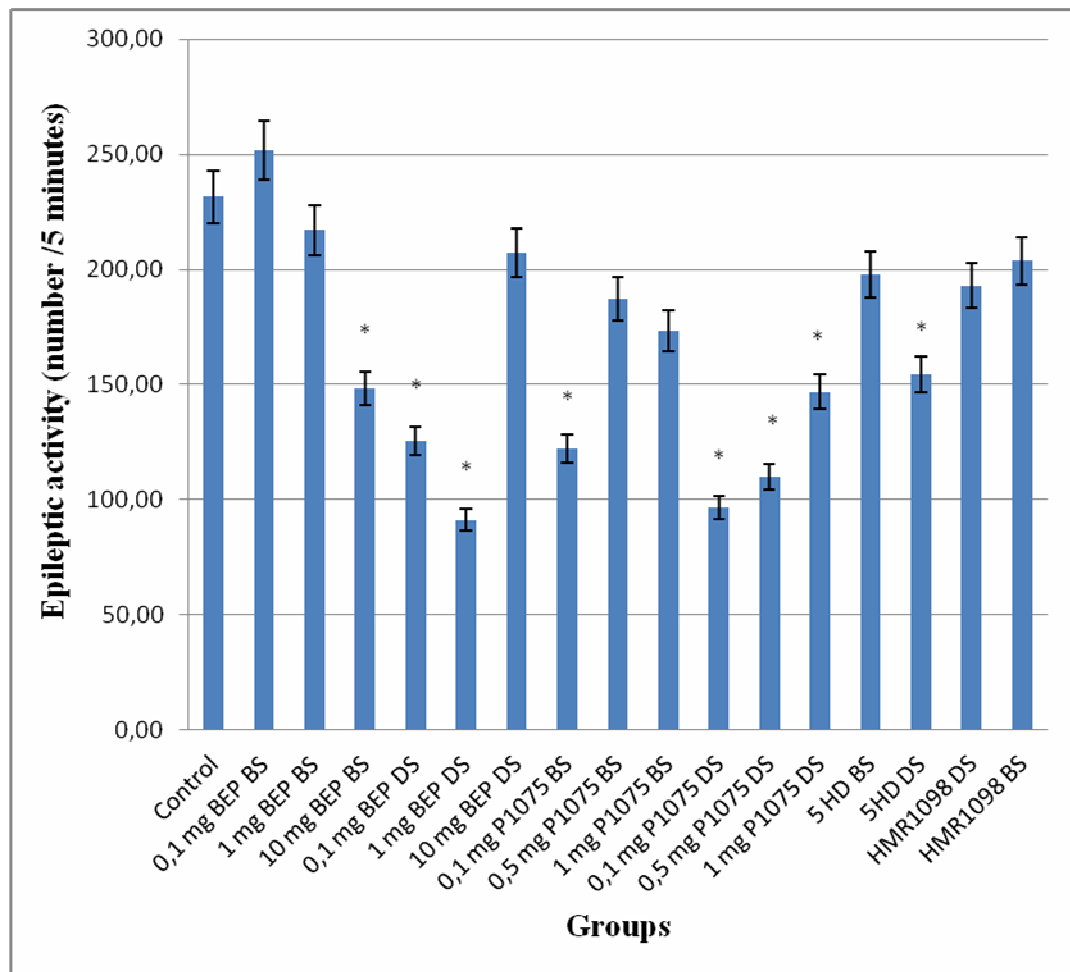


Figure 3.31. Spike wave frequency (number of spike) obtained from 100 to 105 minutes recordings (Period 21). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.22. Epileptic activity between 105 to 110 minutes in terms of spike wave frequency (Period 22)

The spike wave frequency in groups 1 mg BEP BS;10 mg BEP BS;0,1 mg BEP DS;1 mg BEP DS; 0,1 mg P1075 BS; 0,1 mg P1075 DS; 0,5 mg P1075 DS;1 mg P1075 DS; 5HD DS between 105 – 110 minutes time interval are significantly smaller than control group (Table.3.22, Fig.3.32.) ($p<0,05$).

Table 3.22. Spike wave frequency (number of spike) obtained from 105 to 110 minute recordings for all groups (Data are means $\pm$ SE * $P<0.05$: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	243,78	$\pm$	42,35	
0,1mg BEP BS	6	227,50	$\pm$	40,08	0,39
1mg BEP BS	6	172,00	$\pm$	58,83*	0,05
10 mg BEP BS	8	158,00	$\pm$	14,95*	0,01
0,1mg BEP DS	6	121,14	$\pm$	16,58*	0,00
1 mg BEP DS	6	104,50	$\pm$	24,59*	0,00
10 mg BEP DS	8	198,75	$\pm$	26,76	0,12
0,1 mg P1075 BS	6	115,00	$\pm$	31,27*	0,00
0,5 mg P1075 BS	6	194,50	$\pm$	42,93	0,13
1 mg P1075 BS	6	176,33	$\pm$	25,03	0,06
0,1 mg P1075 DS	8	101,63	$\pm$	26,54*	0,00
0,5mg P1075 DS	6	121,00	$\pm$	23,73*	0,00
1 mg P1075 DS	8	164,38	$\pm$	38,10*	0,02
5HD BS	8	186,25	$\pm$	35,61	0,07
5HD DS	10	148,70	$\pm$	27,46*	0,01
HMR 1098 DS	8	194,38	$\pm$	40,00	0,10
HMR 1098 BS	8	185,88	$\pm$	47,74	0,07

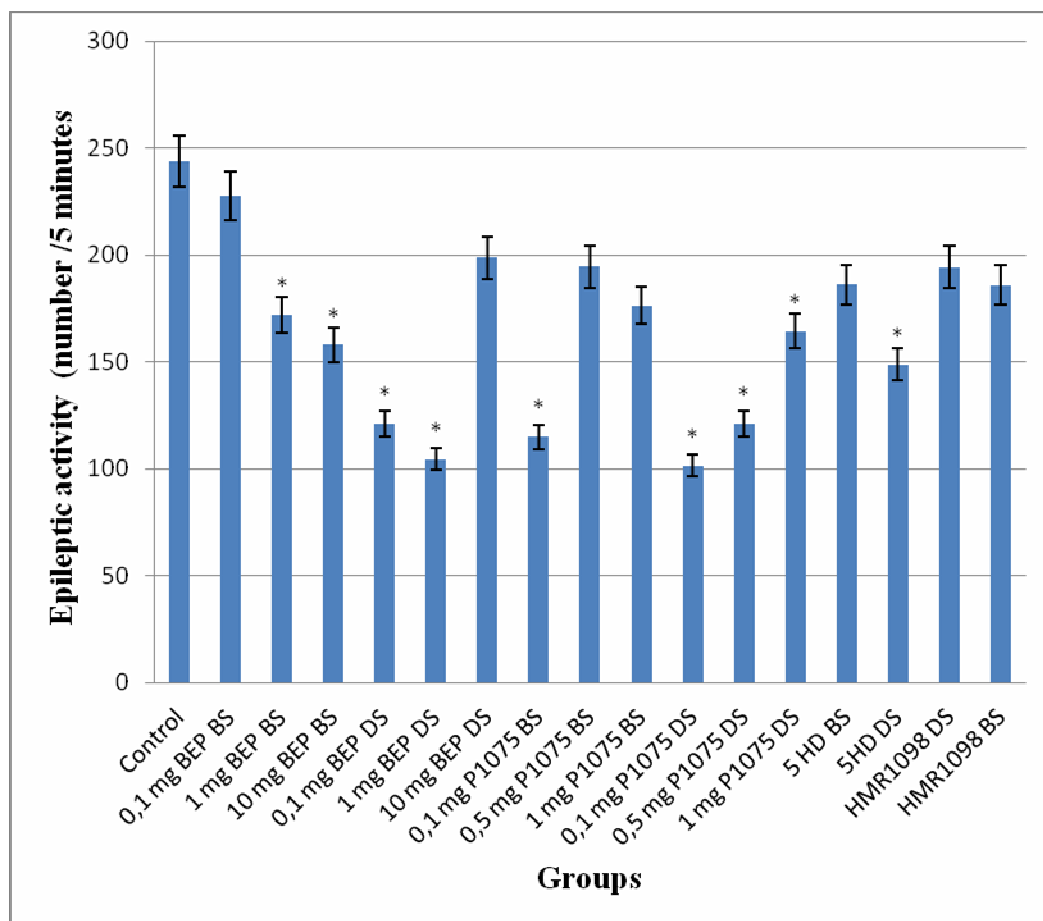


Figure 3.32. Spike wave frequency (number of spike) obtained from 105 to 110 minutes recordings (Period 22). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.23. Epileptic activity between 110 to 115 minutes in terms of spike wave frequency (Period 23)

The spike wave frequency in groups 1 mg BEP BS; 10 mg BEP BS; 0,1 mg BEP DS; 1 mg BEP DS; 0,1 mg P1075 BS ; 0,1 mg P1075 DS ; 0,5 mg P1075 DS; 1 mg P1075 DS ; 5HD DS between 110 – 115 minutes time interval were significantly smaller than the control group (Table.3.23, Fig.3.33.) ($p < 0,05$).

Table 3.23. Spike wave frequency (number of spike) obtained from 110 to 115 minute recordings in all groups (Data are means $\pm$ SE * $P < 0.05$: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	232,67	$\pm$	39,76	
0,1mg BEP BS	6	229,67	$\pm$	38,87	0,55
1mg BEP BS	6	108,17	$\pm$	52,27*	0,00
10 mg BEP BS	8	152,22	$\pm$	17,76*	0,02
0,1mg BEP DS	6	126,29	$\pm$	19,44*	0,01
1 mg BEP DS	6	107,67	$\pm$	26,04*	0,00
10 mg BEP DS	8	192,75	$\pm$	28,92	0,14
0,1 mg P1075 BS	6	110,17	$\pm$	27,67*	0,00
0,5 mg P1075 BS	6	191,67	$\pm$	37,25	0,17
1 mg P1075 BS	6	184,33	$\pm$	26,05	0,12
0,1 mg P1075 DS	8	109,38	$\pm$	26,72*	0,00
0,5mg P1075 DS	6	103,83	$\pm$	30,63*	0,00
1 mg P1075 DS	8	149,50	$\pm$	31,53*	0,02
5HD BS	8	197,88	$\pm$	34,27	0,18
5HD DS	10	142,90	$\pm$	27,66*	0,01
HMR 1098 DS	8	189,88	$\pm$	42,81	0,13
HMR 1098 BS	8	174,00	$\pm$	39,24	0,06

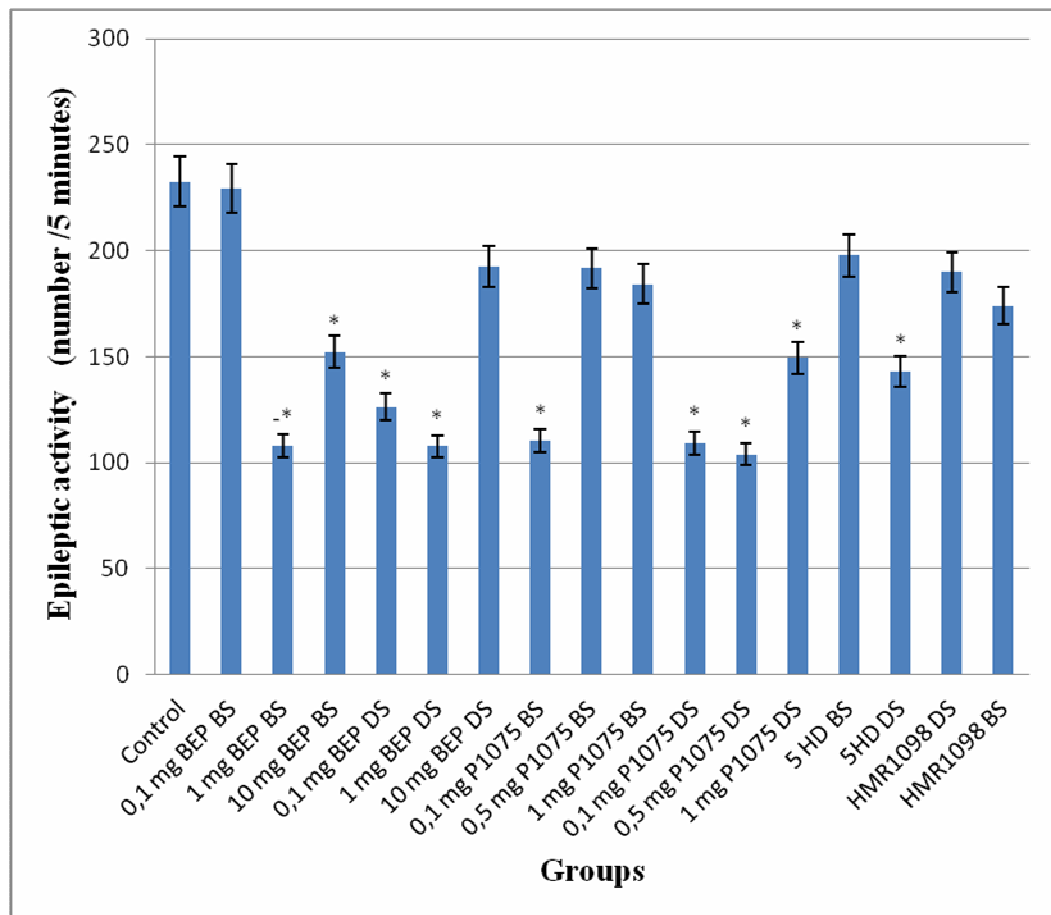


Figure 3.33. Spike wave frequency (number of spike) obtained from 110 to 115 minutes recordings (Period 23) (Data are means $\pm$ SE *P<0.05: Compared to control)

3.8.24. Epileptic activity between 115 to 120 minutes in terms of spike wave frequency (Period 24)

The spike wave frequency in groups 1 mg BEP BS; 10 mg BEP BS; 0,1 mg BEP DS; 1 mg BEP DS; 0,1 mg P1075 BS ; 0,1 mg P1075 DS ; 0,1 mg P1075 DS; 0,5 mg P1075 DS; 5HD DS between 115 – 120 minutes time interval were significantly smaller than the control group (Table.3.24, Fig.3.34) ($p < 0,05$).

Table 3.24. Spike wave frequency (number of spike) obtained from 115 to 120 minute recordings for all groups (Data are means $\pm$ SE *P < 0.05: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	201,00	$\pm$	34,75	
0,1mg BEP BS	6	222,17	$\pm$	33,88	0,97
1mg BEP BS	6	103,17	$\pm$	48,80*	0,01
10 mg BEP BS	8	131,78	$\pm$	26,59*	0,03
0,1mg BEP DS	6	132,00	$\pm$	20,38*	0,04
1 mg BEP DS	6	106,33	$\pm$	25,56*	0,01
10 mg BEP DS	8	189,50	$\pm$	27,10	0,43
0,1 mg P1075 BS	6	87,17	$\pm$	29,52*	0,01
0,5 mg P1075 BS	6	183,00	$\pm$	34,76	0,39
1 mg P1075 BS	6	181,33	$\pm$	24,18	0,37
0,1 mg P1075 DS	8	110,13	$\pm$	27,63*	0,01
0,5mg P1075 DS	6	108,83	$\pm$	26,11*	0,02
1 mg P1075 DS	8	157,88	$\pm$	37,78	0,13
5HD BS	8	195,50	$\pm$	32,80	0,52
5HD DS	10	139,90	$\pm$	28,54*	0,05
HMR 1098 DS	8	187,75	$\pm$	40,67	0,41
HMR 1098 BS	8	193,13	$\pm$	39,49	0,48

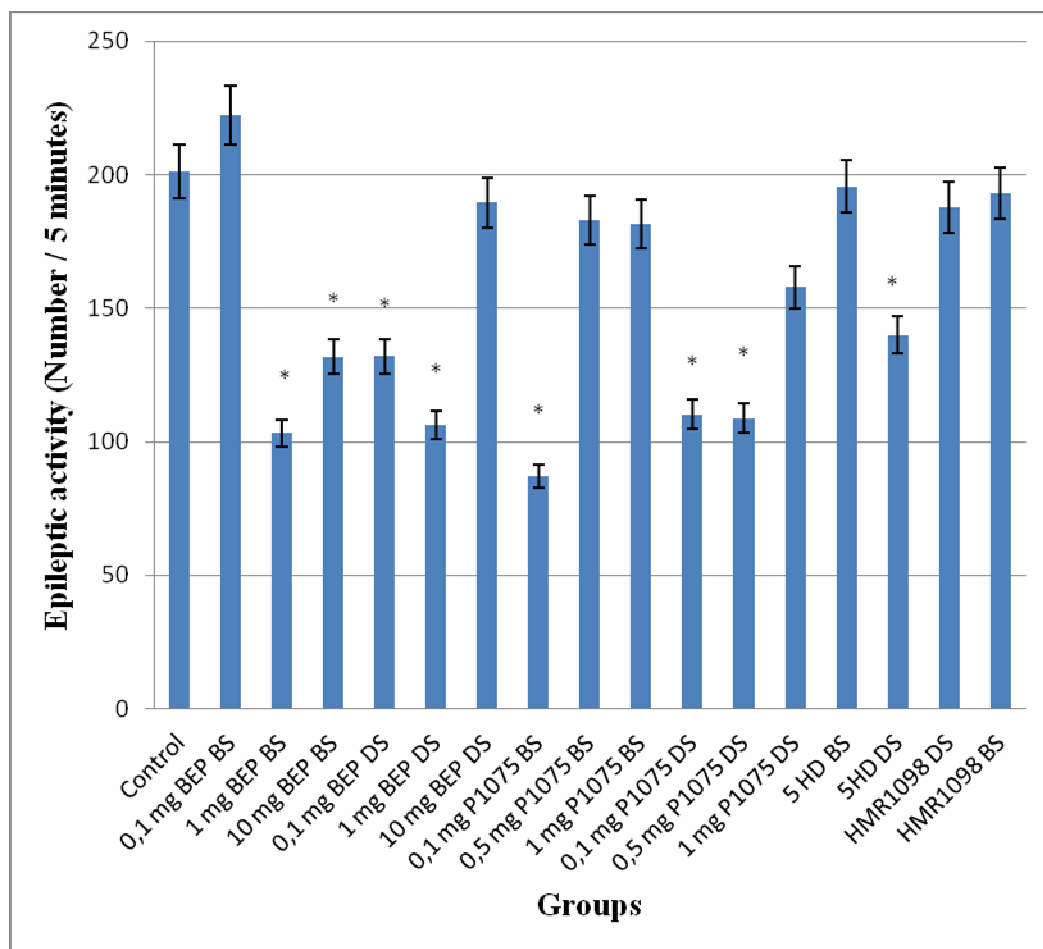


Figure 3.34. Spike wave frequency (number of spike) obtained from 115 to 120 minutes recordings (Period 24). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.25. Epileptic activity between 120 to 125 minutes in terms of spike wave frequency (Period 25)

The spike wave frequency in groups 0,1 mg BEP BS; 1 mg BEP BS; 10 mg BEP BS; 0,1 mg BEP DS; 1 mg BEP DS; 0,1 mg P1075 BS ; 0,1 mg P1075 DS; 0,5 mg P1075 DS; 1 mg P1075 DS; 5HD DS between 120 – 125 minutes time interval are significantly smaller than control group (Table.3.25, Fig.3.35) ($p<0,05$).

Table 3. 25. Spike wave frequency (number of spike) obtained from 120 to 125 minute recordings in all groups. (Data are means $\pm$ SE * $P<0.05$: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	211,22	$\pm$	35,60	
0,1mg BEP BS	6	102,33	$\pm$	36,83*	0,01
1mg BEP BS	6	36,83	$\pm$	11,38*	0,00
10 mg BEP BS	8	121,33	$\pm$	24,81*	0,01
0,1mg BEP DS	6	84,43	$\pm$	24,20*	0,00
1 mg BEP DS	6	100,17	$\pm$	24,87*	0,00
10 mg BEP DS	8	181,13	$\pm$	27,89	0,20
0,1 mg P1075 BS	6	76,83	$\pm$	30,20*	0,00
0,5 mg P1075 BS	6	185,50	$\pm$	34,59	0,28
1 mg P1075 BS	6	182,00	$\pm$	27,90	0,25
0,1 mg P1075 DS	8	109,50	$\pm$	27,25*	0,00
0,5mg P1075 DS	6	101,67	$\pm$	27,29*	0,01
1 mg P1075 DS	8	145,25	$\pm$	40,09*	0,04
5HD BS	8	186,75	$\pm$	33,36	0,25
5HD DS	10	123,40	$\pm$	30,27*	0,01
HMR 1098 DS	8	191,38	$\pm$	42,68	0,30
HMR 1098 BS	8	179,63	$\pm$	39,88	0,19

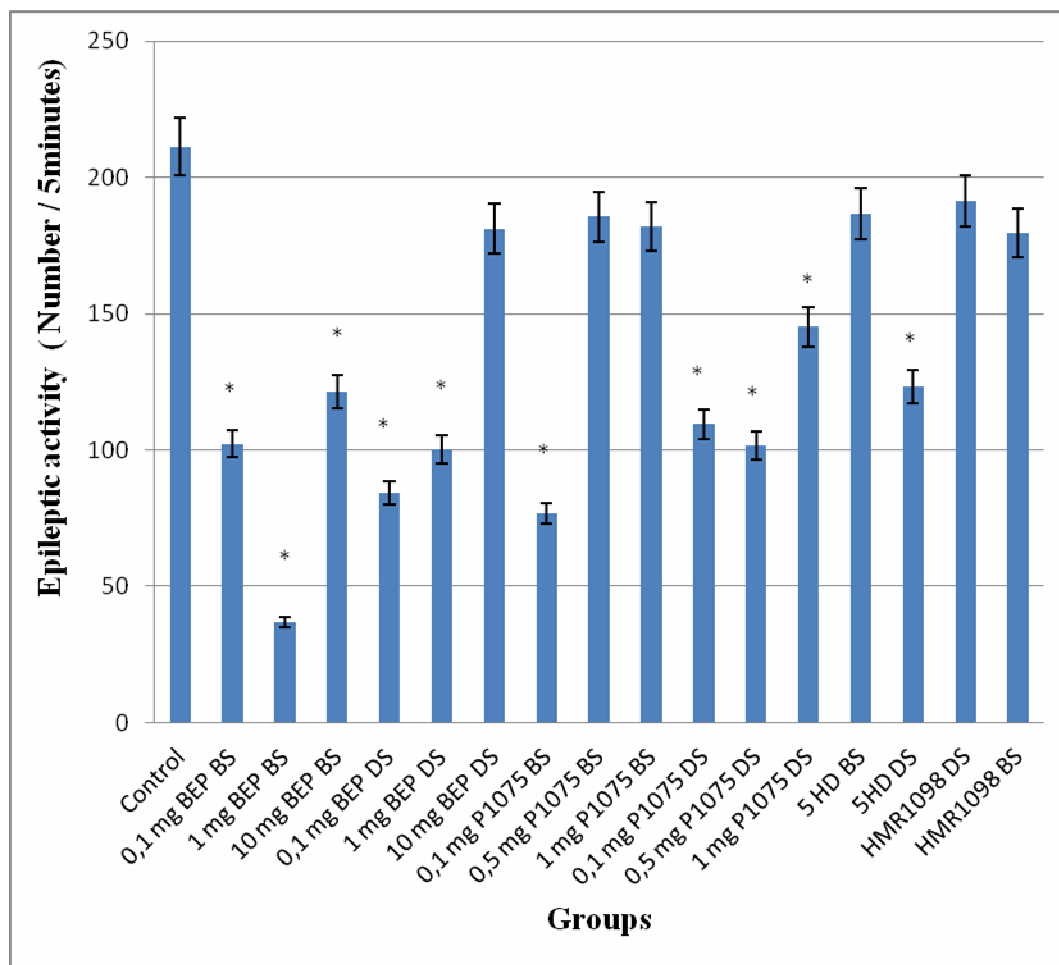


Figure 3.35. Spike wave frequency (number of spike) obtained from 120 to 125 minutes recordings (Period 25). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.26. Epileptic activity between 125 to 130 minutes in terms of spike wave frequency (Period 26)

The spike wave frequency in groups 0,1 mg BEP BS; 1 mg BEP BS; 10 mg BEP BS; 0,1 mg BEP DS; 1 mg BEP DS ; 0,1 mg P1075 BS; 0,1 mg P1075 DS; 0,5 mg P1075 DS; 1 mg P1075 DS; 5HD DS between 125 – 130 minutes time interval were significantly smaller than control group (Table.3.26., Fig.3.36.) ($p < 0,05$).

Table 3.26. Spike wave frequency (number of spike) obtained from 125 to 130 minute recordings in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	218,22	$\pm$	38,49	
0,1mg BEP BS	6	154,30	$\pm$	20,84*	0,05
1mg BEP BS	6	33,33	$\pm$	10,44*	0,00
10 mg BEP BS	8	127,78	$\pm$	24,71*	0,01
0,1mg BEP DS	6	97,29	$\pm$	24,84*	0,00
1 mg BEP DS	6	86,83	$\pm$	22,31*	0,00
10 mg BEP DS	8	172,25	$\pm$	27,50	0,09
0,1 mg P1075 BS	6	81,50	$\pm$	29,44*	0,00
0,5 mg P1075 BS	6	179,00	$\pm$	33,89	0,16
1 mg P1075 BS	6	201,00	$\pm$	18,13	0,35
0,1 mg P1075 DS	8	95,25	$\pm$	28,54*	0,00
0,5mg P1075 DS	6	83,33	$\pm$	27,86*	0,00
1 mg P1075 DS	8	145,88	$\pm$	43,15*	0,02
5HD BS	8	182,38	$\pm$	33,03	0,15
5HD DS	10	119,90	$\pm$	30,42*	0,00
HMR 1098 DS	8	181,63	$\pm$	39,44	0,14
HMR 1098 BS	8	177,63	$\pm$	40,31	0,12

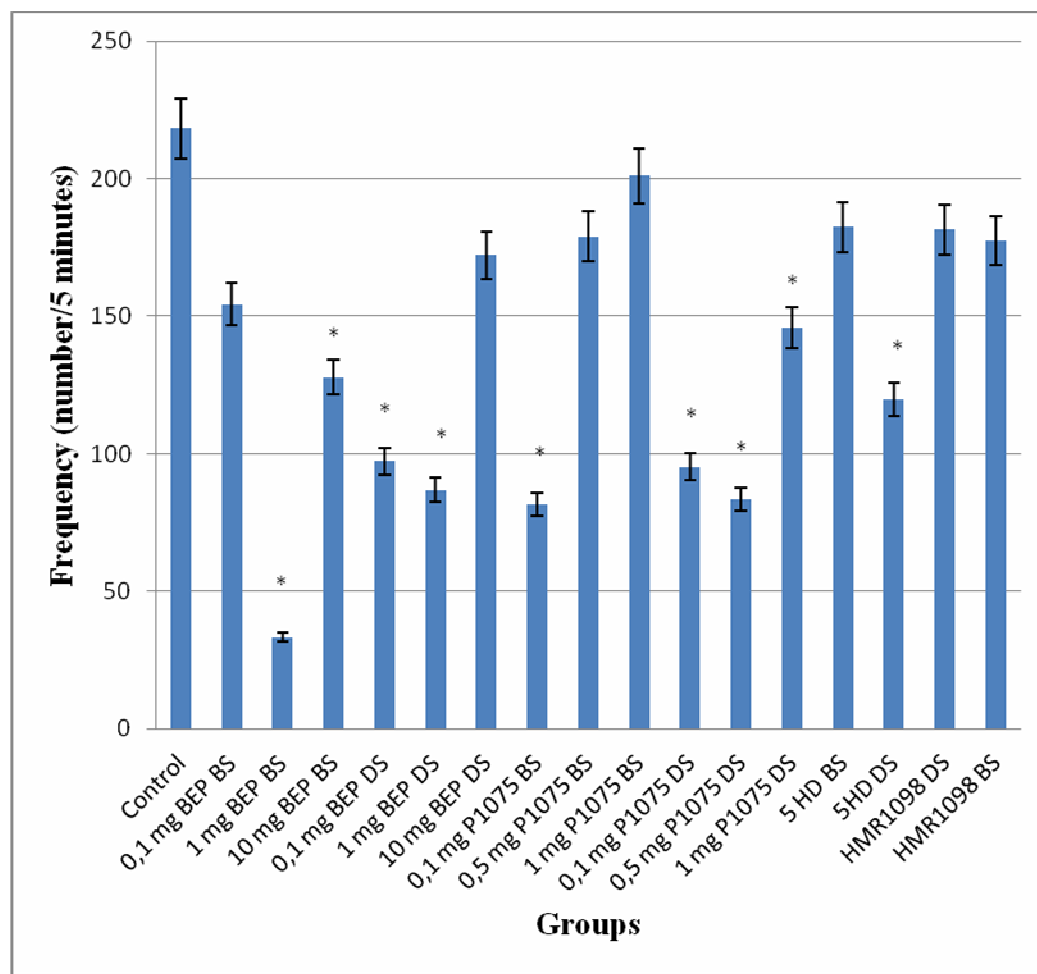


Figure 3.36. Spike wave frequency (number of spike) obtained from 125 to 130 minutes recordings (Period 26). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.27. Epileptic activity between 130 to 135 minutes in terms of spike wave frequency (Period 27)

The spike wave frequency in groups 0,1 mg BEP BS; 1 mg BEP BS; 10 mg BEP BS; 0,1 mg BEP DS; 1 mg BEP DS; 0,1 mg P1075 BS; 0,1 mg P1075 DS; 0,5 mg P1075 DS; 1 mg P1075 DS; 5HD DS between 130–135 minutes time interval were significantly smaller than the control group (Table.3.27, Fig.3.37.) ($p < 0,05$)

Table 3.27. Spike wave frequency (number of spike) obtained from 130 to 135 minute recordings in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	206,00	$\pm$	39,34	
0,1mg BEP BS	6	139,83	$\pm$	21,00*	0,05
1mg BEP BS	6	32,00	$\pm$	9,58*	0,00
10 mg BEP BS	8	133,33	$\pm$	20,31*	0,02
0,1mg BEP DS	6	91,14	$\pm$	26,82*	0,00
1 mg BEP DS	6	58,33	$\pm$	14,11*	0,00
10 mg BEP DS	8	183,63	$\pm$	31,75	0,27
0,1 mg P1075 BS	6	80,17	$\pm$	28,77*	0,00
0,5 mg P1075 BS	6	189,50	$\pm$	37,89	0,37
1 mg P1075 BS	6	201,00	$\pm$	26,26	0,51
0,1 mg P1075 DS	8	95,25	$\pm$	30,16*	0,00
0,5mg P1075 DS	6	63,83	$\pm$	26,15*	0,00
1 mg P1075 DS	8	124,25	$\pm$	39,09*	0,01
5HD BS	8	176,25	$\pm$	32,41	0,20
5HD DS	10	111,00	$\pm$	30,99*	0,00
HMR 1098 DS	8	177,25	$\pm$	39,77	0,21
HMR 1098 BS	8	171,50	$\pm$	39,20	0,16

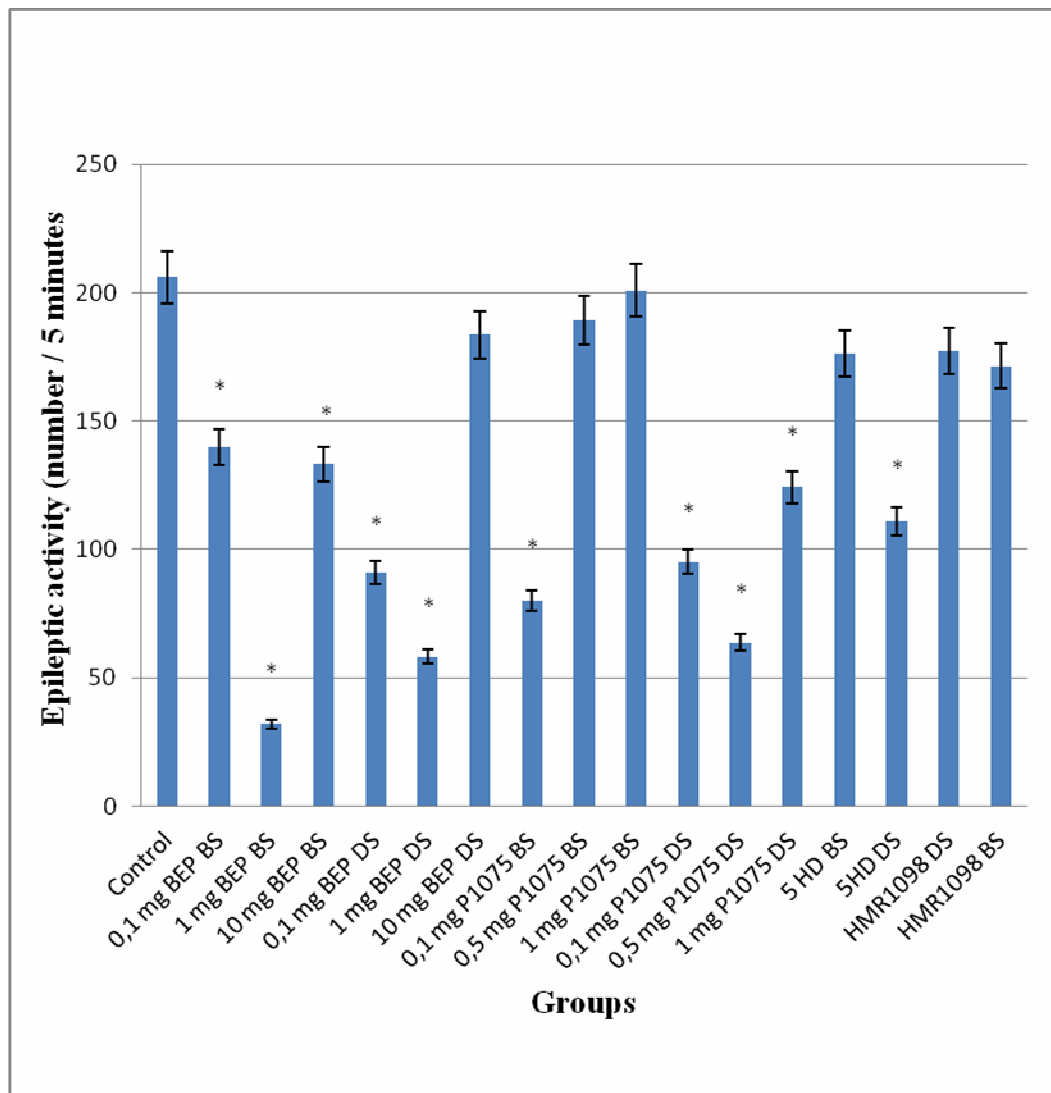


Figure 3.37. Spike wave frequency (number of spike) obtained from 130 to 135 minutes recordings (Period 27). (Data are means $\pm$ SE *P<0.05: Compared to control).

3.8.28. Epileptic activity between 135 to 140 minutes in terms of spike wave frequency (Period 28)

The spike wave frequency in groups 1 mg BEP BS; 10 mg BEP BS; 0,1 mg BEP DS; 1 mg BEP DS; 0,1 mg P1075 BS; 0,1 mg P1075 DS; 0,5 mg P1075 DS; 1 mg P1075 DS; 5HD DS between 135–140 minutes time interval are significantly smaller than control group (Table.3.28, Fig.3.38.) ($p < 0,05$).

Table 3.28. Spike wave frequency (number of spike) obtained from 135 to 140 minute recordings in all groups. (Data are means $\pm$ SE *P < 0.05: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	192,00	$\pm$	37,61	
0,1mg BEP BS	6	149,50	$\pm$	16,44	0,15
1mg BEP BS	6	28,83	$\pm$	10,67*	0,00
10 mg BEP BS	8	132,89	$\pm$	23,41*	0,04
0,1mg BEP DS	6	96,14	$\pm$	25,74*	0,01
1 mg BEP DS	6	57,33	$\pm$	13,96*	0,00
10 mg BEP DS	8	170,63	$\pm$	28,83	0,29
0,1 mg P1075 BS	6	82,67	$\pm$	30,33*	0,00
0,5 mg P1075 BS	6	175,83	$\pm$	31,28	0,38
1 mg P1075 BS	6	193,83	$\pm$	31,58	0,64
0,1 mg P1075 DS	8	90,38	$\pm$	29,06*	0,00
0,5mg P1075 DS	6	45,50	$\pm$	17,24*	0,00
1 mg P1075 DS	8	121,63	$\pm$	38,57*	0,03
5HD BS	8	165,38	$\pm$	31,60	0,23
5HD DS	10	111,40	$\pm$	30,15*	0,01
HMR 1098 DS	8	164,00	$\pm$	40,14	0,22
HMR 1098 BS	8	161,00	$\pm$	34,48	0,19

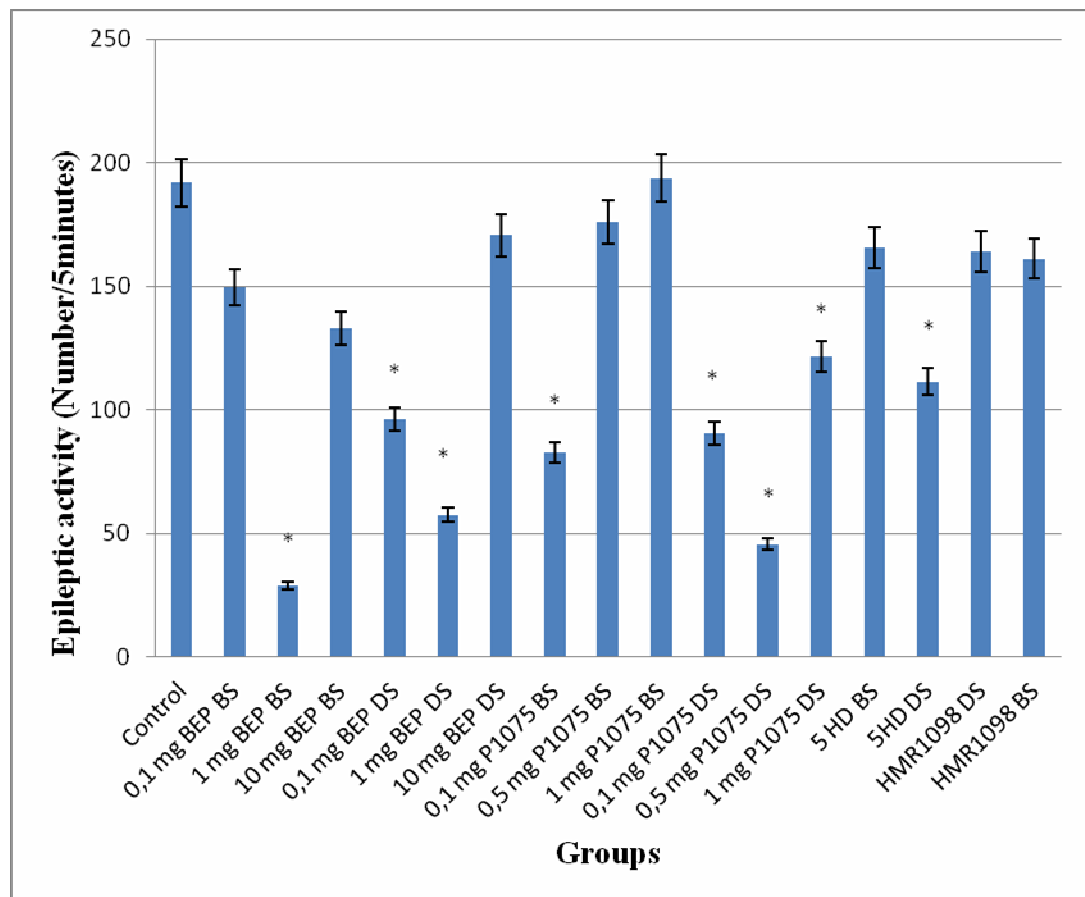


Figure 3.38. Spike wave frequency (number of spike) obtained from 135 to 140 minutes recordings (Period 28). (Data are means $\pm$ SE *P<0.05: Compared to control).

3.8.29. Epileptic activity between 140 to 145 minutes in terms of spike wave frequency (Period 29)

The spike wave frequency in groups 1 mg BEP BS; 0,1 mg BEP DS; 1 mg BEP DS; 0,1 mg P1075 BS; 0,1 mg P1075 DS; 0,5 mg P1075 DS; 1 mg P1075 DS between 140–145 minutes time interval were significantly smaller than the control group (Table3.29, Fig.3.39.) ($p < 0,05$).

Table 3.29. Spike wave frequency (number of spike) obtained from 140 to 145 minute recordings in all groups. (Data are means $\pm$ SE *P < 0.05: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	173,11	$\pm$	42,73	
0,1mg BEP BS	6	108,83	$\pm$	33,70	0,06
1mg BEP BS	6	29,17	$\pm$	9,74*	0,00
10 mg BEP BS	8	133,67	$\pm$	24,77	0,14
0,1mg BEP DS	6	92,71	$\pm$	29,33*	0,02
1 mg BEP DS	6	62,50	$\pm$	8,06*	0,01
10 mg BEP DS	8	159,75	$\pm$	31,24	0,42
0,1 mg P1075 BS	6	58,33	$\pm$	22,90*	0,00
0,5 mg P1075 BS	6	176,67	$\pm$	29,19	0,70
1 mg P1075 BS	6	195,50	$\pm$	26,92	0,97
0,1 mg P1075 DS	8	89,13	$\pm$	31,41*	0,01
0,5mg P1075 DS	6	45,00	$\pm$	16,25*	0,00
1 mg P1075 DS	8	106,13	$\pm$	36,95*	0,04
5HD BS	8	163,50	$\pm$	30,81	0,47
5HD DS	10	116,60	$\pm$	28,74	0,06
HMR 1098 DS	8	146,88	$\pm$	36,92	0,27
HMR 1098 BS	8	166,13	$\pm$	36,65	0,51

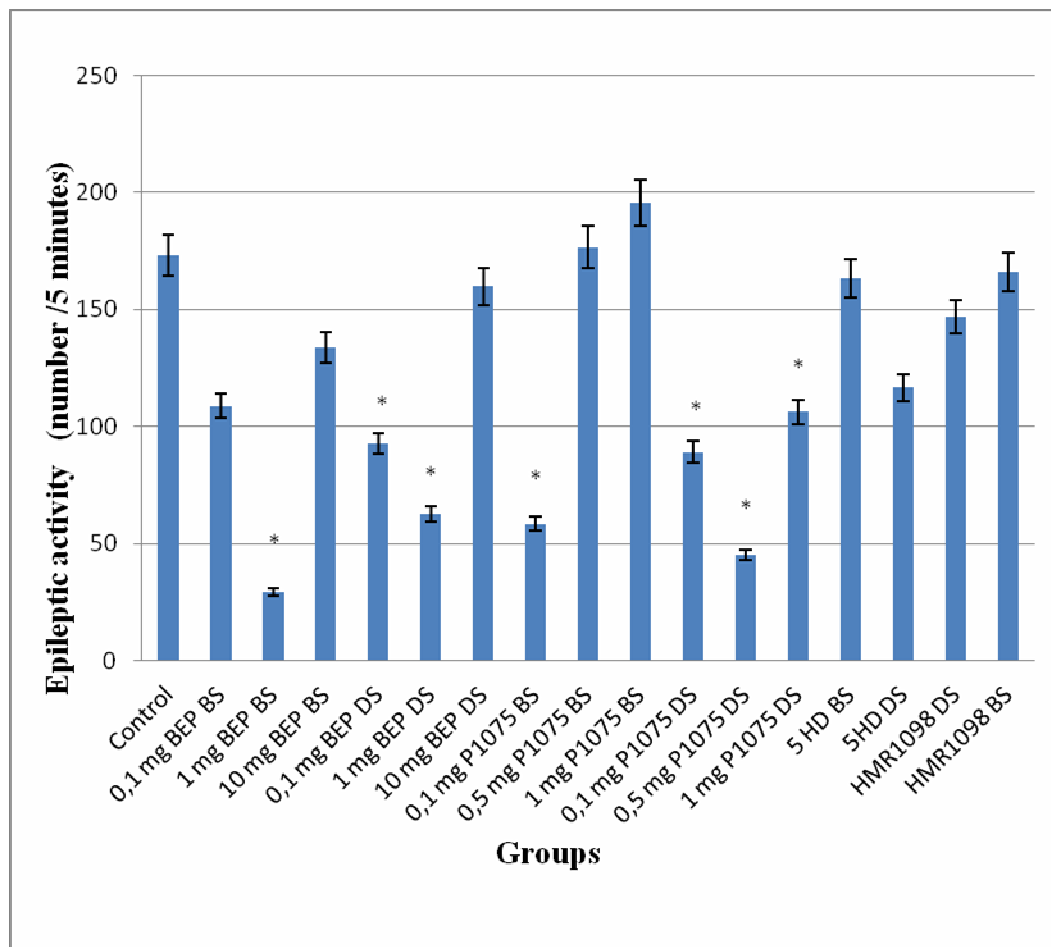


Figure 3.39. Spike wave frequency (number of spike) obtained from 140 to 145 minutes recordings (Period 29). (Data are means $\pm$ SE *P<0.05: Compared to control).

3.8.30. Epileptic activity between 145 to 150 minutes in terms of spike wave frequency (Period 30)

The spike wave frequency in groups 1 mg BEP BS; 1 mg BEP DS; 0,5 mg P1075 DS between 145–150 minutes time interval were significantly smaller than the control group (Table.3.30, Fig.3.30.) ($p < 0,05$).

Table.3.30. Spike wave frequency (number of spike) obtained from 145 to 150 minute recordings in all groups. (Data are means $\pm$ SE *P < 0.05: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	117,22	$\pm$	31,06	
0,1mg BEP BS	6	85,33	$\pm$	26,61	0,27
1mg BEP BS	6	25,17	$\pm$	7,79*	0,01
10 mg BEP BS	8	127,67	$\pm$	24,26	0,92
0,1mg BEP DS	6	93,57	$\pm$	31,68	0,35
1 mg BEP DS	6	37,17	$\pm$	9,72*	0,03
10 mg BEP DS	8	136,13	$\pm$	28,75	0,91
0,1 mg P1075 BS	6	56,67	$\pm$	23,05	0,08
0,5 mg P1075 BS	6	169,83	$\pm$	27,78	0,37
1 mg P1075 BS	6	189,67	$\pm$	26,70	0,17
0,1 mg P1075 DS	8	85,75	$\pm$	29,98	0,24
0,5mg P1075 DS	6	33,67	$\pm$	16,95*	0,02
1 mg P1075 DS	8	94,13	$\pm$	30,52	0,34
5HD BS	8	152,88	$\pm$	29,59	0,59
5HD DS	10	115,30	$\pm$	26,97	0,66
HMR 1098 DS	8	156,63	$\pm$	40,30	0,52
HMR 1098 BS	8	160,63	$\pm$	33,26	0,46

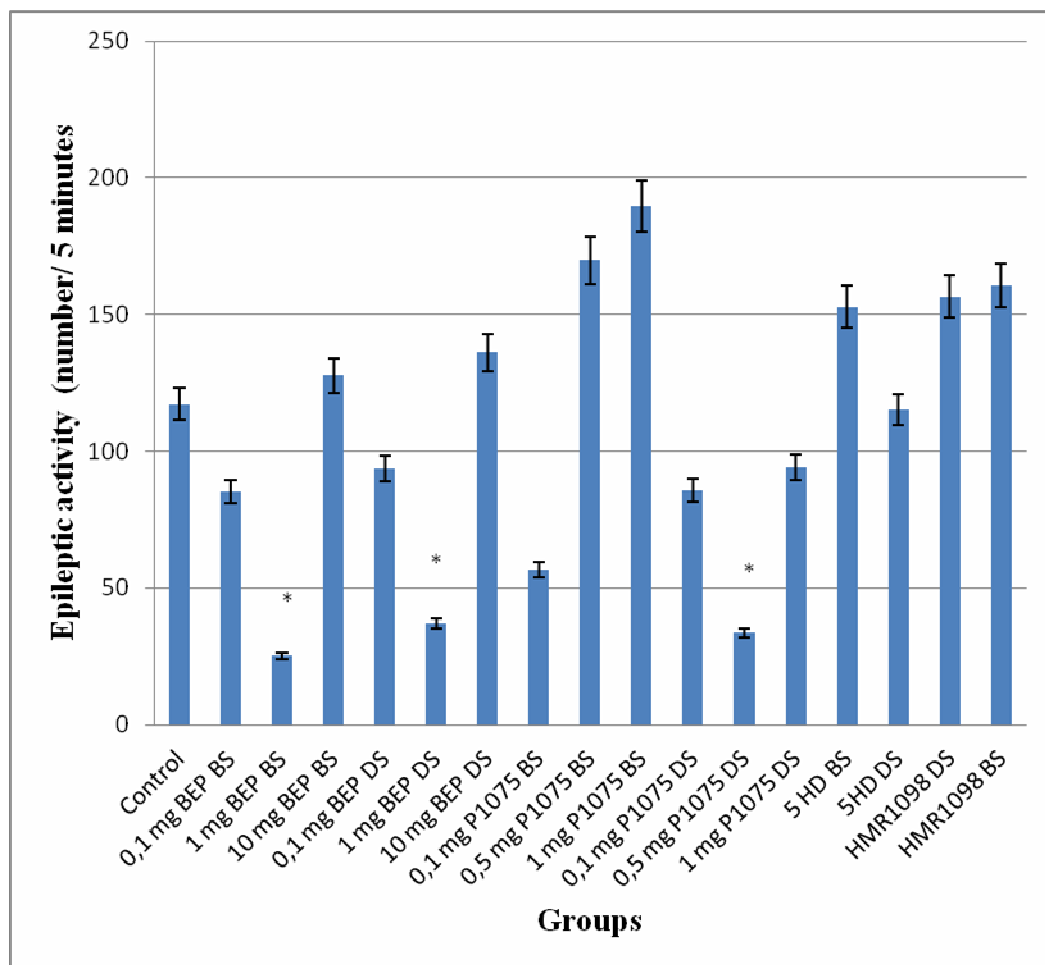


Figure 3.40. Spike wave frequency (number of spike) obtained from 145 to 150 minutes recordings (Period 30). (Data are means $\pm$ SE *P<0.05: Compared to control).

3.8.31. Epileptic activity between 150 to 155 minutes in terms of spike wave frequency (Period 31)

The spike wave frequency in groups 1 mg BEP BS; 1 mg BEP DS; 0,5 mg P1075 DS between 150–155 minutes time interval were significantly smaller than the control group (Table.3.31, Fig.3.41.) ($p < 0,05$).

Table 3.31. Spike wave frequency (number of spike) obtained from 150 to 155 minute recordings in all groups (Data are means $\pm$ SE *P < 0.05: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	105,89	$\pm$	29,58	
0,1mg BEP BS	6	84,00	$\pm$	22,33	0,44
1mg BEP BS	6	12,67	$\pm$	6,75*	0,02
10 mg BEP BS	8	129,56	$\pm$	24,43	0,76
0,1mg BEP DS	6	97,14	$\pm$	33,53	0,62
1 mg BEP DS	6	31,83	$\pm$	7,49*	0,05
10 mg BEP DS	8	134,00	$\pm$	29,44	0,68
0,1 mg P1075 BS	6	56,67	$\pm$	22,58	0,16
0,5 mg P1075 BS	6	156,50	$\pm$	35,38	0,37
1 mg P1075 BS	6	183,83	$\pm$	29,00	0,13
0,1 mg P1075 DS	8	86,88	$\pm$	31,71	0,44
0,5mg P1075 DS	6	34,83	$\pm$	15,21*	0,06
1 mg P1075 DS	8	79,25	$\pm$	29,90	0,34
5HD BS	8	142,00	$\pm$	27,78	0,54
5HD DS	10	103,60	$\pm$	26,24	0,71
HMR 1098 DS	8	155,75	$\pm$	38,76	0,34
HMR 1098 BS	8	149,38	$\pm$	40,17	0,43

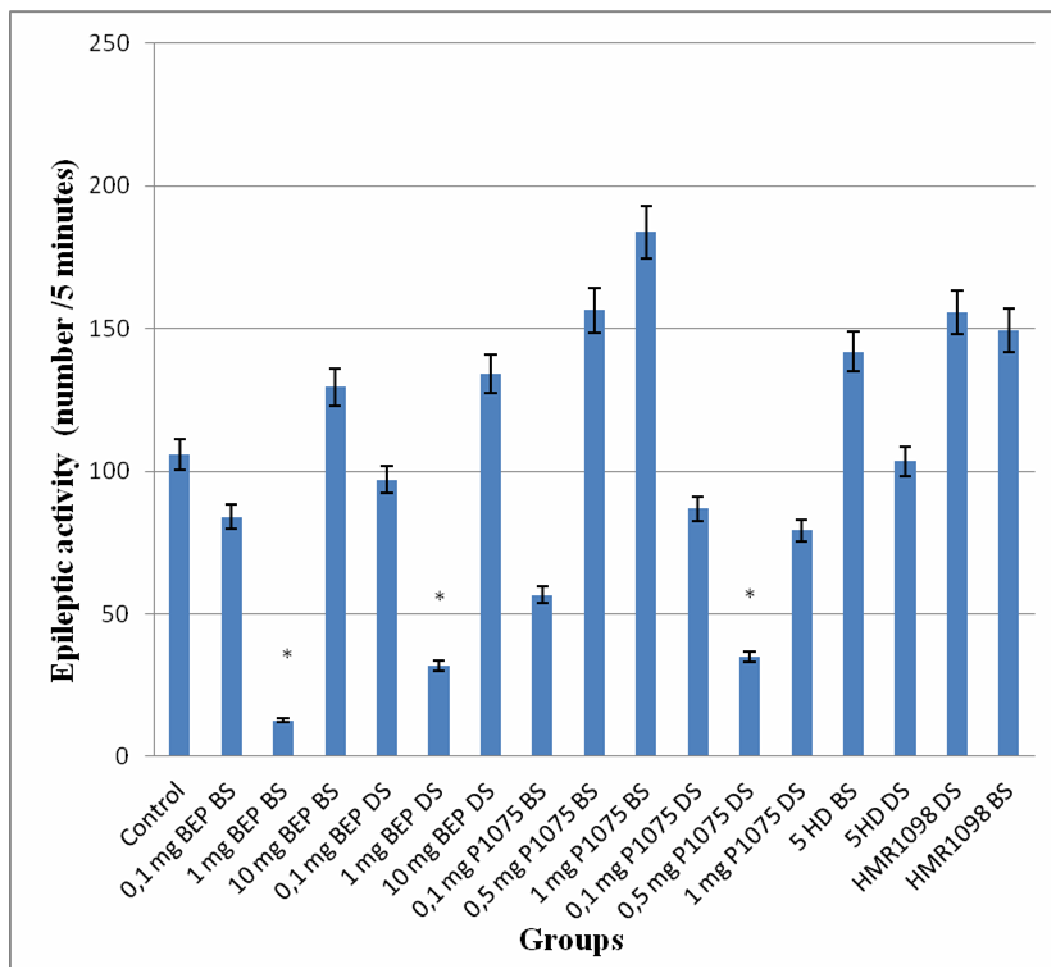


Figure 3.41. Spike wave frequency (number of spike) obtained from 150 to 155 minutes recordings. (Period 31). (Data are means $\pm$ SE *P < 0.05: Compared to control) .

3.8.32. Epileptic activity between 155 to 160 minutes in terms of spike wave frequency (Period 32)

The spike wave frequency in groups 1 mg BEP BS; 1 mg BEP DS; 0,5 mg P1075 DS between 155–160 minutes time interval were significantly smaller than the control group (Table.3.32, Fig.3.42.) ($p < 0,05$).

Table 3.32. Spike wave frequency (number of spike) obtained from 155 to 160 minute recordings in all groups (Data are means $\pm$ SE *P < 0.05: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	132,56	$\pm$	40,17	
0,1mg BEP BS	6	44,17	$\pm$	29,59	0,34
1mg BEP BS	6	28,17	$\pm$	14,71*	0,02
10 mg BEP BS	8	118,11	$\pm$	23,77	0,75
0,1mg BEP DS	6	98,00	$\pm$	31,38	0,62
1 mg BEP DS	6	17,67	$\pm$	7,12*	0,05
10 mg BEP DS	8	124,13	$\pm$	32,58	0,68
0,1 mg P1075 BS	6	42,50	$\pm$	20,50	0,16
0,5 mg P1075 BS	6	151,50	$\pm$	27,86	0,37
1 mg P1075 BS	6	175,83	$\pm$	33,58	0,13
0,1 mg P1075 DS	8	84,00	$\pm$	30,30	0,44
0,5mg P1075 DS	6	15,67	$\pm$	12,42*	0,06
1 mg P1075 DS	8	79,50	$\pm$	33,82	0,34
5HD BS	8	136,75	$\pm$	27,94	0,54
5HD DS	10	96,90	$\pm$	26,81	0,71
HMR 1098 DS	8	155,00	$\pm$	23,84	0,34
HMR 1098 BS	8	153,50	$\pm$	43,89*	0,00

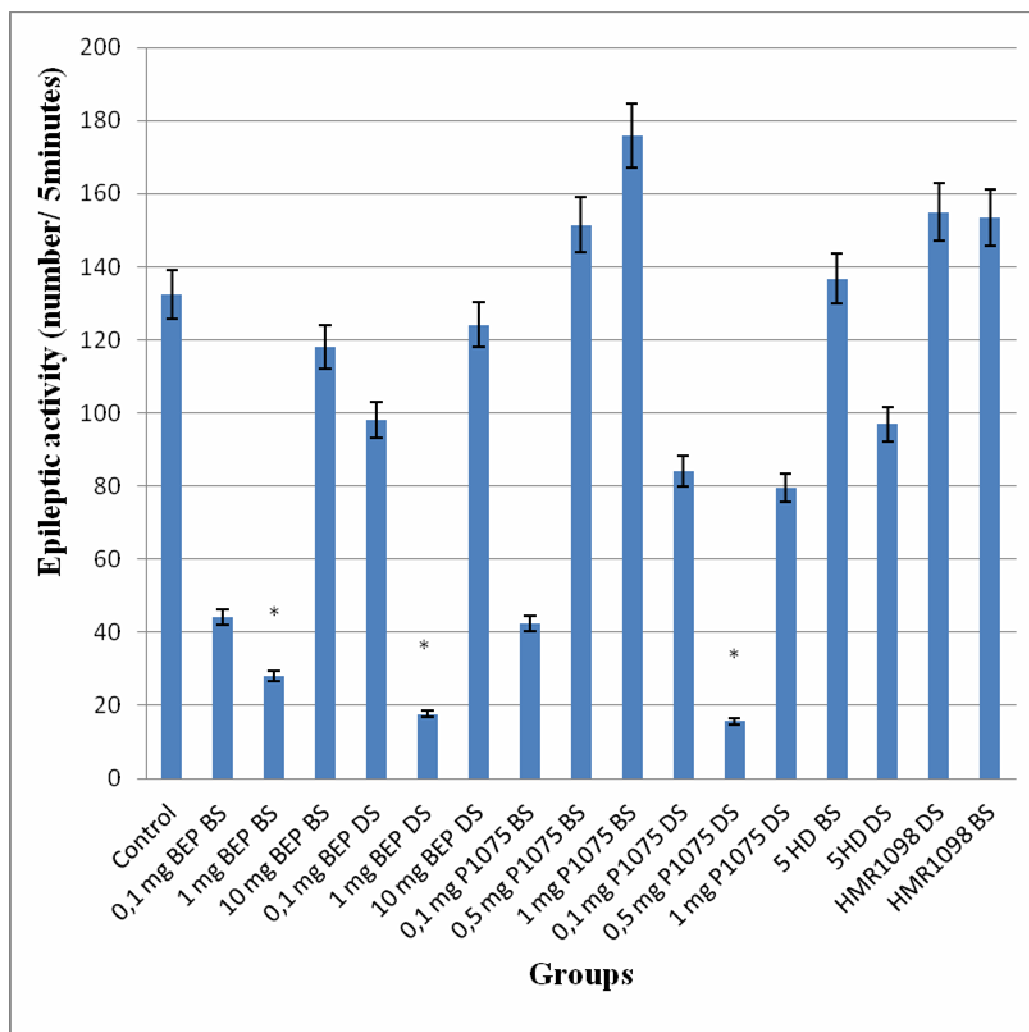


Figure 3.42. Spike wave frequency (number of spike) obtained from 155 to 160 minutes recordings (Period 32). (Data are means $\pm$ SE *P<0.05: Compared to control).

3.8.33. Epileptic activity between 160 to 165 minutes in terms of spike wave frequency (Period 33)

The spike wave frequency in groups 0,1 mg BEP BS; 1 mg BEP BS; 1 mg BEP DS; 0,1 mg P1075 BS; 0,5 mg P1075 DS between 160–165 minutes time interval were significantly smaller than control group (Table 3.33, Fig. 3.43.) ($p < 0,05$).

Table 3.33. Spike wave frequency (number of spike) obtained from 160 to 165 minute recordings in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	132,33	$\pm$	41,57	
0,1mg BEP BS	6	8,50	$\pm$	6,14*	0,02
1mg BEP BS	6	12,67	$\pm$	6,49*	0,01
10 mg BEP BS	8	120,89	$\pm$	25,48	0,45
0,1mg BEP DS	6	96,00	$\pm$	33,63	0,24
1 mg BEP DS	6	17,50	$\pm$	8,72*	0,00
10 mg BEP DS	8	120,13	$\pm$	33,54	0,56
0,1 mg P1075 BS	6	35,67	$\pm$	22,94*	0,02
0,5 mg P1075 BS	6	121,67	$\pm$	35,13	0,94
1 mg P1075 BS	6	176,33	$\pm$	34,15	0,53
0,1 mg P1075 DS	8	87,13	$\pm$	31,40	0,12
0,5mg P1075 DS	6	17,17	$\pm$	13,52*	0,00
1 mg P1075 DS	8	81,25	$\pm$	36,80	0,10
5HD BS	8	128,38	$\pm$	28,10	0,78
5HD DS	10	91,20	$\pm$	26,36	0,19
HMR 1098 DS	8	146,13	$\pm$	29,10	0,87
HMR 1098 BS	8	177,00	$\pm$	50,28	0,90

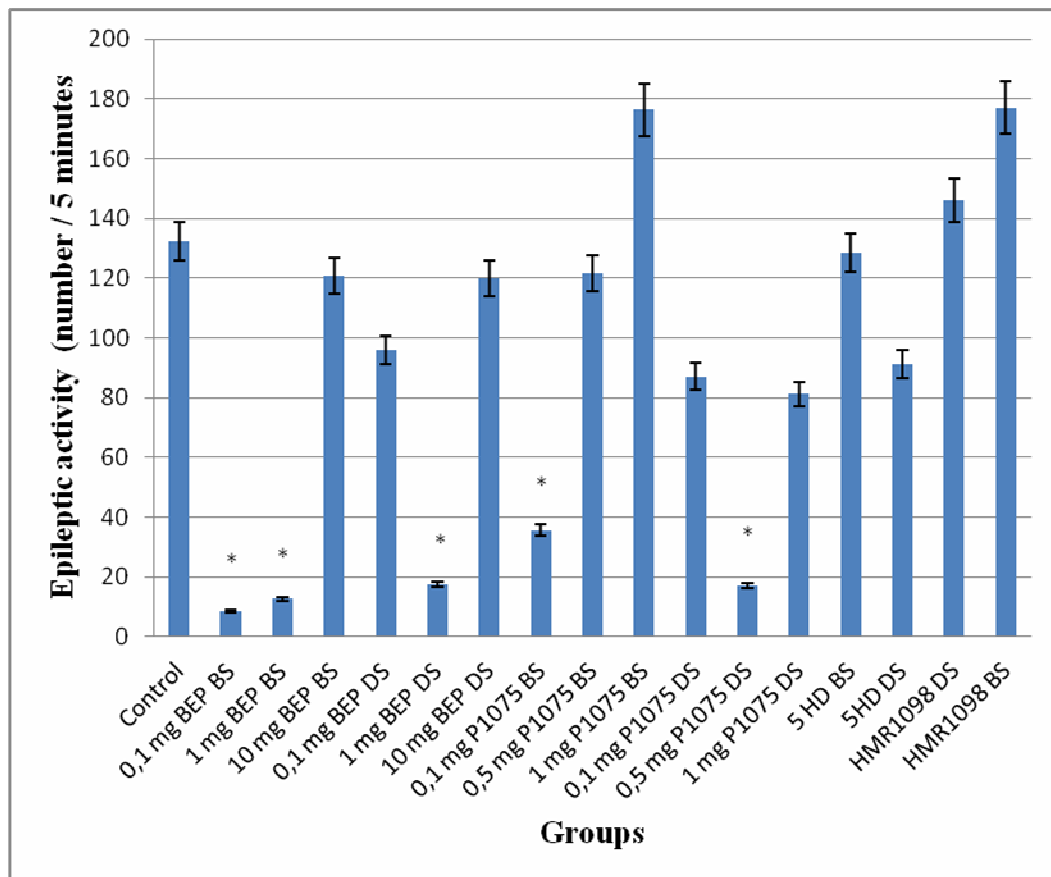


Figure 3.43. Spike wave frequency (number of spike) obtained from 160 to 165 minutes recordings (Period 33). (Data are means $\pm$ SE *P<0.05: Compared to control) .

3.8.34. Epileptic activity between 165 to 170 minutes in terms of spike wave frequency (Period 34)

The spike wave frequency in groups 0,1 mg BEP BS; 1 mg BEP BS; 1 mg BEP DS; 0,5 mg P1075 DS; 0,1 mg P1075 BS; HMR1098 BS between 160–165 minutes time interval were significantly smaller than the control group (Table3.34, Fig.3.44) ($p < 0,05$).

Table 3.34. Spike wave frequency (number of spike) obtained from 165 to 170 minute recordings in all groups. (Data are means $\pm$ SE *P < 0.05: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	107,44	$\pm$	33,67	
0,1mg BEP BS	6	2,83	$\pm$	2,01*	0,01
1mg BEP BS	6	6,67	$\pm$	5,87*	0,01
10 mg BEP BS	8	126,22	$\pm$	25,97	0,89
0,1mg BEP DS	6	96,14	$\pm$	32,97	0,57
1 mg BEP DS	6	14,17	$\pm$	7,40*	0,02
10 mg BEP DS	8	118,13	$\pm$	32,85	0,95
0,1 mg P1075 BS	6	34,67	$\pm$	23,41*	0,06
0,5 mg P1075 BS	6	119,17	$\pm$	37,06	0,97
1 mg P1075 BS	6	170,83	$\pm$	29,92	0,26
0,1 mg P1075 DS	8	83,50	$\pm$	31,08	0,37
0,5mg P1075 DS	6	20,00	$\pm$	13,12*	0,03
1 mg P1075 DS	8	68,75	$\pm$	27,41	0,21
5HD BS	8	122,75	$\pm$	28,05	0,96
5HD DS	10	88,80	$\pm$	25,59	0,42
HMR 1098 DS	8	123,63	$\pm$	30,45	0,94
HMR 1098 BS	8	199,38	$\pm$	54,02*	0,06

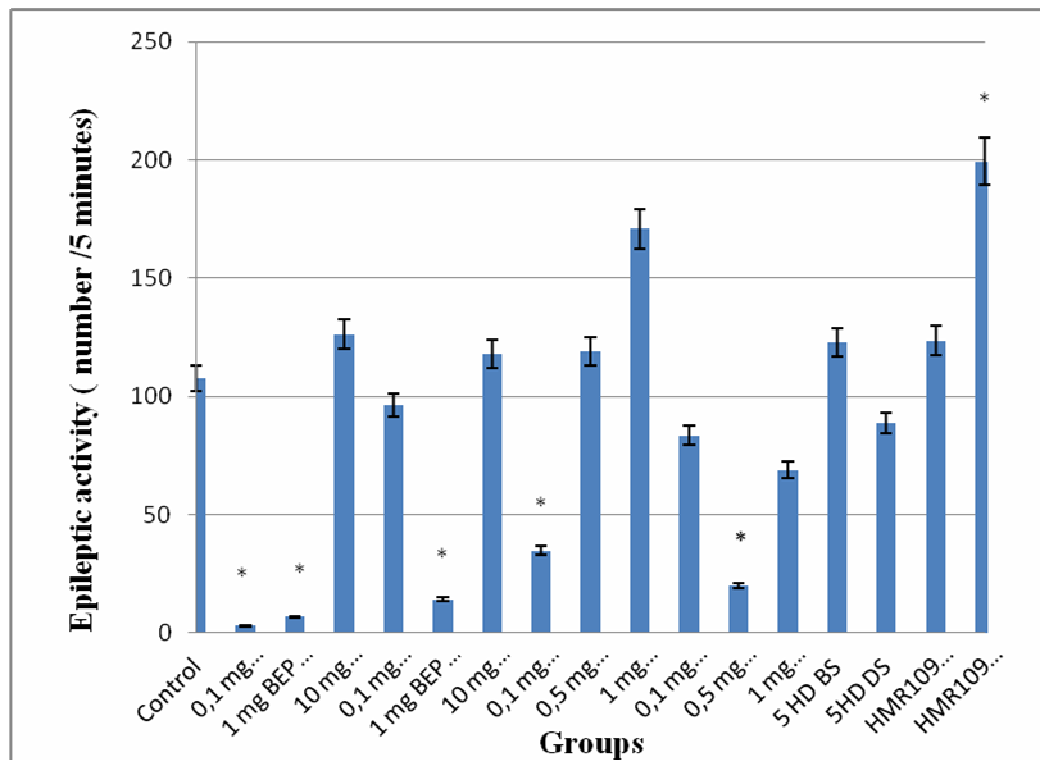


Figure 3.44. Spike wave frequency (number of spike) obtained from 165 to 170 minutes recordings (Period 34). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.35. Epileptic activity between 170 to 175 minutes in terms of spike wave frequency (Period 35)

The spike wave frequency in groups 0,1 mg BEP BS; 1 mg BEP BS; 1 mg BEP DS; 0,5 mg P1075 DS; 0,1 mg P1075 BS; HMR1098 BS between 170–175 minutes time interval were significantly smaller than the control group (Table.3.35, Fig.3.45.) ($p < 0,05$).

Table 3.35. Spike wave frequency (number of spike) obtained from 170 to 175 minute recordings for all groups (Data are means $\pm$ SE *P < 0.05: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	100,00	$\pm$	32,64	
0,1mg BEP BS	6	0,50	$\pm$	0,50*	0,01
1mg BEP BS	6	6,17	$\pm$	5,57*	0,02
10 mg BEP BS	8	124,22	$\pm$	25,45	0,75
0,1mg BEP DS	6	96,14	$\pm$	34,06	0,71
1 mg BEP DS	6	13,83	$\pm$	7,09*	0,03
10 mg BEP DS	8	93,88	$\pm$	34,92	0,66
0,1 mg P1075 BS	6	27,17	$\pm$	17,35*	0,05
0,5 mg P1075 BS	6	120,50	$\pm$	33,53	0,84
1 mg P1075 BS	6	160,00	$\pm$	24,20	0,27
0,1 mg P1075 DS	8	83,75	$\pm$	30,51	0,48
0,5mg P1075 DS	6	26,50	$\pm$	16,82*	0,05
1 mg P1075 DS	8	58,38	$\pm$	23,93	0,18
5HD BS	8	112,38	$\pm$	21,70	0,99
5HD DS	10	81,90	$\pm$	20,66	0,43
HMR 1098 DS	8	110,63	$\pm$	29,87	0,98
HMR 1098 BS	8	194,88	$\pm$	56,79*	0,04

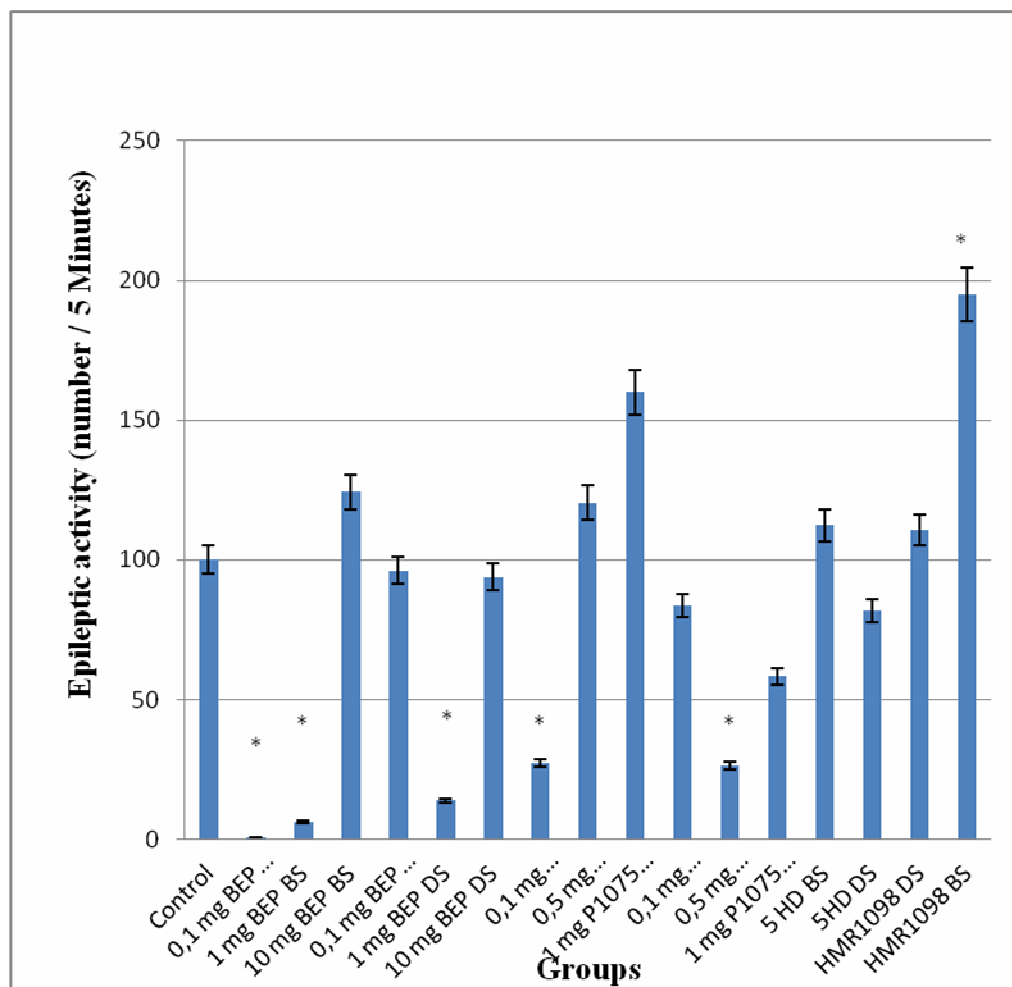


Figure 3.45. Spike wave frequency (number of spike) obtained from 170 to 175 minutes recordings (Period 35). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.8.36. Epileptic activity between 175 To 180 minutes in terms of spike wave frequency (Period 36)

The spike wave frequency in groups 0,1 mg BEP BS; 1 mg BEP BS; 1 mg BEP DS; 0,5 mg P1075 DS; 0,1 mg P1075 BS ; HMR1098 BS between 175–180 minutes time interval are significantly smaller than the control group (Table.3.36., Fig.3.46.) ($p < 0,05$).

Table 3.36. Spike wave frequency (number of spike) obtained from 175 to 180 minute recordings in all groups. (Data are means $\pm$ SE *P < 0.05: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	128,00	$\pm$	39,55	
0,1mg BEP BS	6	0,33	$\pm$	0,33*	0,00
1mg BEP BS	6	3,33	$\pm$	2,75*	0,00
10 mg BEP BS	8	124,11	$\pm$	23,28	0,60
0,1mg BEP DS	6	91,71	$\pm$	33,14	0,19
1 mg BEP DS	6	12,50	$\pm$	7,65*	0,00
10 mg BEP DS	8	89,75	$\pm$	36,05	0,16
0,1 mg P1075 BS	6	26,67	$\pm$	16,08*	0,01
0,5 mg P1075 BS	6	107,00	$\pm$	37,60	0,37
1 mg P1075 BS	6	133,17	$\pm$	28,20	0,80
0,1 mg P1075 DS	8	43,13	$\pm$	16,30*	0,01
0,5mg P1075 DS	6	24,17	$\pm$	15,33*	0,00
1 mg P1075 DS	8	56,38	$\pm$	25,87*	0,02
5HD BS	8	95,88	$\pm$	15,92	0,21
5HD DS	10	65,80	$\pm$	15,72*	0,03
HMR 1098 DS	8	101,38	$\pm$	28,57	0,27
HMR 1098 BS	8	191,63	$\pm$	49,75*	0,02

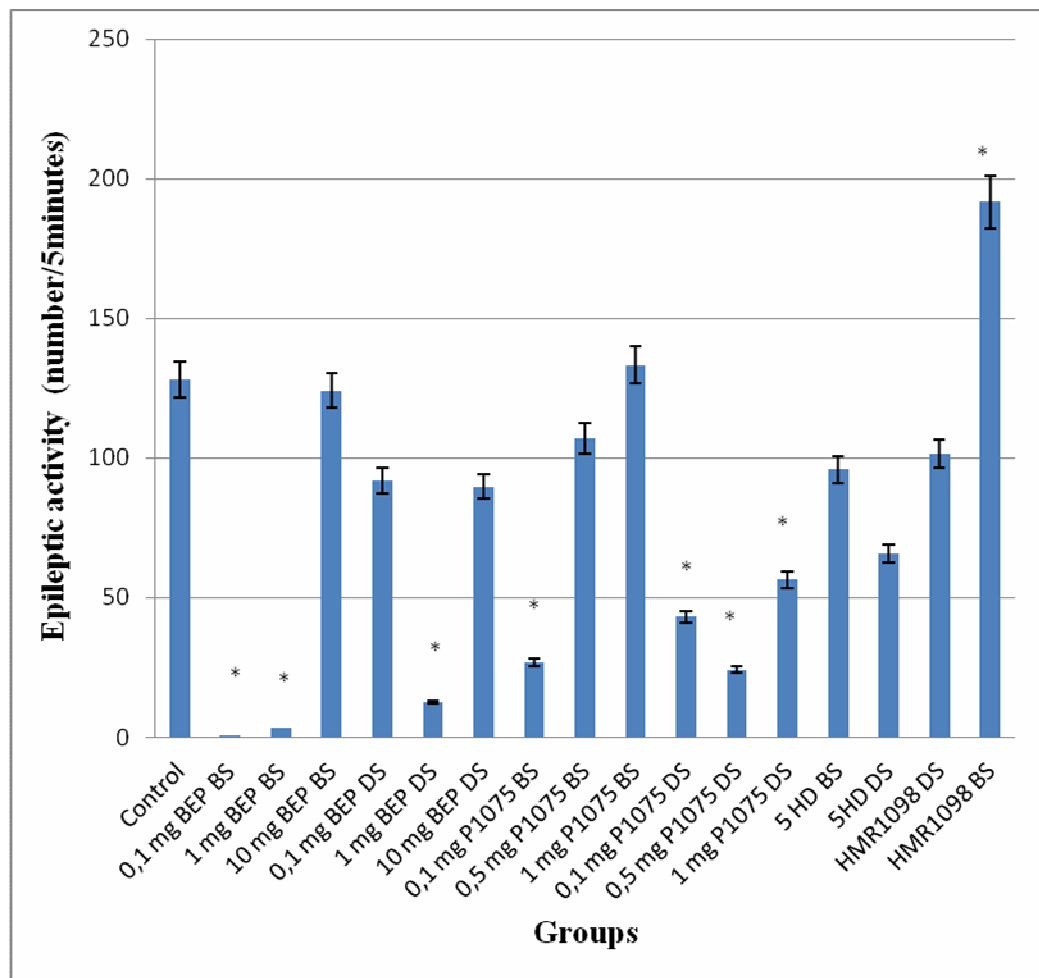


Figure 3.46. Spike wave frequency (number of spike) obtained from 175 to 180 minutes recordings (Period 36). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.9. The effect of bepridil on the spike wave amplitude occurred during epileptic seizure

Amplitude of waves in all doses of bepridil which were applied before seizure were significantly smaller than the control group ($P < 0,05$). The dose of 1 mg/kg bepridil were applied during seizure significantly decreased spike wave amplitude between 10. and 36. period compared to control group ($p < 0,05$). There were no significant differences at other doses of bepridil in terms of spike wave amplitude ($p > 0,05$).

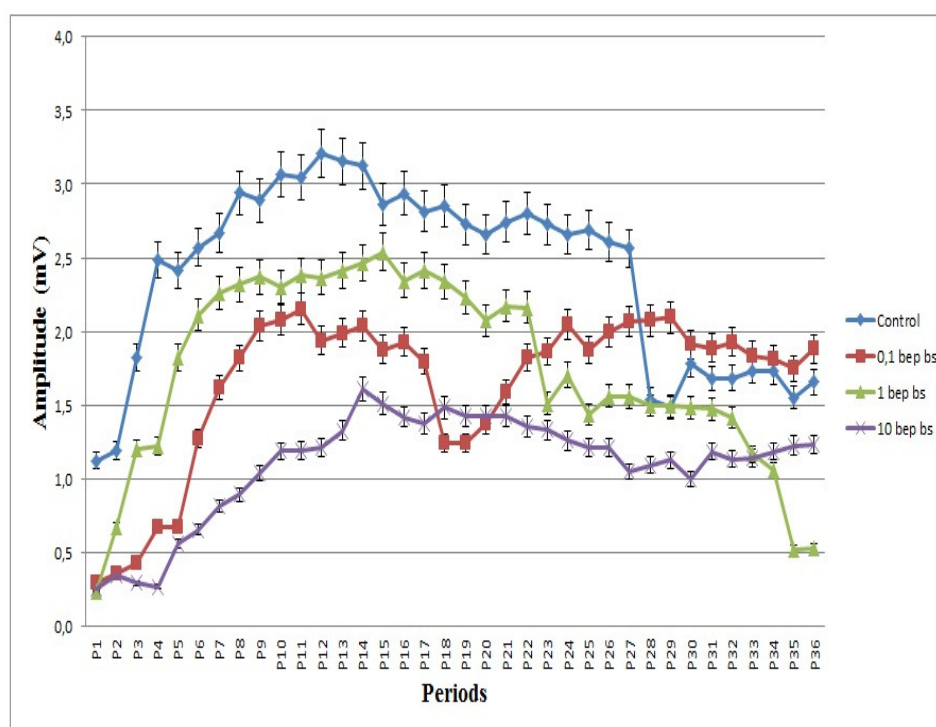


Figure 3.47. Maximum amplitude value of spike wave during 180 minutes ECoG records in bepridil before seizure groups.

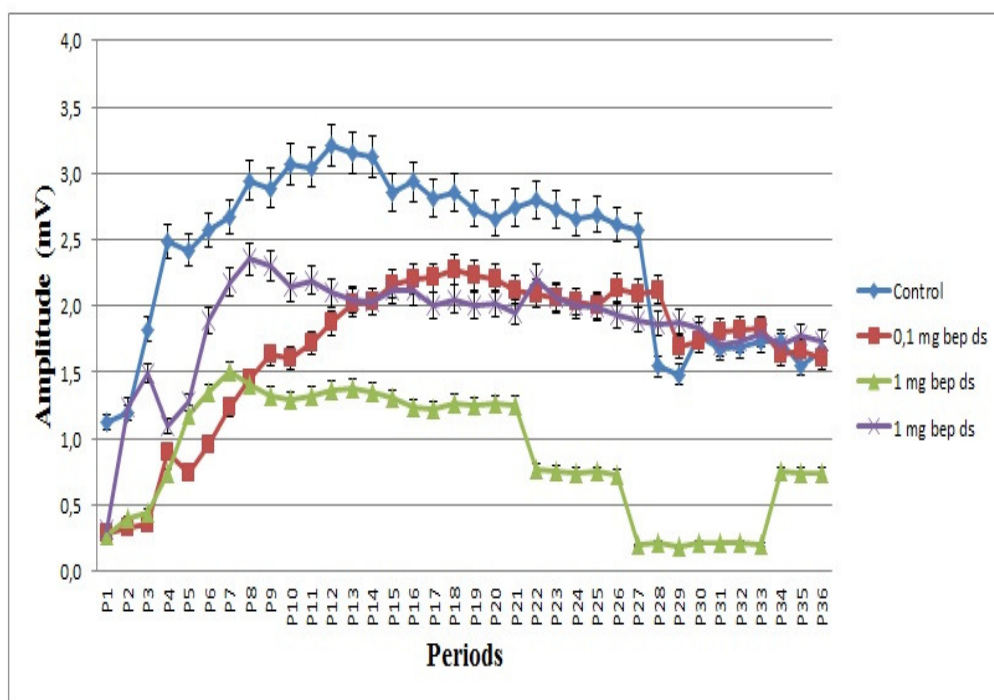


Figure 3.48. Maximum amplitude of spike wave during 180 minutes ECoG records in bepridil during seizure groups.

3.10. The effect of P1075 on the spike wave amplitude occurred during epileptic seizure

Amplitude of waves in 0,1 mg/kg dose of P1075 which was applied before seizure was significantly smaller than the control group ($P < 0,05$). The dose of 0,5 mg/kg P1075 decreased spike wave amplitude between 3. and 13. periods compared to control group ($p < 0,05$). Application of P1075 during seizure at all three doses, decreased spike wave amplitude starting from 3. period ($p < 0,05$).

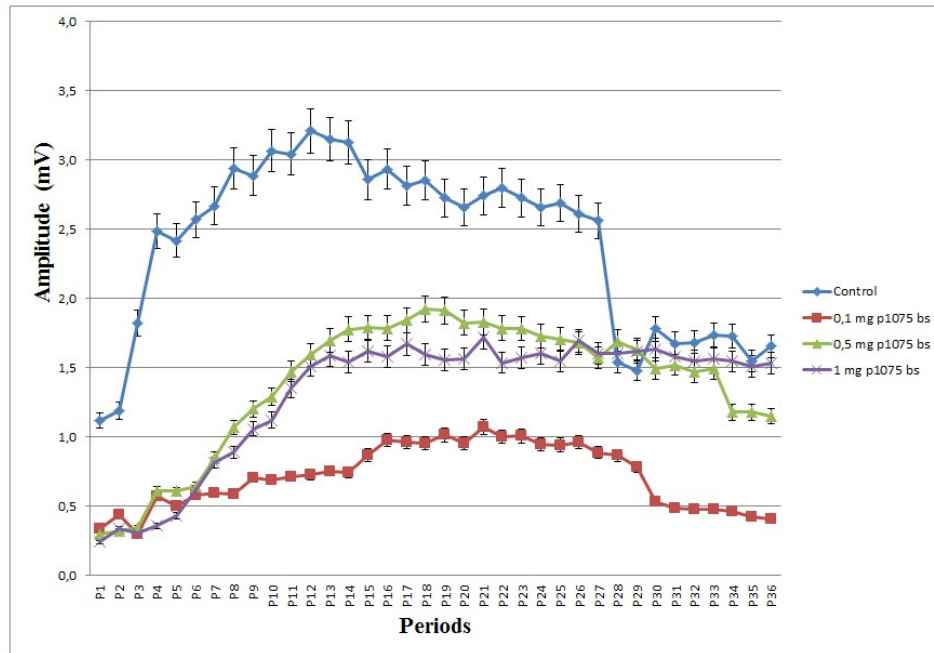


Figure 3.49. Maximum amplitude of spike wave during 180 minutes ECoG records in P1075 before seizure groups.

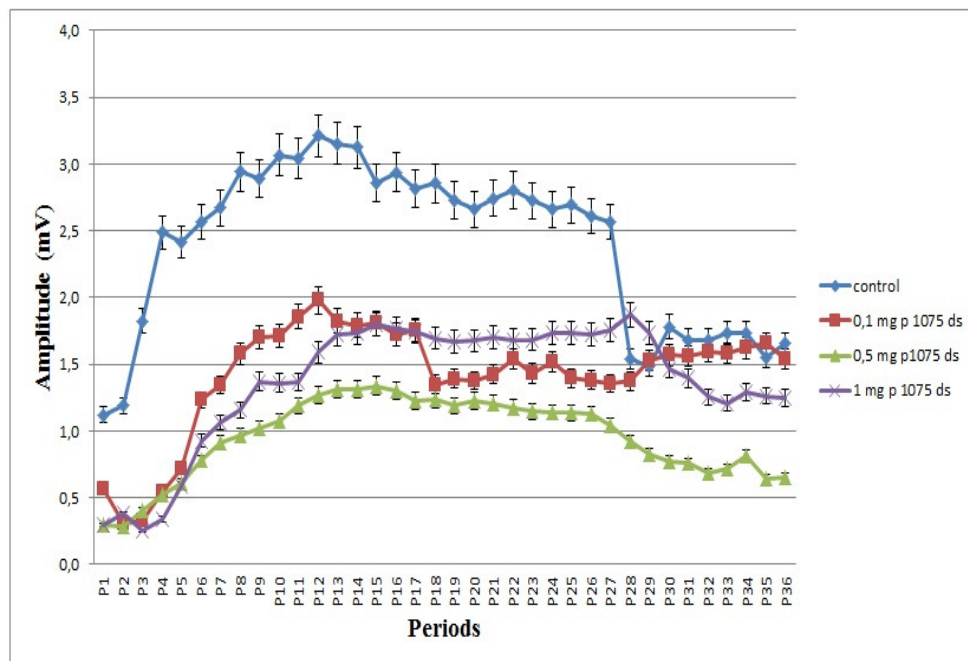


Figure 3.50. Maximum amplitude of spike wave during 180 minutes ECoG records in P1075 during seizure groups.

3.11. The effect of HMR 1098 on the spike wave amplitude occurred during epileptic seizure

HMR 1098 applied before seizure significantly decreased spike wave amplitude just after the 3. period compared to control group whereas HMR 1098 applied during seizure significantly decreased spike wave amplitude just after the 9. period compared to control group ($p < 0,05$).

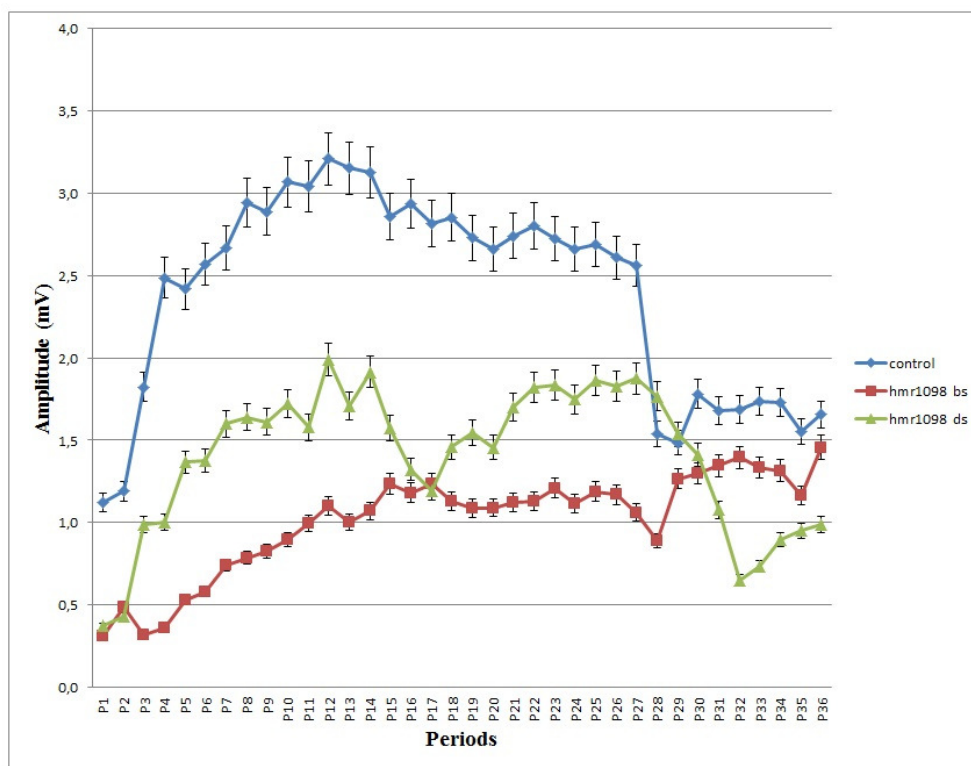


Figure 3.51. Maximum amplitude of spike wave during 180 minutes ECoG records in HMR 1098 before and during seizure groups.

3.12. The effect of HMR 1098 on the spike wave amplitude occurred during epileptic seizure

5HD applied both during seizure and before seizure had no significant effect in terms of spike wave amplitude ($p>0,05$).

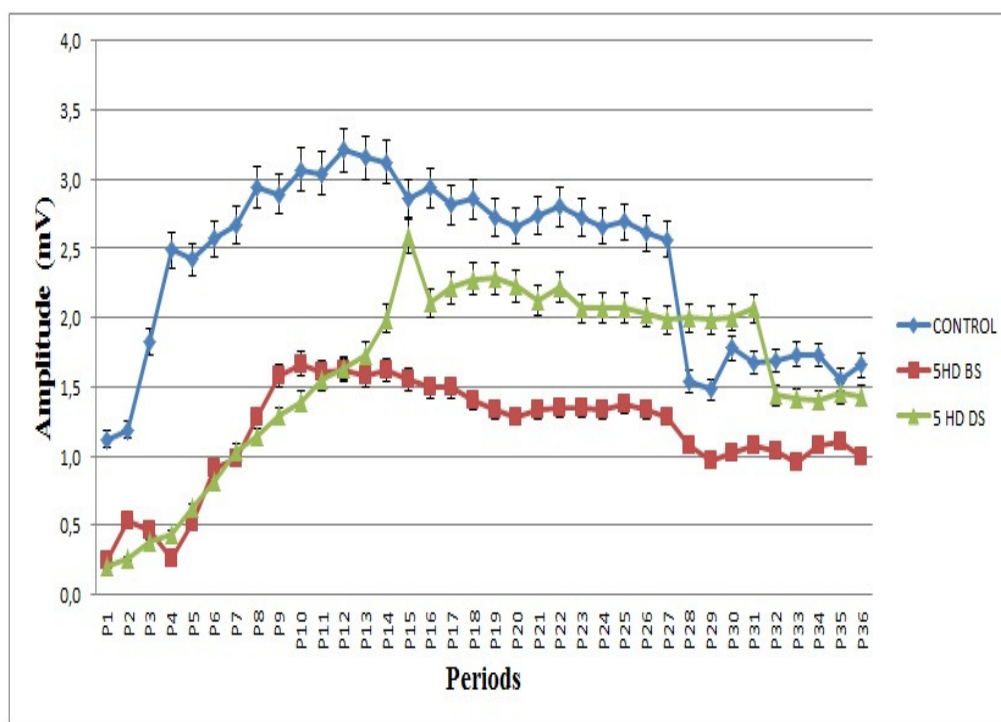


Figure 3.52. Maximum amplitude of spike wave during 180 minutes ECoG records in 5HD before and during seizure groups.

3.13. Epileptic activity between 0-180 min in terms of spike wave amplitude

The record was taken and the wave amplitude was evaluated with 5 min interval.

3.13.1. The amplitude of spike wave between 0-5 minutes in all groups (Period 1).

The spike wave amplitudes in all groups in period 1 were significantly smaller than the control group (Table.3.37, Figure.3. 53.) ($p < 0,05$).

Table 3.37. Spike wave amplitude (mV) in 0-5 min (Data are means $\pm$ SE *P < 0.05: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	1,12	$\pm$	0,64	
0,1mg BEP BS	6	0,30	$\pm$	0,04*	0,05
1mg BEP BS	6	0,23	$\pm$	0,03*	0,03
10 mg BEP BS	8	0,25	$\pm$	0,04*	0,01
0,1mg BEP DS	6	0,28	$\pm$	0,05*	0,04
1 mg BEP DS	6	0,27	$\pm$	0,05*	0,04
10 mg BEP DS	8	0,31	$\pm$	0,03*	0,03
0,1 mg P1075 BS	6	0,34	$\pm$	0,05*	0,08
0,5 mg P1075 BS	6	0,30	$\pm$	0,02*	0,05
1 mg P1075 BS	6	0,24	$\pm$	0,03*	0,03
0,1 mg P1075 DS	8	0,57	$\pm$	0,16*	0,04
0,5mg P1075 DS	6	0,30	$\pm$	0,03*	0,05
1 mg P1075 DS	8	0,29	$\pm$	0,06*	0,02
5HD BS	8	0,24	$\pm$	0,05*	0,01
5HD DS	10	0,21	$\pm$	0,03*	0,00
HMR 1098 DS	8	0,26	$\pm$	0,04*	0,02
HMR 1098 BS	8	0,24	$\pm$	0,03*	0,01

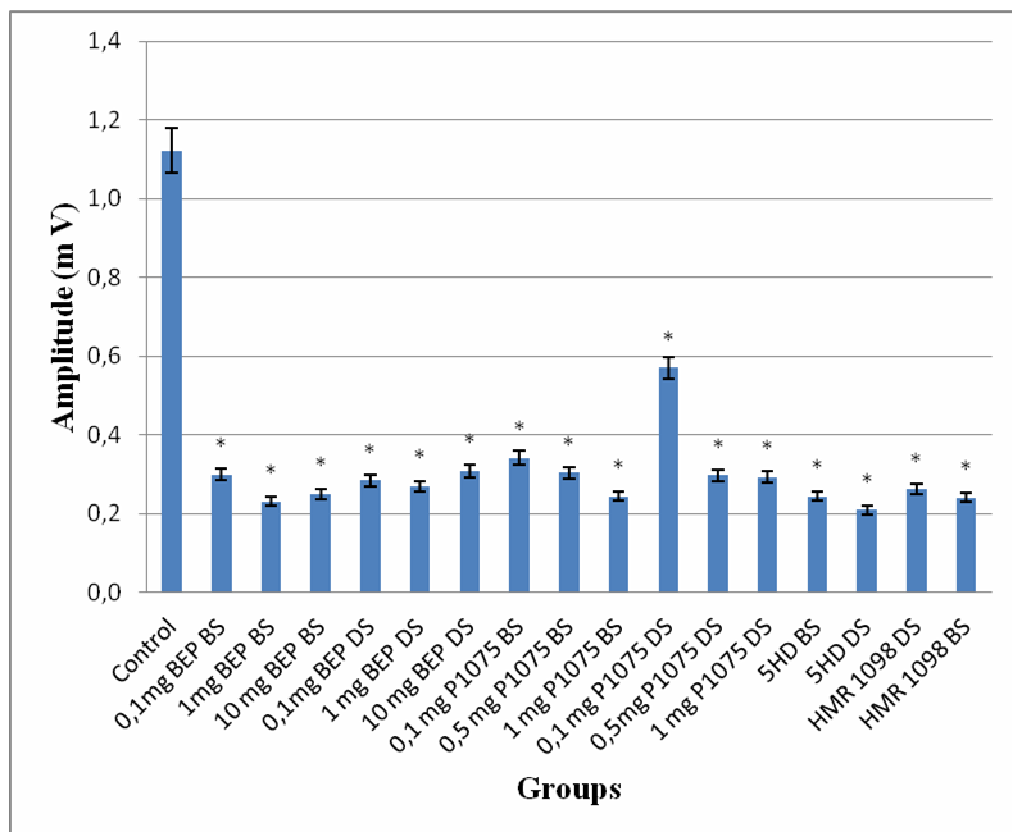


Figure 3.53. Spike wave amplitudes in mV obtained from recordings in 0-5 min (Period 1) (Data are means $\pm$ SE *P < 0.05: Compared to control) .

3.13.2. The amplitude of spike wave between 5-10 minutes in all groups (Period 2).

The spike wave amplitudes in groups 10 mg/kg Bepridil BS; 0,1 mg P1075 DS; 0,5 mg P1075 DS; 0,1 mg P1075 DS; 0,5mg P1075 DS; 5 HD DS ve HMR 1098 BS between 5–10 minutes time interval were significantly smaller than the control group (Table.3.38, Fig.3.54.) ($p < 0,05$).

Table 3.38. Spike wave amplitude (mV) obtained from 5 to 10 minute recordings and P values in all groups (Data are means $\pm$ SE *P < 0.05: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	1,19	$\pm$	0,73	
0,1mg BEP BS	6	0,36	$\pm$	0,04	0,06
1mg BEP BS	6	0,67	$\pm$	0,16	0,24
10 mg BEP BS	8	0,34	$\pm$	0,08*	0,04
0,1mg BEP DS	6	0,32	$\pm$	0,05*	0,05
1 mg BEP DS	6	0,39	$\pm$	0,08	0,07
10 mg BEP DS	8	1,24	$\pm$	0,76	0,90
0,1 mg P1075 BS	6	0,44	$\pm$	0,11	0,10
0,5 mg P1075 BS	6	0,32	$\pm$	0,03*	0,05
1 mg P1075 BS	6	0,34	$\pm$	0,06*	0,06
0,1 mg P1075 DS	8	0,31	$\pm$	0,08*	0,03
0,5mg P1075 DS	6	0,28	$\pm$	0,06*	0,04
1 mg P1075 DS	8	0,38	$\pm$	0,11*	0,05
5HD BS	8	0,53	$\pm$	0,21	0,11
5HD DS	10	0,26	$\pm$	0,05*	0,02
HMR 1098 DS	8	0,44	$\pm$	0,13	0,07
HMR 1098 BS	8	0,21	$\pm$	0,05*	0,02

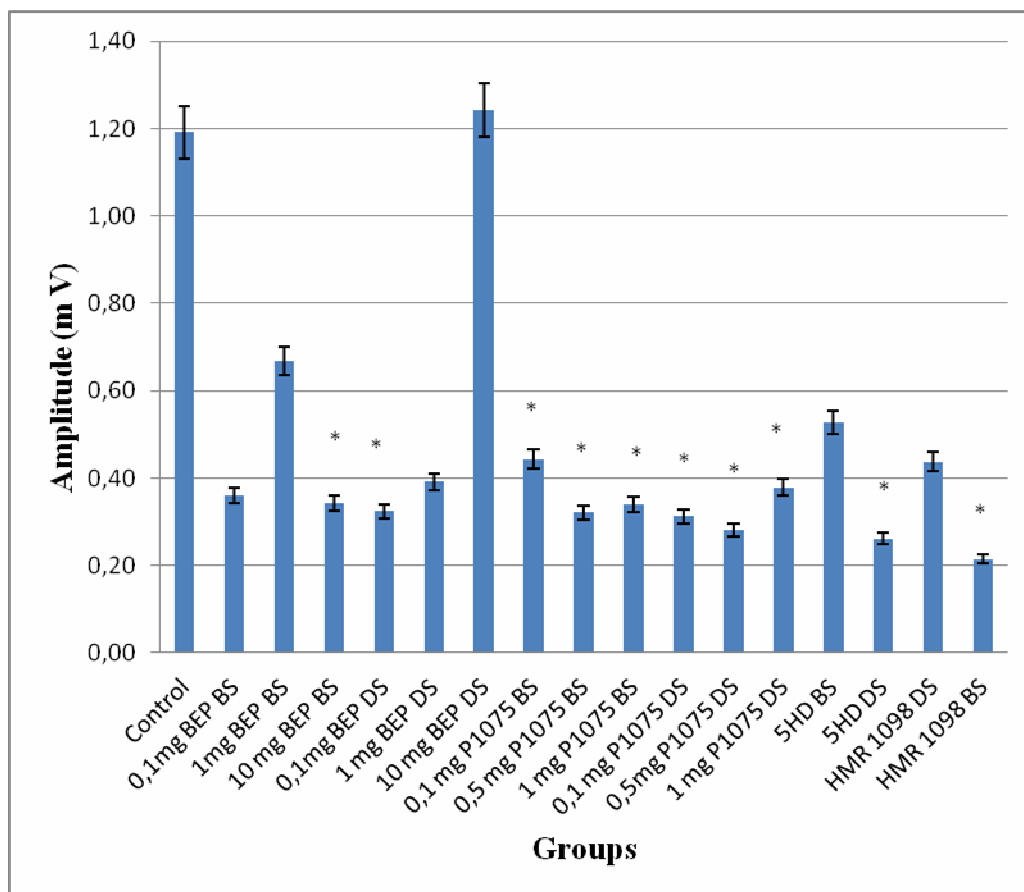


Figure 3.54. Spike wave amplitudes in mVolts obtained from 5 to 10 minutes recordings (Period 2). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.13.3. The amplitude of spike wave between 10-15 minutes in all groups (Period 3)

The spike wave amplitudes in groups 1mg BEP BS; 10 mg BEP DS between 10 - 15 minutes time interval are significantly smaller than the control group ($p < 0,05$) (Table.3.39., Fig.3.55).

Table 3.39. Spike wave amplitude (mV) obtained from 5 to 10 minute recordings and P values in all groups. (Data are means $\pm$ SE *P < 0.05: Compared to control)

Groups	N	Mean $\pm$ SE			p Value
Control	9	1,82	$\pm$	0,82	
0,1mg BEP BS	6	0,43	$\pm$	0,14*	0,04
1mg BEP BS	6	1,21	$\pm$	0,43	0,20
10 mg BEP BS	8	0,29	$\pm$	0,04*	0,01
0,1mg BEP DS	6	0,35	$\pm$	0,06*	0,03
1 mg BEP DS	6	0,44	$\pm$	0,17*	0,05
10 mg BEP DS	8	1,49	$\pm$	0,72	0,45
0,1 mg P1075 BS	6	0,30	$\pm$	0,06*	0,02
0,5 mg P1075 BS	6	0,34	$\pm$	0,04*	0,02
1 mg P1075 BS	6	0,31	$\pm$	0,04*	0,02
0,1 mg P1075 DS	8	0,32	$\pm$	0,09*	0,01
0,5mg P1075 DS	6	0,41	$\pm$	0,13*	0,04
1 mg P1075 DS	8	0,26	$\pm$	0,05*	0,01
5HD BS	8	0,47	$\pm$	0,22*	0,03
5HD DS	10	0,38	$\pm$	0,07*	0,01
HMR 1098 DS	8	0,32	$\pm$	0,08*	0,01
HMR 1098 BS	8	0,35	$\pm$	0,13*	0,01

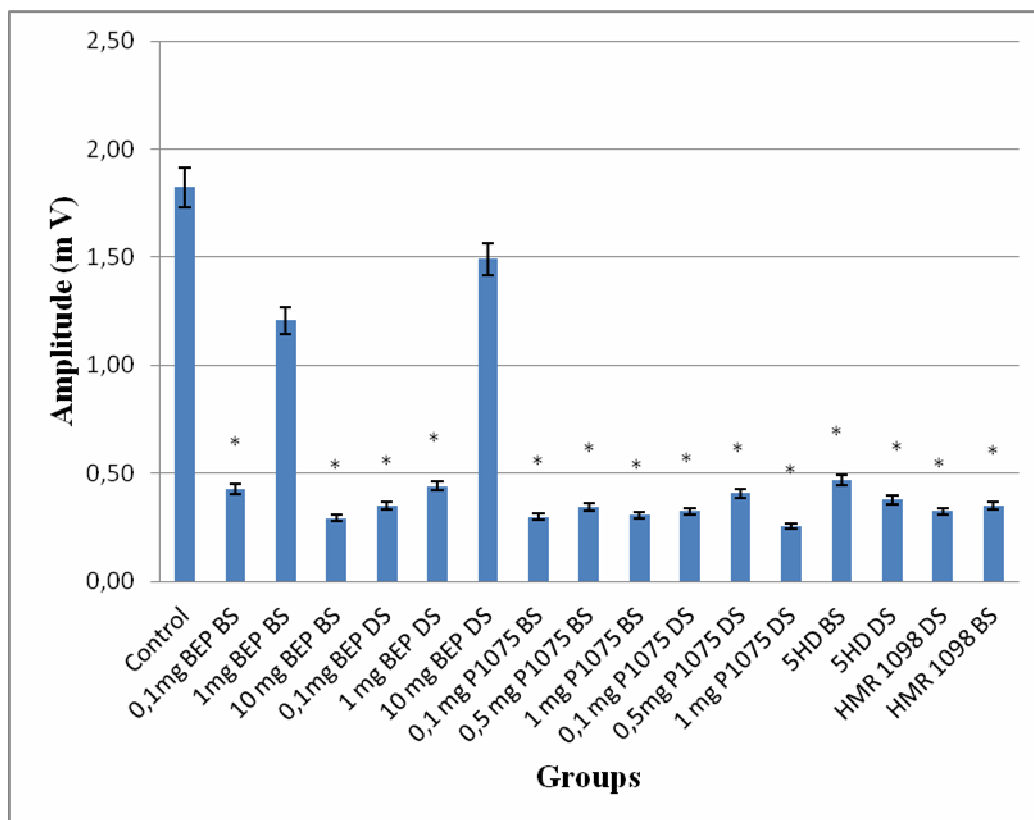


Figure 3.55. Spike wave amplitudes in mVolts obtained from 10 to 15 minutes recordings (Period 3). (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.13.4. The amplitude of spike wave between 15-20 minutes in all groups (Period 4)

The spike wave amplitudes in all groups between 15 -20 minutes time interval are significantly smaller than the control group ($p < 0,05$) (Table.3.40, Fig.3.56.).

Table 3.40. Spike wave amplitude (mV) obtained from 10 to 15 minute recordings and P values in all groups. (Data are means $\pm$ SE *P < 0.05: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	2,49	$\pm$	0,95	
0,1mg BEP BS	6	0,67	$\pm$	0,18*	0,00
1mg BEP BS	6	1,22	$\pm$	0,54*	0,01
10 mg BEP BS	8	0,27	$\pm$	0,04*	0,00
0,1mg BEP DS	6	0,89	$\pm$	0,40*	0,02
1 mg BEP DS	6	0,74	$\pm$	0,26*	0,01
10 mg BEP DS	8	1,10	$\pm$	0,35*	0,03
0,1 mg P1075 BS	6	0,57	$\pm$	0,18*	0,00
0,5 mg P1075 BS	6	0,62	$\pm$	0,16*	0,00
1 mg P1075 BS	6	0,36	$\pm$	0,09*	0,00
0,1 mg P1075 DS	8	0,54	$\pm$	0,16*	0,00
0,5mg P1075 DS	6	0,52	$\pm$	0,08*	0,00
1 mg P1075 DS	8	0,34	$\pm$	0,08*	0,00
5HD BS	8	0,26	$\pm$	0,06*	0,00
5HD DS	10	0,44	$\pm$	0,12*	0,00
HMR 1098 DS	8	0,33	$\pm$	0,07*	0,00
HMR 1098 BS	8	0,58	$\pm$	0,18*	0,00

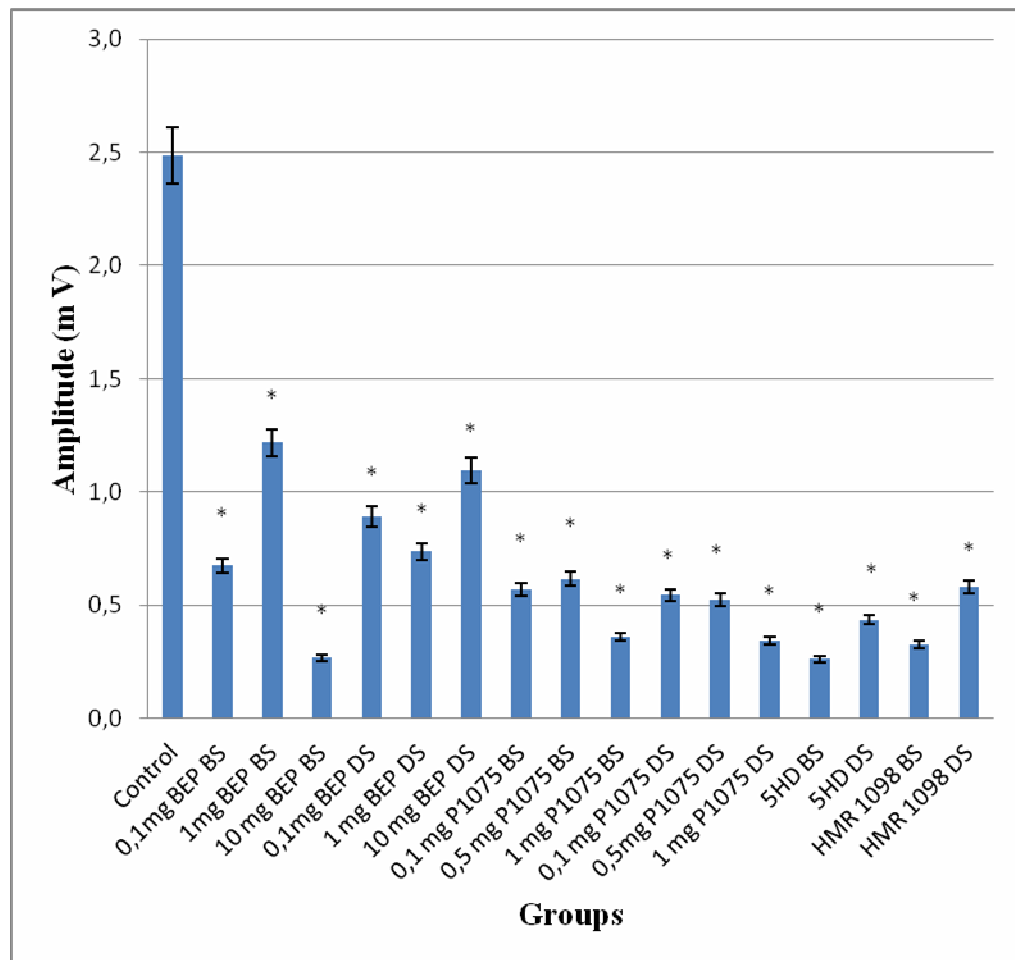


Figure 3.56. Spike wave amplitudes in mVolts obtained from 15 to 20 minutes recordings (Period 4) (Data are means $\pm$ SE *P<0.05: Compared to control).

3.13.5. The amplitude of spike wave between 20-25 minutes in all groups (Period 5)

The spike wave amplitudes in groups 1 mg Bep bs between 20 -25 minutes time interval are significantly smaller than the control group ($p < 0,05$) (Table.3.41, Fig.3.57.).

Table 3.41. Spike wave amplitude (mV) obtained from 20 to 25 minute recordings and P values in all groups. (Data are means $\pm$ SE *P < 0.05: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	2,42		0,88	
0,1mg BEP BS	6	0,67	$\pm$	0,29*	0,01
1mg BEP BS	6	1,82	$\pm$	0,51	0,24
10 mg BEP BS	8	0,56	$\pm$	0,15*	0,00
0,1mg BEP DS	6	0,74	$\pm$	0,13*	0,01
1 mg BEP DS	6	1,18	$\pm$	0,27*	0,01
10 mg BEP DS	8	1,27	$\pm$	0,48*	0,01
0,1 mg P1075 BS	6	0,51	$\pm$	0,17*	0,00
0,5 mg P1075 BS	6	0,61	$\pm$	0,28*	0,01
1 mg P1075 BS	6	0,43	$\pm$	0,19*	0,00
0,1 mg P1075 DS	8	0,72	$\pm$	0,18*	0,00
0,5mg P1075 DS	6	0,61	$\pm$	0,15*	0,01
1 mg P1075 DS	8	0,59	$\pm$	0,22*	0,00
5HD BS	8	0,51	$\pm$	0,13*	0,00
5HD DS	10	0,62	$\pm$	0,11*	0,00
HMR 1098 DS	8	0,41	$\pm$	0,10*	0,00
HMR 1098 BS	8	0,78	$\pm$	0,22*	0,01

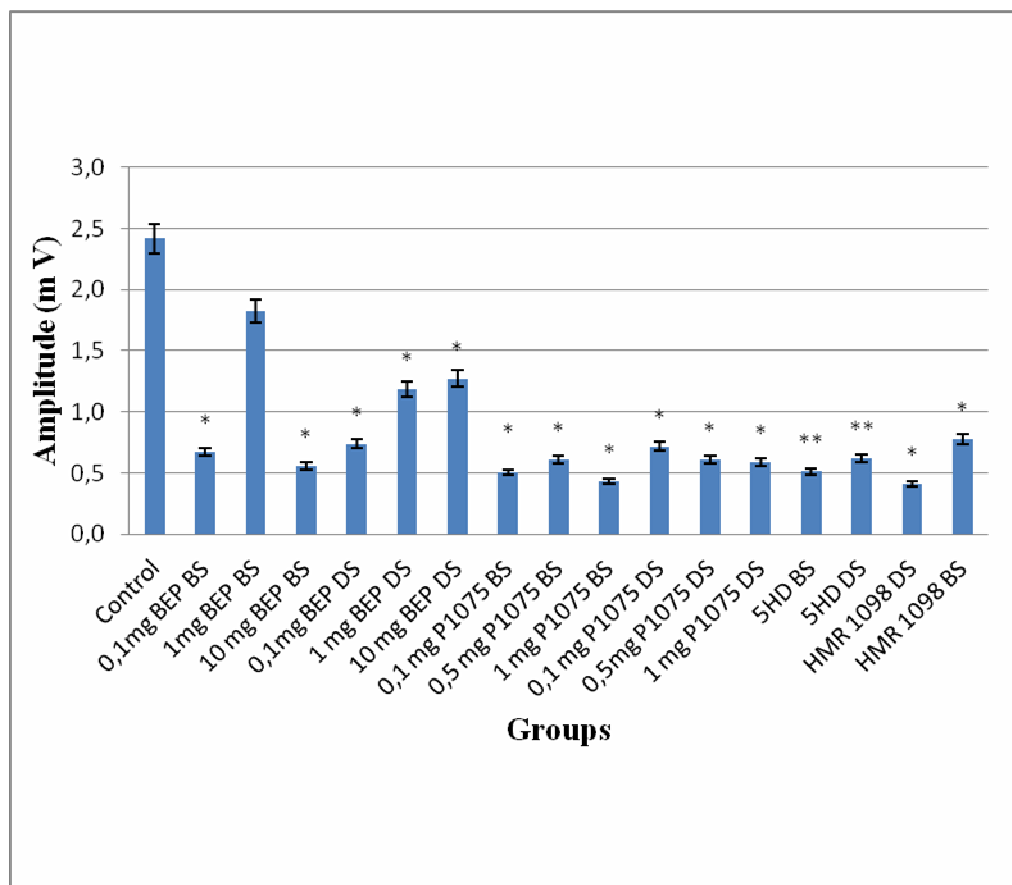


Figure 3.57. Spike wave amplitudes (results mean $\pm$ SE) in mVolts obtained from 20 to 25 minutes recordings (Period 5) (Data are means $\pm$ SE *P<0.05: Compared to control).

3.13.6. The amplitude of spike wave between 25-30 minutes in all groups (Period 6)

The spike wave amplitudes in groups 1mg BEP BS ; 10 mg BEP DS; between 25-30 minutes time interval are significantly smaller than control group ($p < 0,05$) (Table.3.42., Fig.3.58.).

Table 3.42. Spike wave amplitude (mV) obtained from 25 to 30 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	2,57	$\pm$	1,01	
0,1mg BEP BS	6	1,27	$\pm$	0,31*	0,02
1mg BEP BS	6	2,11	$\pm$	0,51	0,42
10 mg BEP BS	8	0,66	$\pm$	0,18*	0,00
0,1mg BEP DS	6	0,95	$\pm$	0,20*	0,05
1 mg BEP DS	6	1,34	$\pm$	0,30*	0,03
10 mg BEP DS	8	1,89	$\pm$	0,43	0,19
0,1 mg P1075 BS	6	0,58	$\pm$	0,18*	0,01
0,5 mg P1075 BS	6	0,64	$\pm$	0,31*	0,01
1 mg P1075 BS	6	0,62	$\pm$	0,24*	0,01
0,1 mg P1075 DS	8	1,23	$\pm$	0,27*	0,01
0,5mg P1075 DS	6	0,78	$\pm$	0,16*	0,02
1 mg P1075 DS	8	0,93	$\pm$	0,27*	0,02
5HD BS	8	0,91	$\pm$	0,18*	0,02
5HD DS	10	0,82	$\pm$	0,17*	0,01
HMR 1098 DS	8	0,51	$\pm$	0,13*	0,00
HMR 1098 BS	8	0,84	$\pm$	0,28*	0,01

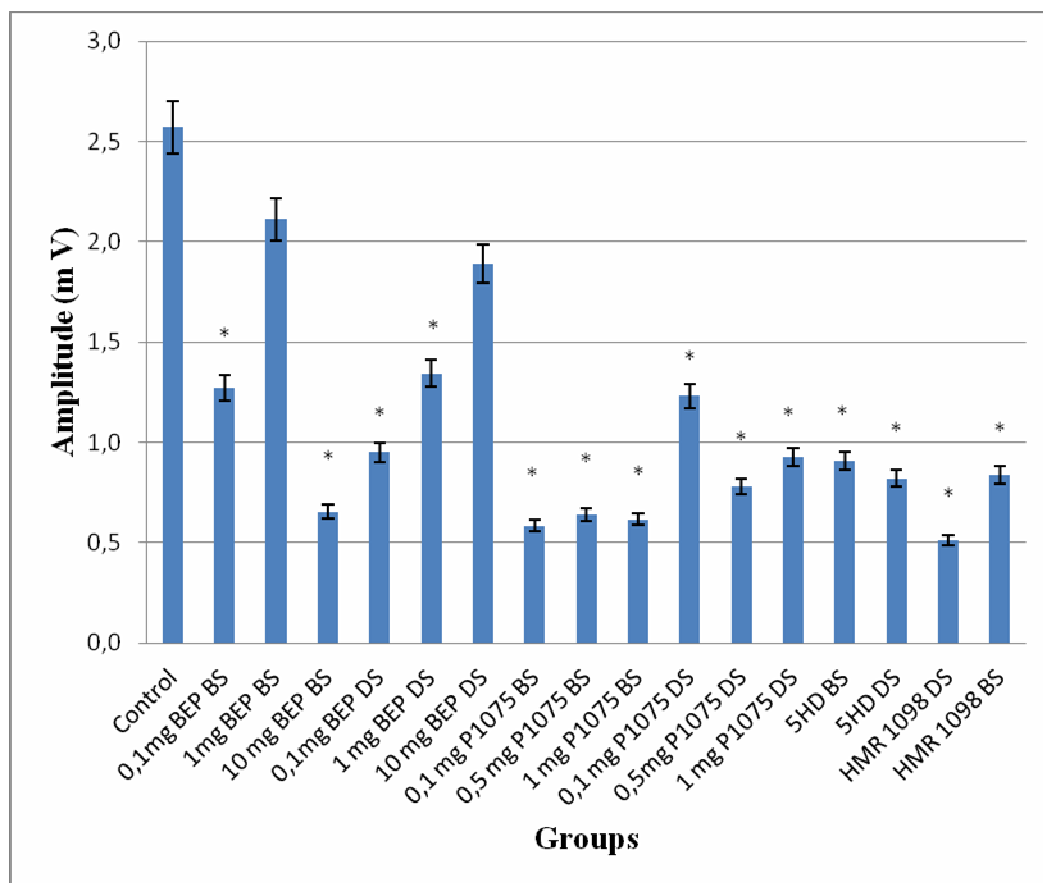


Figure 3.58. Spike wave amplitudes in mVolts obtained from 25 to 30 minutes recordings (Period 6). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.7. The amplitude of spike wave between 35-40 minutes in all groups
(Period 7)**

The spike wave amplitudes in groups 0,1mg BEP BS, 1mg BEP BS, 10 mg BEP DS, between 30-35 minutes time interval are significantly smaller than control group ($p < 0,05$) (Table 3.43., Fig. 3.59.).

Table 3.43. Spike wave amplitude (mV) obtained from 30 to 35 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	2,67	$\pm$	0,93	
0,1mg BEP BS	6	1,62	$\pm$	0,34	0,07
1mg BEP BS	6	2,26	$\pm$	0,53	0,48
10 mg BEP BS	8	0,82	$\pm$	0,21*	0,01
0,1mg BEP DS	6	1,23	$\pm$	0,30*	0,01
1 mg BEP DS	6	1,50	$\pm$	0,31*	0,04
10 mg BEP DS	8	2,18	$\pm$	0,52	0,36
0,1 mg P1075 BS	6	0,59	$\pm$	0,17*	0,01
0,5 mg P1075 BS	6	0,85	$\pm$	0,33*	0,02
1 mg P1075 BS	6	0,81	$\pm$	0,36*	0,02
0,1 mg P1075 DS	8	1,34	$\pm$	0,25*	0,01
0,5mg P1075 DS	6	0,92	$\pm$	0,19*	0,03
1 mg P1075 DS	8	1,06	$\pm$	0,30*	0,04
5HD BS	8	0,98	$\pm$	0,24*	0,02
5HD DS	10	1,04	$\pm$	0,21*	0,02
HMR 1098 DS	8	0,68	$\pm$	0,18*	0,00
HMR 1098 BS	8	1,01	$\pm$	0,33*	0,03

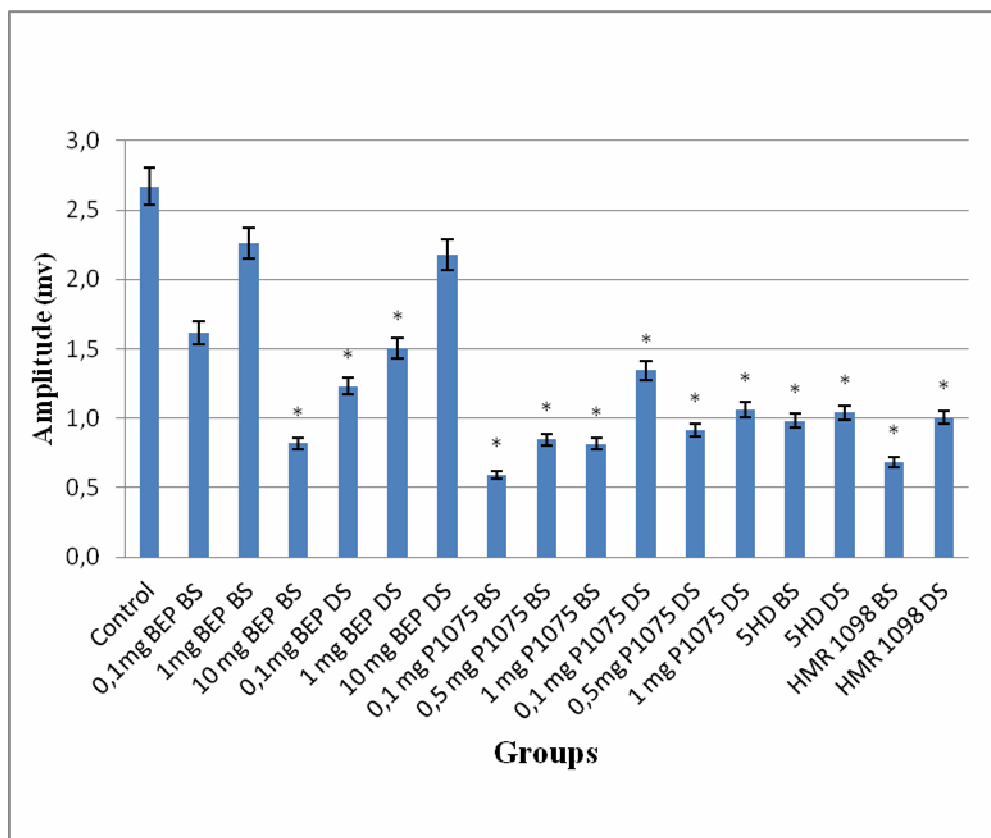


Figure 3.59. Spike wave amplitudes in mVolts obtained from 30 To 35 minutes recordings (Period 7) (Data are means $\pm$ SE *P < 0.05: Compared to control).

3.13.8. The amplitude of spike wave between 35 to 40 minutes in all groups (Period 8)

The spike wave amplitudes in groups 0,1mg BEP BS, 1mg BEP BS, 10 mg BEP DS, between 35-40 minutes time interval are significantly smaller than control group ($p < 0,05$) (Table.3.44, Fig.3.60).

Table 3.44. Spike wave amplitude (mV) obtained from 35 to 40 minute recordings and P values in all groups. (Data are means $\pm$ SE *P < 0.05: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	2,94	$\pm$	0,88	
0,1mg BEP BS	6	1,82	$\pm$	0,47	0,08
1mg BEP BS	6	2,32	$\pm$	0,52	0,33
10 mg BEP BS	8	0,89	$\pm$	0,17*	0,01
0,1mg BEP DS	6	1,44	$\pm$	0,23*	0,02
1 mg BEP DS	6	1,41	$\pm$	0,35*	0,01
10 mg BEP DS	8	2,35	$\pm$	0,50	0,32
0,1 mg P1075 BS	6	0,59	$\pm$	0,15*	0,00
0,5 mg P1075 BS	6	1,07	$\pm$	0,36*	0,04
1 mg P1075 BS	6	0,89	$\pm$	0,38*	0,02
0,1 mg P1075 DS	8	1,58	$\pm$	0,32*	0,02
0,5mg P1075 DS	6	0,97	$\pm$	0,20*	0,03
1 mg P1075 DS	8	1,16	$\pm$	0,29*	0,03
5HD BS	8	1,29	$\pm$	0,31*	0,06
5HD DS	10	1,14	$\pm$	0,30*	0,02
HMR 1098 DS	8	1,29	$\pm$	0,67*	0,06
HMR 1098 BS	8	1,23	$\pm$	0,37*	0,05

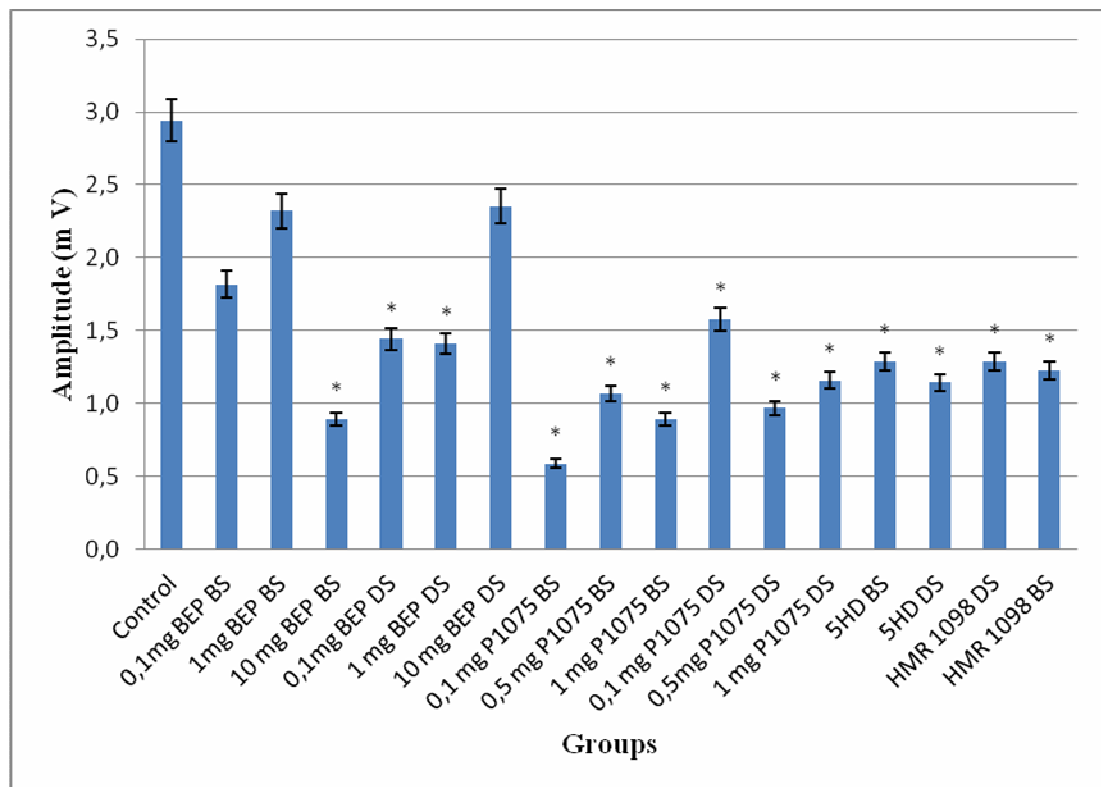


Figure 3.60. Spike wave amplitudes in mV obtained from 35 to40 minutes recordings (Period 8) (Data are means $\pm$ SE *P<0.05: Compared to control).

3.13.9. The amplitude of spike wave between 40 to 45 minutes in all groups (Period 9)

The spike wave amplitudes in groups 0,1mg BEP BS, 1mg BEP BS, 10 mg BEP DS, between 40-45 minutes time interval are significantly smaller than the control group ($p < 0,05$) (Table.3.45., Fig.).

Table 3.45. Spike wave amplitude (mV) obtained from 40 to 45 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	2,89	$\pm 0,88$		
0,1mg BEP BS	6	2,04	$\pm 0,47$		0,154
1mg BEP BS	6	2,37	$\pm 0,52$		0,383
10 mg BEP BS	8	1,04	$\pm 0,17$	*	0,001
0,1mg BEP DS	6	1,63	$\pm 0,23$	*	0,036
1 mg BEP DS	6	1,33	$\pm 0,35$	*	0,01
10 mg BEP DS	8	2,30	$\pm 0,50$		0,287
0,1 mg P1075 BS	6	0,71	$\pm 0,15$	*	0,000
0,5 mg P1075 BS	6	1,20	$\pm 0,36$	*	0,005
1 mg P1075 BS	6	1,06	$\pm 0,38$	*	0,003
0,1 mg P1075 DS	8	1,70	$\pm 0,32$	*	0,032
0,5mg P1075 DS	6	1,03	$\pm 0,20$	*	0,002
1 mg P1075 DS	8	1,37	$\pm 0,29$	*	0,007
5HD BS	8	1,58	$\pm 0,31$	*	0,019
5HD DS	10	1,29	$\pm 0,30$	*	0,003
HMR 1098 DS	8	0,73	$\pm 0,67$	*	0,000
HMR 1098 BS	8	1,54	$\pm 0,37$	*	0,015

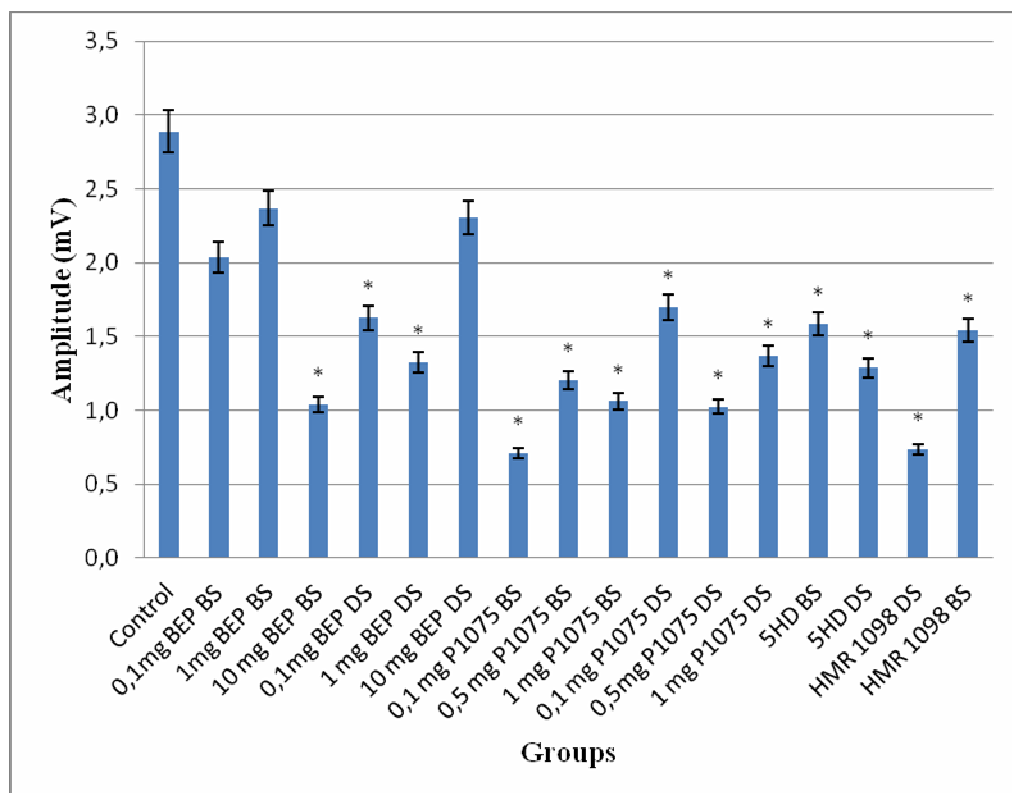


Figure 3.61. Spike wave amplitudes in mVolts obtained from 40 to 45 minutes recordings (Period 9). (Data are means $\pm$ SE *P < 0.05: Compared to control).

**3.13.10. The amplitude of spike wave between 45 to 50 minutes in all groups
(Period 10)**

The spike wave amplitudes in groups 0,1mg BEP BS, 1mg BEP BS, 10 mg BEP DS, between 40-45 minutes time interval were significantly smaller than the control group ($p < 0,05$) (Table.3.45, Fig.3.62.).

Table 3.45. Spike wave amplitude (mV) values obtained from 45 to 50 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	3,07	$\pm$	0,84	
0,1mg BEP BS	6	2,08	$\pm$	0,40	0,103
1mg BEP BS	6	2,30	$\pm$	0,58	0,208
10 mg BEP BS	8	1,19	$\pm$	0,20*	0,001
0,1mg BEP DS	6	1,60	$\pm$	0,33*	0,017
1 mg BEP DS	6	1,29	$\pm$	0,40*	0,004
10 mg BEP DS	8	2,14	$\pm$	0,49	0,098
0,1 mg P1075 BS	6	0,69	$\pm$	0,17*	0,000
0,5 mg P1075 BS	6	1,29	$\pm$	0,32*	0,004
1 mg P1075 BS	6	1,12	$\pm$	0,40*	0,002
0,1 mg P1075 DS	8	1,72	$\pm$	0,32*	0,017
0,5mg P1075 DS	6	1,07	$\pm$	0,18*	0,001
1 mg P1075 DS	8	1,36	$\pm$	0,31*	0,003
5HD BS	8	1,67	$\pm$	0,34*	0,013
5HD DS	10	1,40	$\pm$	0,39*	0,002
HMR 1098 DS	8	0,75	$\pm$	0,18*	0,000
HMR 1098 BS	8	1,54	$\pm$	0,34*	0,007

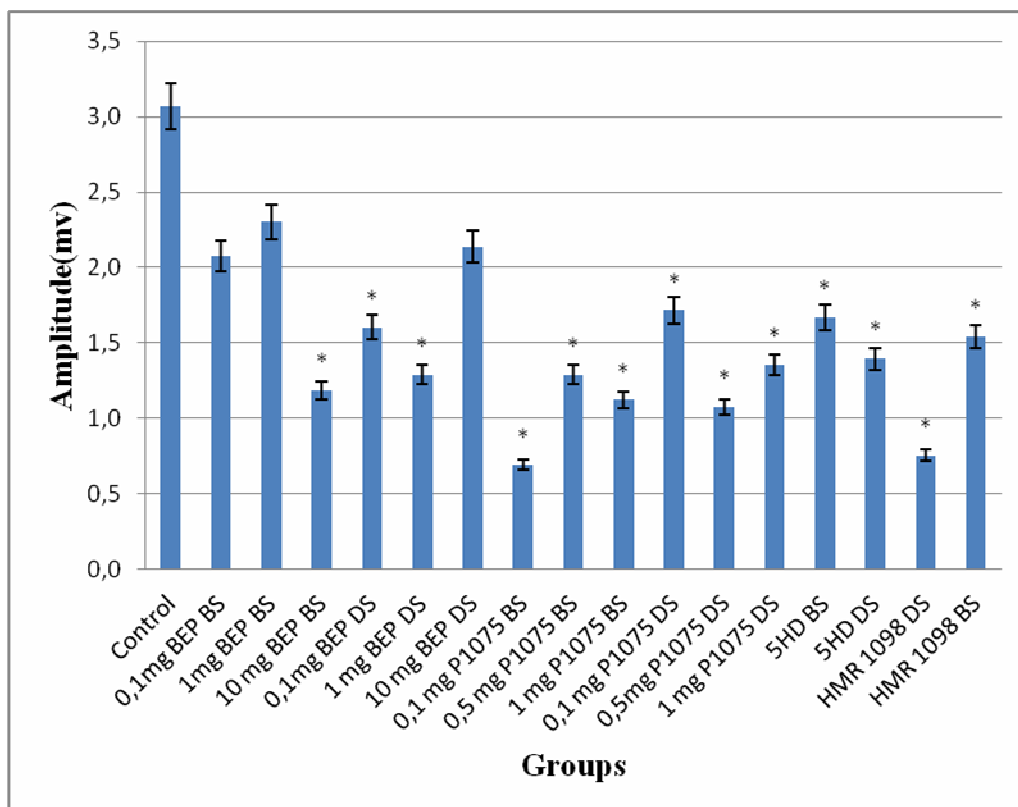


Figure 3.62. Spike wave amplitudes in mV obtained from 45 to 50 minutes recordings (Period 10). (Data are mean $\pm$ SE *P<0.05: Compared to control).

**3.13.11. The amplitude of spike wave between 50 to 55 minutes in all groups
(Period 11)**

The spike wave amplitudes in groups 0,1mg BEP BS; 1mg BEP BS; 10 mg BEP DS, between 50-55 minutes time interval are significantly smaller than the control group ($p < 0,05$) (Table.3.46, Fig.3.63)

Table 3.46. Spike wave amplitude (mV) obtained from 50 to 55 minute recordings and P values in all groups. (Data are means $\pm$ SE *P < 0.05: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	3,04	$\pm$	0,80	
0,1mg BEP BS	6	2,15	$\pm$	0,39	0,14
1mg BEP BS	6	2,38	$\pm$	0,59	0,27
10 mg BEP BS	8	1,19	$\pm$	0,17*	0,01
0,1mg BEP DS	6	1,72	$\pm$	0,32*	0,03
1 mg BEP DS	6	1,33	$\pm$	0,40*	0,05
10 mg BEP DS	8	2,19	$\pm$	0,48	0,12
0,1 mg P1075 BS	6	0,72	$\pm$	0,19*	0,00
0,5 mg P1075 BS	6	1,48	$\pm$	0,30*	0,01
1 mg P1075 BS	6	1,35	$\pm$	0,40*	0,06
0,1 mg P1075 DS	8	1,86	$\pm$	0,37*	0,03
0,5mg P1075 DS	6	1,19	$\pm$	0,16*	0,03
1 mg P1075 DS	8	1,37	$\pm$	0,34*	0,03
5HD BS	8	1,61	$\pm$	0,35*	0,01
5HD DS	10	1,55	$\pm$	0,43*	0,05
HMR 1098 DS	8	0,82	$\pm$	0,17*	0,00
HMR 1098 BS	8	1,32	$\pm$	0,36*	0,03

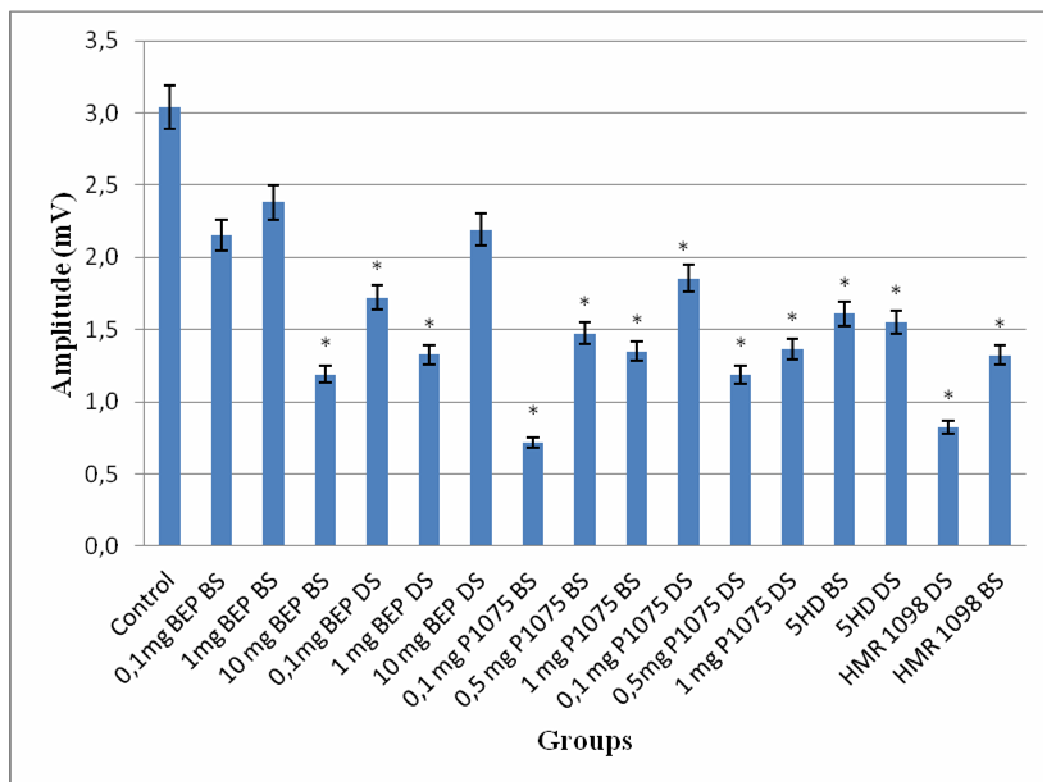


Figure 3.63. Spike wave amplitudes in mV obtained from 50 to 55 minutes recordings (Period 11). (Data are means $\pm$ SE *P<0.05: Compared to control).

3.13.12. The amplitude of spike wave between 55 to 60 minutes in all groups (Period 12).

The spike wave amplitudes in groups 1mg BEP BS between 55-60. minutes time interval are significantly smaller than control group ($p < 0,05$) (Table.3.47, Fig.3.64.).

Table 3.47. Spike wave amplitude (mV) obtained from 55 to 60 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	3,21	$\pm$	0,82	
0,1mg BEP BS	6	1,94	$\pm$	0,37*	0,03
1mg BEP BS	6	2,37	$\pm$	0,56	0,16
10 mg BEP BS	8	1,22	$\pm$	0,20*	0,01
0,1mg BEP DS	6	1,87	$\pm$	0,27*	0,02
1 mg BEP DS	6	1,37	$\pm$	0,44*	0,03
10 mg BEP DS	8	2,10	$\pm$	0,47*	0,04
0,1 mg P1075 BS	6	0,73	$\pm$	0,19*	0,00
0,5 mg P1075 BS	6	1,59	$\pm$	0,30*	0,09
1 mg P1075 BS	6	1,51	$\pm$	0,39*	0,06
0,1 mg P1075 DS	8	1,98	$\pm$	0,39*	0,02
0,5mg P1075 DS	6	1,27	$\pm$	0,15*	0,02
1 mg P1075 DS	8	1,59	$\pm$	0,32*	0,04
5HD BS	8	1,62	$\pm$	0,34*	0,05
5HD DS	10	1,64	$\pm$	0,44*	0,04
HMR 1098 DS	8	0,87	$\pm$	0,18*	0,00
HMR 1098 BS	8	1,28	$\pm$	0,33*	0,01

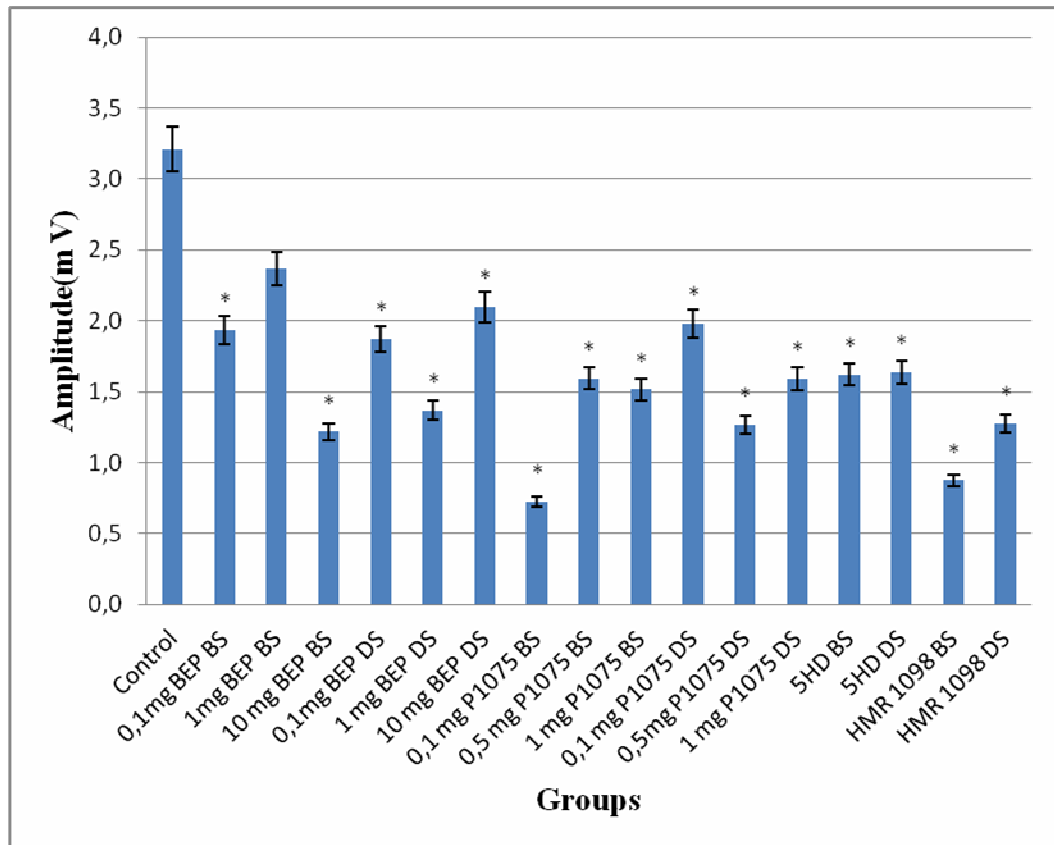


Figure.3.64. Spike wave amplitudes in mV obtained from 55 to 60 minutes recordings (Period 12) (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.13. The amplitude of spike wave between 60 to 65 minutes in all groups
(Period 13)**

The spike wave amplitudes in groups 1mg BEP BS, 1mg BEP DS, 0,1mg BEP DS between 55–60 minutes time interval are significantly smaller than control group ($p < 0,05$) (Table.3.48, Fig.3.65.).

Table 3.48. Spike wave amplitude (mV) obtained from 60 to 65 minute recordings and P values in all groups (Data are means $\pm$ S E *P < 0.05: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	3,15	$\pm$	0,80	
0,1mg BEP BS	6	1,99	$\pm$	0,35	0,05
1mg BEP BS	6	2,42	$\pm$	0,55	0,22
10 mg BEP BS	8	1,32	$\pm$	0,21*	0,01
0,1mg BEP DS	6	2,02	$\pm$	0,31	0,06
1 mg BEP DS	6	1,38	$\pm$	0,45*	0,04
10 mg BEP DS	8	2,05	$\pm$	0,41*	0,05
0,1 mg P1075 BS	6	0,76	$\pm$	0,16*	0,00
0,5 mg P1075 BS	6	1,70	$\pm$	0,29*	0,01
1 mg P1075 BS	6	1,59	$\pm$	0,47*	0,01
0,1 mg P1075 DS	8	1,82	$\pm$	0,35*	0,01
0,5mg P1075 DS	6	1,32	$\pm$	0,14*	0,03
1 mg P1075 DS	8	1,72	$\pm$	0,29*	0,01
5HD BS	8	1,58	$\pm$	0,36*	0,06
5HD DS	10	1,73	$\pm$	0,49*	0,08
HMR 1098 DS	8	0,84	$\pm$	0,20*	0,00
HMR 1098 BS	8	1,23	$\pm$	0,34*	0,01

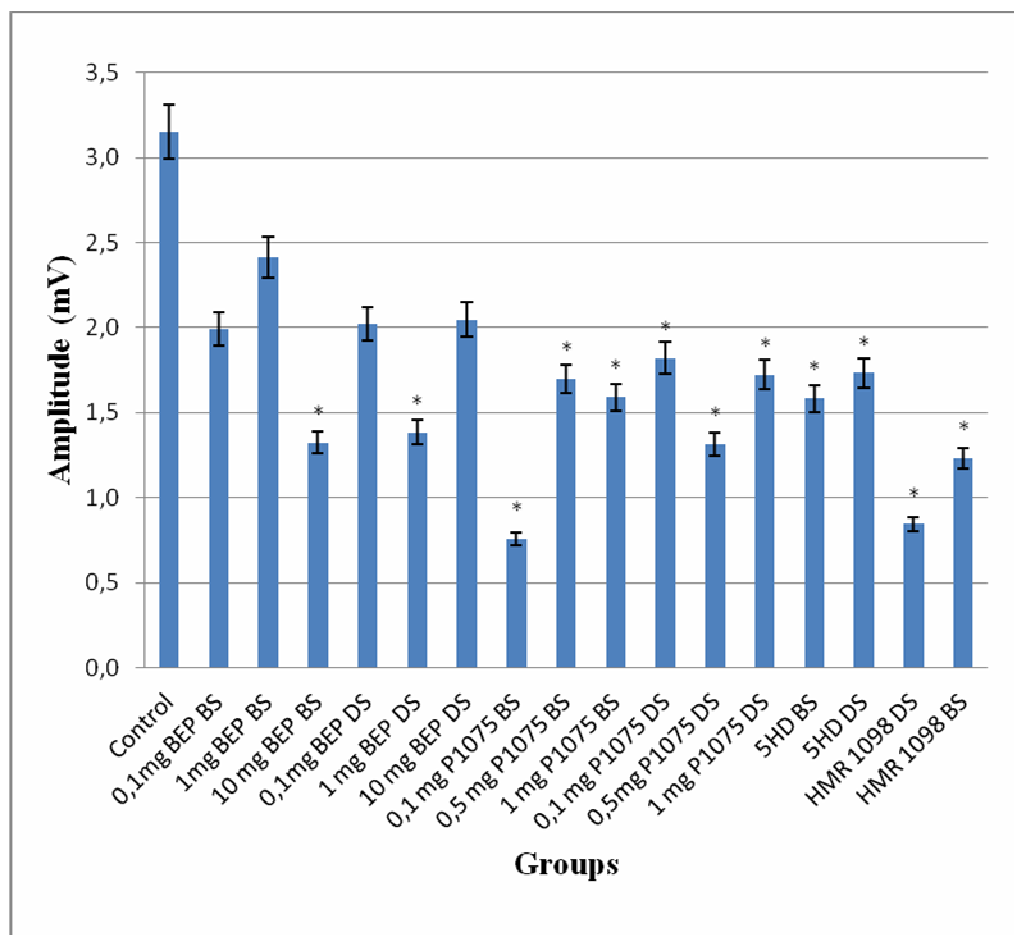


Figure 3.65. Spike wave amplitudes in mVolts obtained from 55 to 60 minutes recordings (Period 13). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.14. The amplitude of spike wave between 65 to 70 minutes in all groups
(Period 14)**

The spike wave amplitudes in groups 10 mg BEP BS; 1 mg BEP DS; 1 mg BEP DS; 0,5 mg P1075 BS ; 1 mg P1075 BS; 0,1 mg P1075 DS; 0,5mg P1075 DS; 1 mg P1075 DS; 5HD BS; 5HD DS; HMR 1098 DS; HMR 1098 BS between 65-70 minutes time interval are significantly smaller than the control group ($p < 0,05$) (Table.3.49., Fig.3.66).

Table 3.49. Spike wave amplitude (mV) obtained from 65 to 70 minute recordings and P values for all groups (Data are means $\pm$ SE *P < 0.05: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	3,13	$\pm$	0,81	
0,1mg BEP BS	6	2,04	$\pm$	0,31	0,08
1mg BEP BS	6	2,47	$\pm$	0,58	0,29
10 mg BEP BS	8	1,61	$\pm$	0,31*	0,01
0,1mg BEP DS	6	2,03	$\pm$	0,37	0,08
1 mg BEP DS	6	1,35	$\pm$	0,45*	0,05
10 mg BEP DS	8	2,03	$\pm$	0,43	0,05
0,1 mg P1075 BS	6	0,74	$\pm$	0,16*	0,00
0,5 mg P1075 BS	6	1,78	$\pm$	0,28*	0,03
1 mg P1075 BS	6	1,55	$\pm$	0,49*	0,01
0,1 mg P1075 DS	8	1,79	$\pm$	0,37*	0,02
0,5mg P1075 DS	6	1,31	$\pm$	0,13*	0,04
1 mg P1075 DS	8	1,73	$\pm$	0,29*	0,01
5HD BS	8	1,62	$\pm$	0,34*	0,01
5HD DS	10	1,99	$\pm$	0,51*	0,04
HMR 1098 DS	8	0,91	$\pm$	0,22*	0,00
HMR 1098 BS	8	1,34	$\pm$	0,35*	0,02

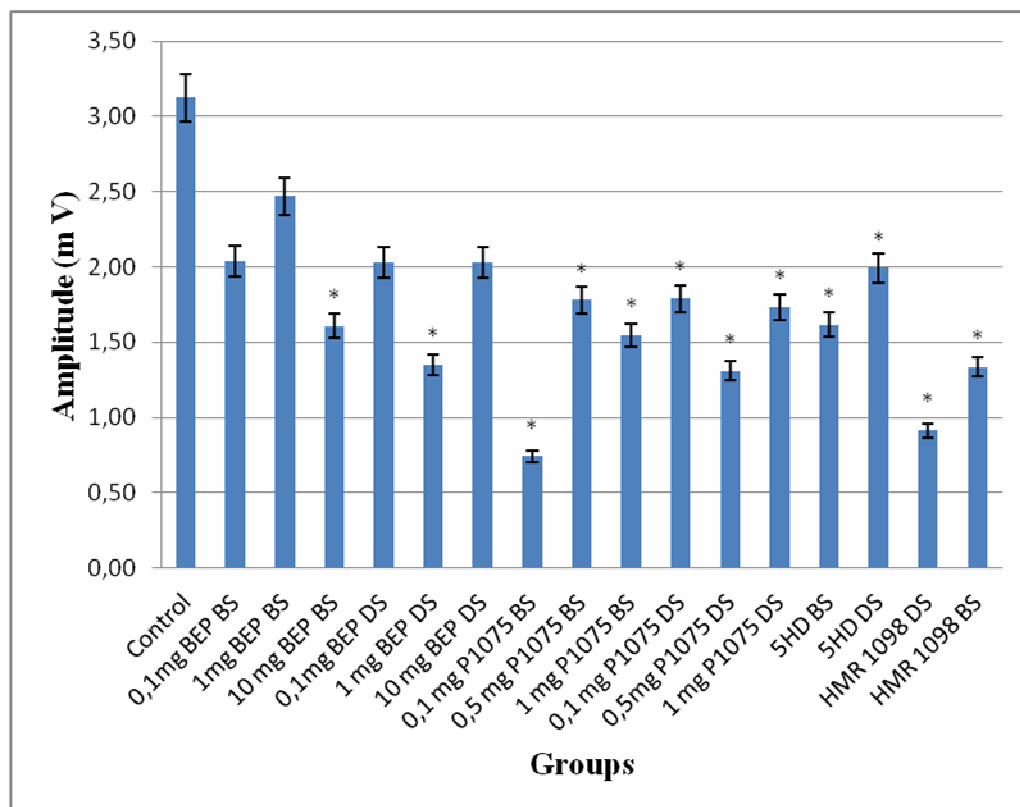


Figure 3.66. Spike wave amplitudes in mVolts obtained from 65 to 70 minutes recordings (Period 14). (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

**3.13.15. The amplitude of spike wave between 70 to 75 minutes in all groups
(Period 15)**

The spike wave amplitudes in groups 10 mg BEP BS; 1 mg BEP DS; 0,1 mg P1075 BS; 0,5mg P1075 DS; 5HD BS; HMR 1098 DSHMR 1098 BS between 70 -75 minutes time interval were significantly smaller than control group ($p<0,05$) (Table.3.50, Fig.3.67.).

Table 3.50. Spike wave amplitude (mV) obtained from 70 to 75 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P<0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	2,86	$\pm$	0,82	
0,1mg BEP BS	6	1,88	$\pm$	0,31	0,15
1mg BEP BS	6	2,54	$\pm$	0,60	0,64
10 mg BEP BS	8	1,51	$\pm$	0,23*	0,03
0,1mg BEP DS	6	2,16	$\pm$	0,41	0,31
1 mg BEP DS	6	1,30	$\pm$	0,40*	0,02
10 mg BEP DS	8	2,12	$\pm$	0,44	0,24
0,1 mg P1075 BS	6	0,87	$\pm$	0,24*	0,04
0,5 mg P1075 BS	6	1,79	$\pm$	0,27	0,12
1 mg P1075 BS	6	1,62	$\pm$	0,52	0,07
0,1 mg P1075 DS	8	1,81	$\pm$	0,37	0,09
0,5mg P1075 DS	6	1,34	$\pm$	0,13*	0,02
1 mg P1075 DS	8	1,80	$\pm$	0,27	0,09
5HD BS	8	1,55	$\pm$	0,34*	0,04
5HD DS	10	2,59	$\pm$	0,78	0,65
HMR 1098 DS	8	0,88	$\pm$	0,20*	0,02
HMR 1098 BS	8	1,43	$\pm$	0,31*	0,02

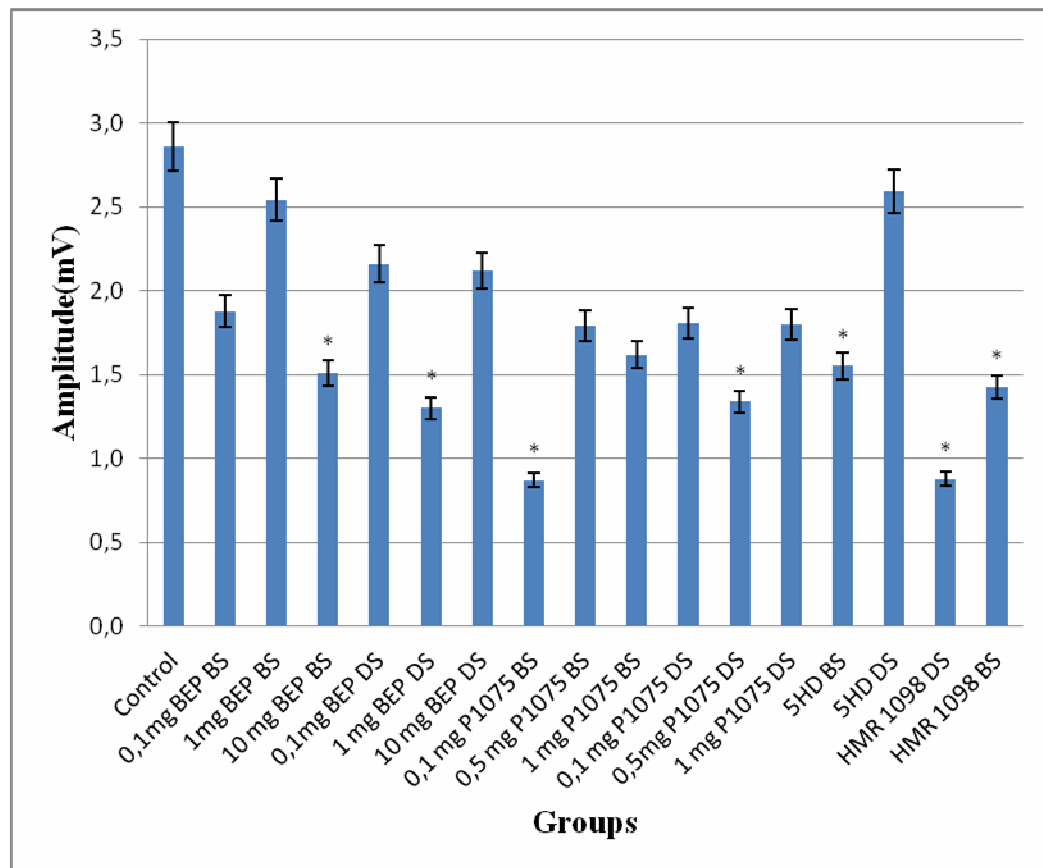


Figure 3.67. Spike wave amplitudes in mV obtained from 70 to 75 minutes recordings (Period 15). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.16. The amplitude of spike wave between 75 To 80 minutes in all groups
(Period 16)**

The spike wave amplitudes in groups 10 mg BEP BS; 1 mg BEP DS; 0,1 mg P1075 BS; 0,1 mg P1075 BS; 0,5 mg P1075 BS; 1 mg P1075 BS; 0,1 mg P1075 DS; 0,5mg P1075 DS; 1 mg P1075 DS; 5HD BSHMR 1098 DS; HMR 1098 BS between 75-80 minutes time interval are significantly smaller than control group ($p < 0,05$) (Table.3.51, Fig.3.68.).

Table 3.51. Spike wave amplitude (mV) obtained from 75 to 80 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P < 0,05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	2,94	$\pm$	0,83	
0,1mg BEP BS	6	1,93	$\pm$	0,33	0,09
1mg BEP BS	6	2,35	$\pm$	0,47	0,32
10 mg BEP BS	8	1,42	$\pm$	0,21*	0,07
0,1mg BEP DS	6	2,20	$\pm$	0,40	0,22
1 mg BEP DS	6	1,24	$\pm$	0,37*	0,06
10 mg BEP DS	8	2,11	$\pm$	0,44	0,13
0,1 mg P1075 BS	6	0,98	$\pm$	0,22*	0,01
0,5 mg P1075 BS	6	1,79	$\pm$	0,24	0,05
1 mg P1075 BS	6	1,58	$\pm$	0,50*	0,02
0,1 mg P1075 DS	8	1,72	$\pm$	0,33*	0,03
0,5mg P1075 DS	6	1,30	$\pm$	0,12*	0,07
1 mg P1075 DS	8	1,76	$\pm$	0,27*	0,03
5HD BS	8	1,49	$\pm$	0,35*	0,01
5HD DS	10	2,10	$\pm$	0,50	0,11
HMR 1098 DS	8	1,11	$\pm$	0,21*	0,01
HMR 1098 BS	8	0,98	$\pm$	0,26*	0,01

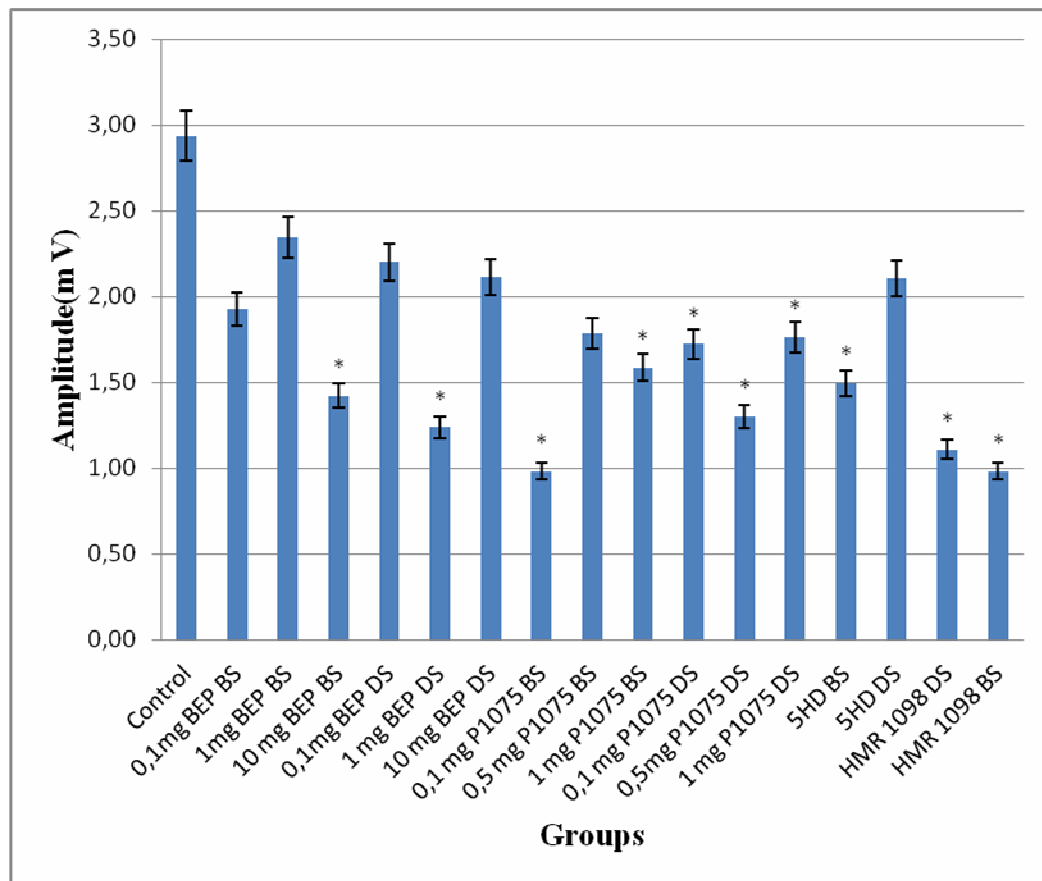


Figure 3.68. Spike wave amplitudes in mV obtained from 75 to 80 minutes recordings (Period 16). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.17. The amplitude of spike wave between 80 to 85 minutes in all groups
(Period 17)**

The spike wave amplitudes in groups 10 mg BEP BS; 1 mg BEP DS; 0,1 mg P1075 BS; 0,5 mg P1075 BS; 1 mg P1075 BS; 0,1 mg P1075 DS; 0,5mg P1075 DS; 1 mg P1075 DS; 5HD BS; HMR 1098 DS; HMR 1098 BS between 80-85 minutes time interval are significantly smaller than the control group ($p < 0,05$) (Table.3.52, Fig.3.69.)

Table 3.52. Spike wave amplitude (mV) obtained from 80 to 85 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	2,82	$\pm$	0,80	
0,1mg BEP BS	6	1,80	$\pm$	0,31	0,09
1mg BEP BS	6	2,41	$\pm$	0,48	0,51
10 mg BEP BS	8	1,38	$\pm$	0,18*	0,01
0,1mg BEP DS	6	2,21	$\pm$	0,42	0,32
1 mg BEP DS	6	1,22	$\pm$	0,37*	0,01
10 mg BEP DS	8	2,00	$\pm$	0,40*	0,15
0,1 mg P1075 BS	6	0,96	$\pm$	0,20*	0,03
0,5 mg P1075 BS	6	1,84	$\pm$	0,22	0,11
1 mg P1075 BS	6	1,67	$\pm$	0,51	0,06
0,1 mg P1075 DS	8	1,75	$\pm$	0,51	0,06
0,5mg P1075 DS	6	1,23	$\pm$	0,11*	0,01
1 mg P1075 DS	8	1,75	$\pm$	0,25*	0,06
5HD BS	8	1,50	$\pm$	0,34*	0,02
5HD DS	10	2,21	$\pm$	0,54	0,26
HMR 1098 DS	8	1,05	$\pm$	0,19*	0,02
HMR 1098 BS	8	0,98	$\pm$	0,24*	0,01

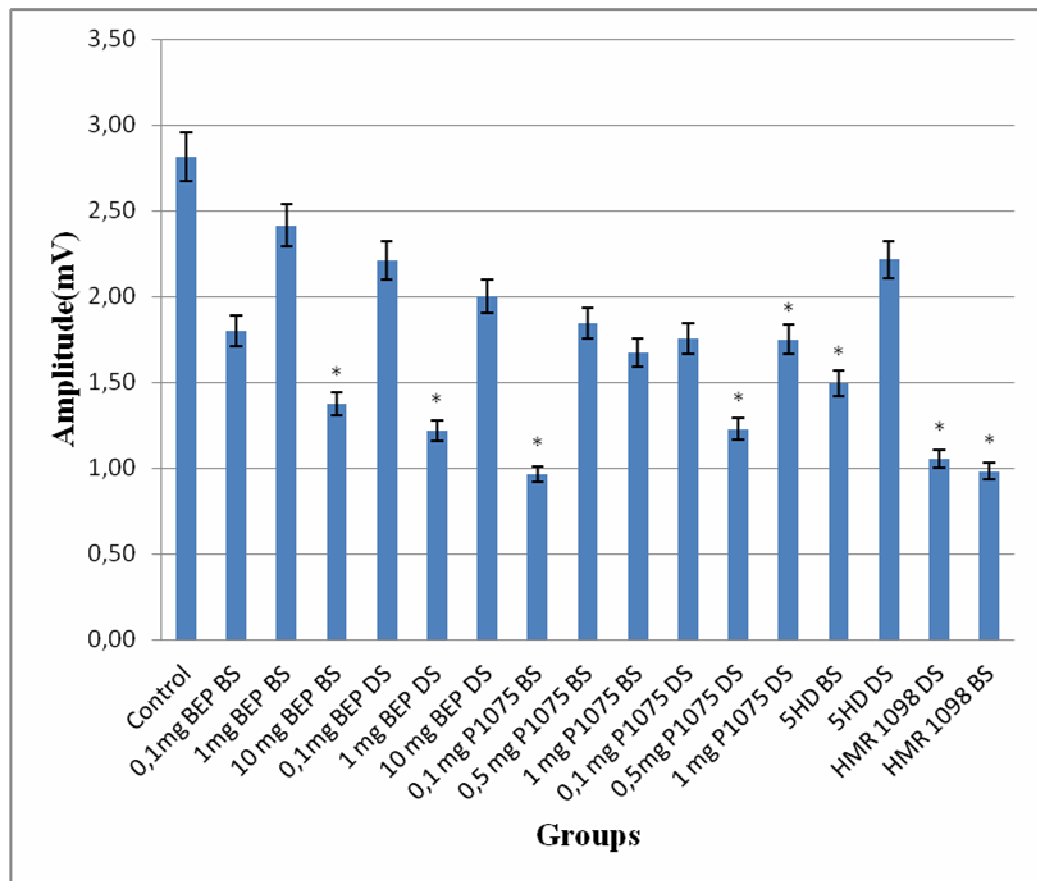


Figure 3.69. Spike wave amplitudes in mVolts obtained from 80 To 85 minutes recordings (Period 17). (Data are means $\pm$ SE *P < 0.05: Compared to control).

**3.13.18. The amplitude of spike wave between 85 to 90 minutes in all groups
(Period 18)**

The spike wave amplitudes in groups 10 mg BEP BS ,1 mg BEP DS, 0,1 mg P1075 BS ,1 mg P1075 BS, 0,1 mg P1075 DS, 0,5mg P1075 DS, 1 mg P1075 DS, 5HD BSHMR 1098 DS, HMR 1098 BS between 85.-90. minutes time interval are significantly smaller than the control group ($p < 0,05$) (Table.3.53, Fig.3.70.).

Table 3.53. Spike wave amplitude (mV) obtained from 85 to 90 minute recordings and P values in all groups. (Data are means $\pm$ SE *P < 0.05: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	2,85	$\pm$	0,84	
0,1mg BEP BS	6	1,24	$\pm$	0,40	0,09
1mg BEP BS	6	2,34	$\pm$	0,51	0,40
10 mg BEP BS	8	1,48	$\pm$	0,16*	0,01
0,1mg BEP DS	6	2,27	$\pm$	0,31	0,34
1 mg BEP DS	6	1,26	$\pm$	0,38*	0,01
10 mg BEP DS	8	2,05	$\pm$	0,40	0,15
0,1 mg P1075 BS	6	0,96	$\pm$	0,20*	0,02
0,5 mg P1075 BS	6	1,92	$\pm$	0,24	0,13
1 mg P1075 BS	6	1,60	$\pm$	0,50*	0,04
0,1 mg P1075 DS	8	1,35	$\pm$	0,43*	0,09
0,5mg P1075 DS	6	1,24	$\pm$	0,12*	0,09
1 mg P1075 DS	8	1,70	$\pm$	0,23*	0,04
5HD BS	8	1,40	$\pm$	0,30*	0,01
5HD DS	10	2,28	$\pm$	0,55	0,28
HMR 1098 DS	8	1,07	$\pm$	0,15*	0,02
HMR 1098 BS	8	0,98	$\pm$	0,24*	0,01

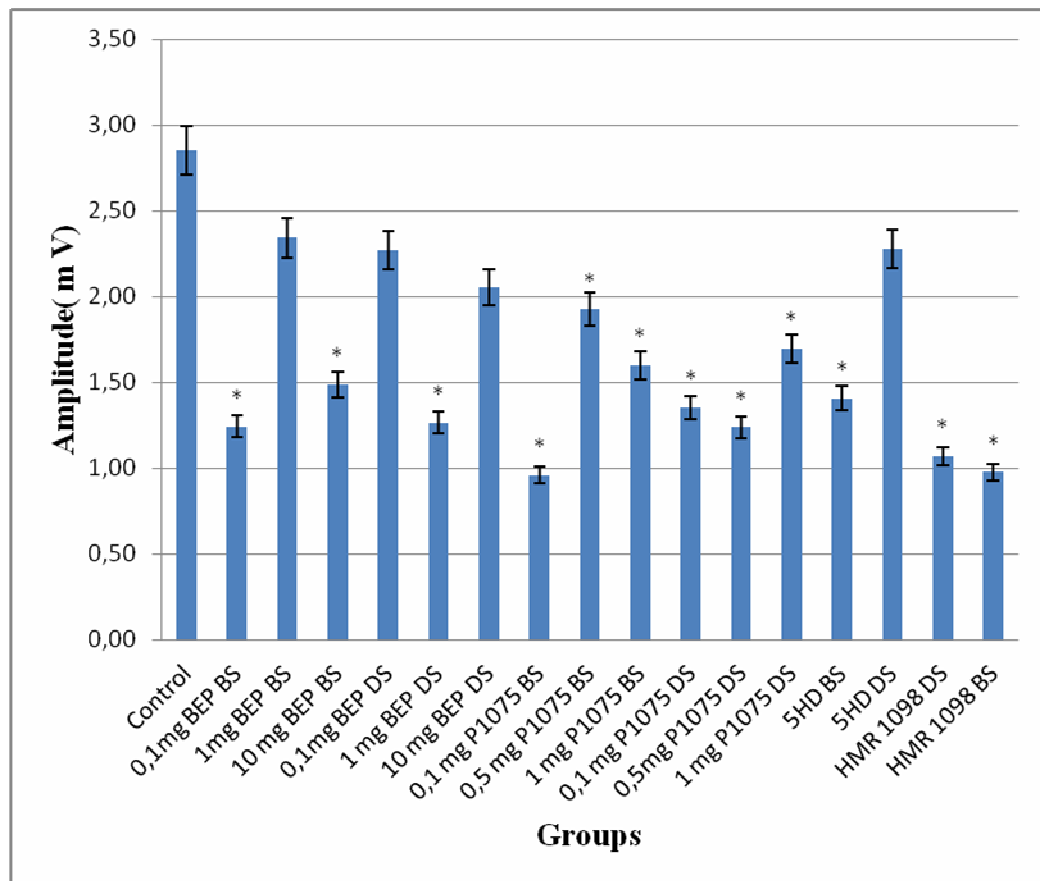


Figure 3.70. Spike wave amplitudes in mV obtained from 85 to 90 minutes recordings (Period 18). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.19. The amplitude of spike wave between 90 to 95 minutes in all groups
(Period 19)**

The spike wave amplitudes in groups 0,1mg BEP BS; 10 mg BEP BS; 1 mg BEP DS; 1 mg P1075 BS; 0,1 mg P1075 DS; 0,5mg P1075 DS; 5HD BS; HMR 1098 DS; HMR 1098 BS between 90-95 minutes time interval were significantly smaller than the control group ($p < 0,05$) (Table.3.54, Fig.3.71).

Table 3.54. Spike wave amplitude (mV) values obtained from 90 to 95 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	2,73	$\pm$	0,79	
0,1mg BEP BS	6	1,24	$\pm$	0,40*	0,01
1mg BEP BS	6	2,24	$\pm$	0,54	0,42
10 mg BEP BS	8	1,43	$\pm$	0,170*	0,02
0,1mg BEP DS	6	2,23	$\pm$	0,35	0,41
1 mg BEP DS	6	1,25	$\pm$	0,38*	0,01
10 mg BEP DS	8	2,00	$\pm$	0,40	0,20
0,1 mg P1075 BS	6	1,02	$\pm$	0,30	0,06
0,5 mg P1075 BS	6	1,91	$\pm$	0,26	0,18
1 mg P1075 BS	6	1,56	$\pm$	0,47*	0,05
0,1 mg P1075 DS	8	1,39	$\pm$	0,45*	0,02
0,5mg P1075 DS	6	1,19	$\pm$	0,13*	0,01
1 mg P1075 DS	8	1,67	$\pm$	0,23	0,06
5HD BS	8	1,33	$\pm$	0,31*	0,01
5HD DS	10	2,28	$\pm$	0,56	0,40
HMR 1098 DS	8	1,09	$\pm$	0,19*	0,04
HMR 1098 BS	8	1,00	$\pm$	0,25*	0,03

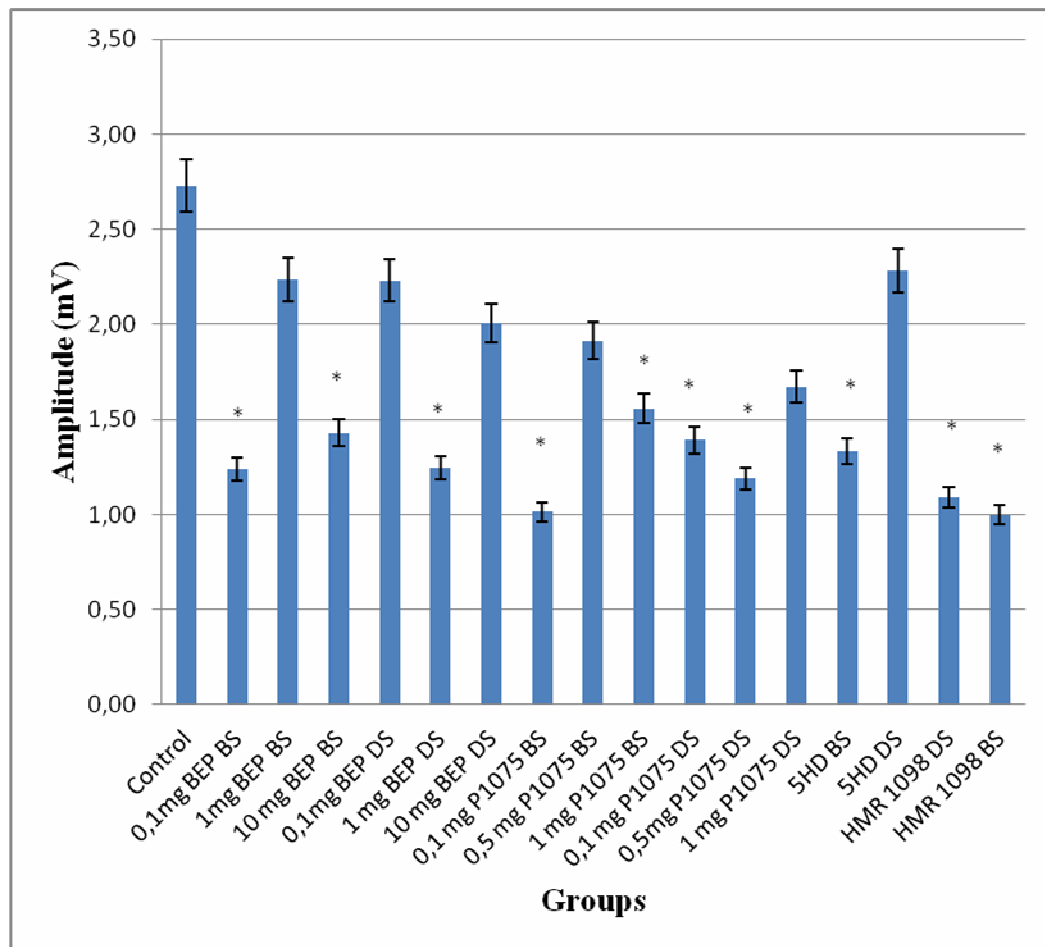


Figure 3.71. Spike wave amplitudes in mV obtained from 90 to 95 minutes recordings (Period 19). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.20. The amplitude of spike wave between 95 to 100 minutes in all groups
(Period 20)**

The spike wave amplitudes in all groups between 95- 100 minutes time interval are significantly smaller than the control group ($p < 0,05$) (Table.3.55, Fig.3.72.).

Table 3.55. Spike wave amplitude (mV) obtained from 95 to 100 minute recordings and P values in all groups (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	2,66	$\pm$	0,80	
0,1mg BEP BS	6	1,37	$\pm$	0,25*	0,03
1mg BEP BS	6	2,07	$\pm$	0,55	0,33
10 mg BEP BS	8	1,43	$\pm$	0,15*	0,03
0,1mg BEP DS	6	2,20	$\pm$	0,36	0,45
1 mg BEP DS	6	1,26	$\pm$	0,38*	0,02
10 mg BEP DS	8	2,02	$\pm$	0,45	0,25
0,1 mg P1075 BS	6	0,96	$\pm$	0,28	0,06
0,5 mg P1075 BS	6	1,83	$\pm$	0,21	0,17
1 mg P1075 BS	6	1,57	$\pm$	0,45	0,07
0,1 mg P1075 DS	8	1,38	$\pm$	0,43*	0,02
0,5mg P1075 DS	6	1,23	$\pm$	0,10*	0,02
1 mg P1075 DS	8	1,67	$\pm$	0,24	0,08
5HD BS	8	1,28	$\pm$	0,32*	0,01
5HD DS	10	2,23	$\pm$	0,58	0,41
HMR 1098 DS	8	0,95	$\pm$	0,14*	0,03
HMR 1098 BS	8	0,96	$\pm$	0,23*	0,03

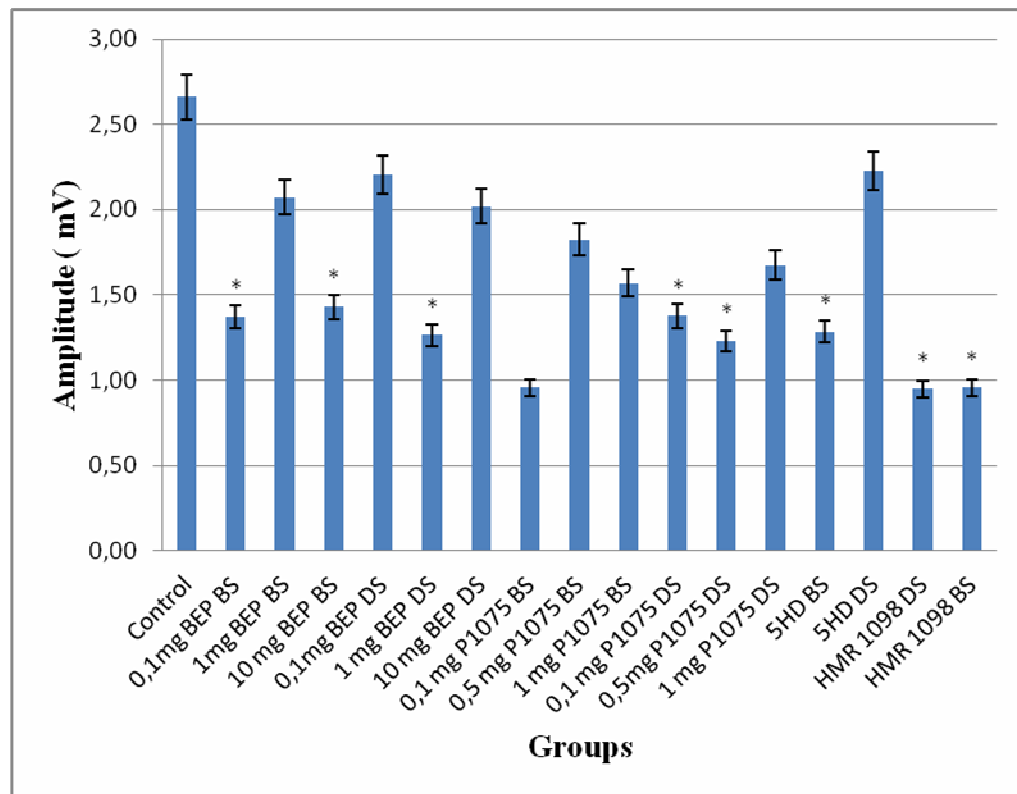


Figure 3.72. Spike wave amplitudes in mV obtained from 95 to 100 minutes recordings (Period 20). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.21. The amplitude of spike wave between 100 to 105 minutes in all groups
(Period 21)**

The spike wave amplitudes in groups 1mg BEP BS; 10 mg BEP BS; 1 mg BEP DS; 0,1 mg P1075 DS; 0,5mg P1075 DS; 5HD BS; HMR 1098 DS, HMR 1098 BS groups between 100-105 minutes time interval are significantly smaller than the control group ($p < 0,05$) (Table.3.56., Fig.3.73).

Table 3.56. Spike wave amplitude (mV) values obtained from 100 to 105 minute recordings and P values for all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	2,74	$\pm$	0,79	
0,1mg BEP BS	6	1,59	$\pm$	0,25	0,08
1mg BEP BS	6	2,17	$\pm$	0,56*	0,40
10 mg BEP BS	8	1,42	$\pm$	0,18*	0,03
0,1mg BEP DS	6	2,12	$\pm$	0,37	0,35
1 mg BEP DS	6	1,25	$\pm$	0,37*	0,02
10 mg BEP DS	8	1,95	$\pm$	0,40	0,20
0,1 mg P1075 BS	6	1,78	$\pm$	0,99	0,15
0,5 mg P1075 BS	6	1,83	$\pm$	0,21	0,17
1 mg P1075 BS	6	1,73	$\pm$	0,55	0,13
0,1 mg P1075 DS	8	1,42	$\pm$	0,44*	0,03
0,5mg P1075 DS	6	1,21	$\pm$	0,10*	0,02
1 mg P1075 DS	8	1,70	$\pm$	0,26	0,09
5HD BS	8	1,33	$\pm$	0,35*	0,02
5HD DS	10	2,12	$\pm$	0,60	0,29
HMR 1098 DS	8	0,94	$\pm$	0,13*	0,04
HMR 1098 BS	8	0,94	$\pm$	0,21*	0,04

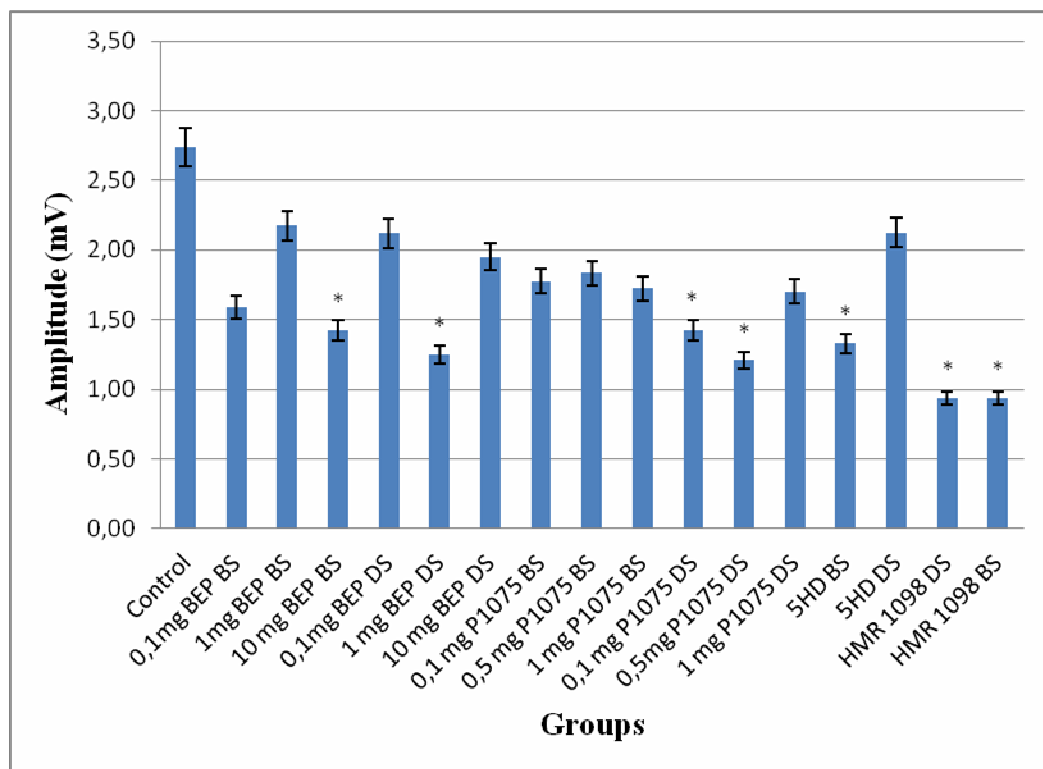


Figure 3.73. Spike wave amplitudes in mV obtained from 100 to 105 minutes recordings (Period 21). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.22. The amplitude of spike wave between 105 to 110 minutes in all groups
(Period 22)**

The spike wave amplitudes in groups 0,1mg BEP BS, 10 mg BEP BS, 1 mg BEP DS, 0,1 mg P1075 BS, 1mg P1075 BS, 0,1mg P1075 DS, 0,5mg P1075 DS, 1 mg P1075 DS, 5HD BS groups between 105-110 minutes time interval are significantly smaller than the control group ($p < 0,05$) (Table.3.57, Fig.3.74).

Table 3.57. Spike wave amplitude (mV) obtained from 105 to 110 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	2,80	$\pm$	0,77	
0,1mg BEP BS	6	1,82	$\pm$	0,29*	0,12
1mg BEP BS	6	2,16	$\pm$	0,58	0,30
10 mg BEP BS	8	1,36	$\pm$	0,18*	0,01
0,1mg BEP DS	6	2,09	$\pm$	0,38	0,25
1 mg BEP DS	6	0,77	$\pm$	0,37*	0,02
10 mg BEP DS	8	2,20	$\pm$	0,43	0,30
0,1 mg P1075 BS	6	1,00	$\pm$	0,25*	0,05
0,5 mg P1075 BS	6	1,79	$\pm$	0,20	0,10
1 mg P1075 BS	6	1,54	$\pm$	0,44*	0,04
0,1 mg P1075 DS	8	1,54	$\pm$	0,54*	0,03
0,5mg P1075 DS	6	1,17	$\pm$	0,10*	0,01
1 mg P1075 DS	8	1,68	$\pm$	0,27*	0,05
5HD BS	8	1,35	$\pm$	0,37*	0,01
5HD DS	10	2,22	$\pm$	0,59	0,28
HMR 1098 DS	8	0,93	$\pm$	0,12*	0,01
HMR 1098 BS	8	0,95	$\pm$	0,22*	0,02

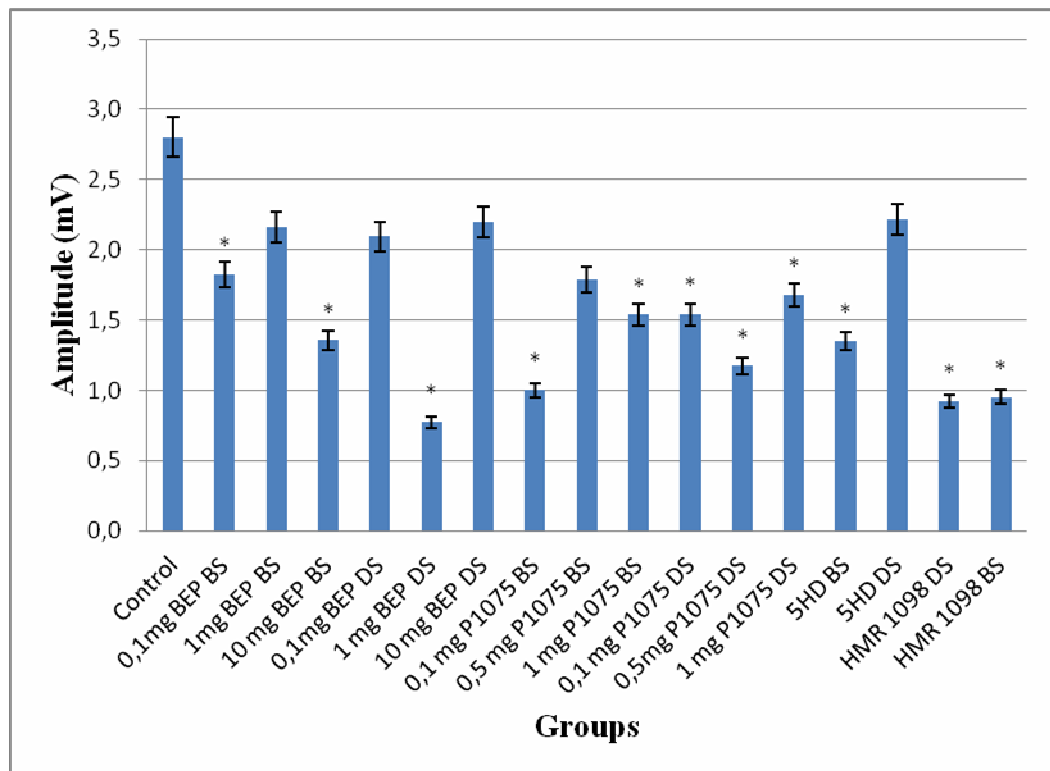


Figure 3.74. Spike wave amplitudes in mV obtained from 105 to 110 minutes recordings (Period 22). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.23. The amplitude of spike wave between 110 to 115 Minutes in all groups
(Period 23)**

The spike wave amplitudes in groups 1mg BEP BS;10 mg BEP BS;1 mg BEP DS; 0,1 mg P1075 DS; 0,5mg P1075 DS; 5HD BS; HMR 1098 DS; HMR 1098 BS groups between 110- 115 minutes time interval are significantly smaller than control group ($p<0,05$) (Table.3.58, Fig.3.75).

Table 3.58. Spike wave amplitude (mV) values obtained from 110 to 115 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P<0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	2,73	$\pm$	0,79	
0,1mg BEP BS	6	1,86	$\pm$	0,27	0,16
1mg BEP BS	6	1,51	$\pm$	0,48*	0,05
10 mg BEP BS	8	1,33	$\pm$	0,17*	0,01
0,1mg BEP DS	6	2,05	$\pm$	0,43	0,28
1 mg BEP DS	6	0,75	$\pm$	0,36*	0,02
10 mg BEP DS	8	2,06	$\pm$	0,42	0,25
0,1 mg P1075 BS	6	1,01	$\pm$	0,24	0,07
0,5 mg P1075 BS	6	1,78	$\pm$	0,19	0,13
1 mg P1075 BS	6	1,57	$\pm$	0,43	0,06
0,1 mg P1075 DS	8	1,43	$\pm$	0,45*	0,02
0,5mg P1075 DS	6	1,15	$\pm$	0,11*	0,01
1 mg P1075 DS	8	1,68	$\pm$	0,34	0,07
5HD BS	8	1,34	$\pm$	0,37*	0,01
5HD DS	10	2,07	$\pm$	0,60	0,22
HMR 1098 DS	8	1,03	$\pm$	0,21*	0,04
HMR 1098 BS	8	1,02	$\pm$	0,21*	0,04

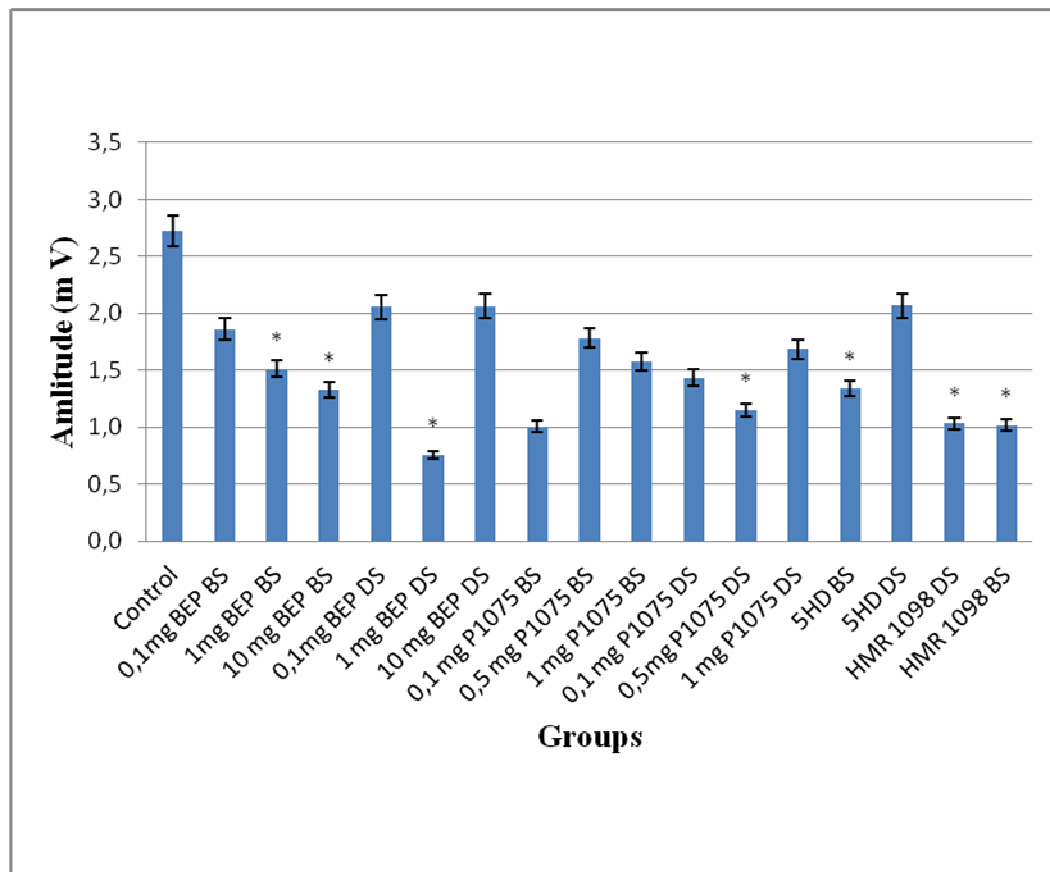


Figure 3.75. Spike wave amplitudes in mV obtained from 110 to 115 minutes recordings (Period 23). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.24. The amplitude of spike wave between 115 to 120 minutes in all groups
(Period 24)**

The spike wave amplitudes in groups 10 mg BEP BS; 1 mg BEP DS; 0,1 mg P1075 DS; 0,5mg P1075 DS; 5HD BS; HMR 1098 DS; HMR 1098 BS groups between 115- 120 minutes time interval are significantly smaller than the control group ($p < 0,05$) (Table.3.59, Fig.3.75).

Table 3.59. Spike wave amplitude (mV) obtained from 115 to 120 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	2,66	$\pm$	0,74	
0,1mg BEP BS	6	2,04	$\pm$	0,36	0,31
1mg BEP BS	6	1,70	$\pm$	0,44	0,12
10 mg BEP BS	8	1,26	$\pm$	0,17*	0,01
0,1mg BEP DS	6	2,03	$\pm$	0,43	0,30
1 mg BEP DS	6	0,74	$\pm$	0,35*	0,02
10 mg BEP DS	8	2,00	$\pm$	0,41	0,24
0,1 mg P1075 BS	6	0,95	$\pm$	0,23*	0,06
0,5 mg P1075 BS	6	1,73	$\pm$	0,22	0,13
1 mg P1075 BS	6	1,61	$\pm$	0,45	0,08
0,1 mg P1075 DS	8	1,52	$\pm$	0,51*	0,04
0,5mg P1075 DS	6	1,14	$\pm$	0,11*	0,01
1 mg P1075 DS	8	1,73	$\pm$	0,38	0,10
5HD BS	8	1,33	$\pm$	0,37*	0,02
5HD DS	10	2,07	$\pm$	0,60	0,27
HMR 1098 DS	8	0,95	$\pm$	0,14*	0,03
HMR 1098 BS	8	1,02	$\pm$	0,21*	0,05

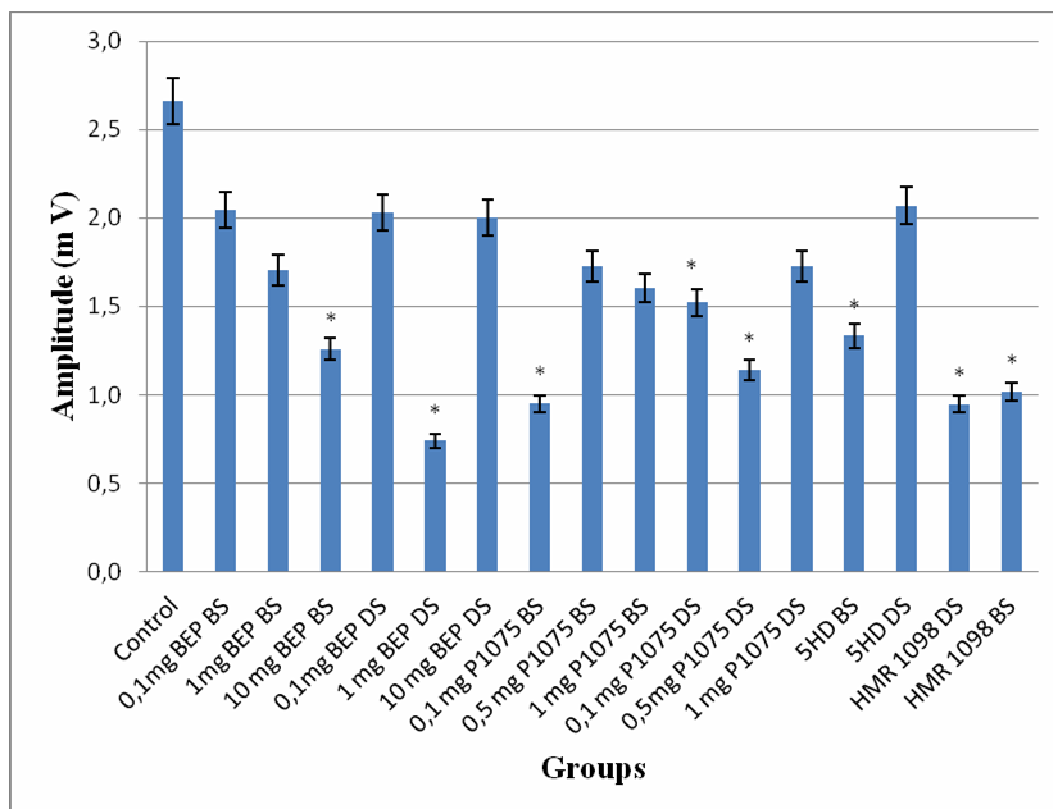


Figure 3.76. Spike wave amplitudes in mV obtained from 115 to 120 minutes recordings (Period 24) (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.25. The amplitude of spike wave between 120 to 125 minutes in all groups
(Period 25)**

The spike wave amplitudes in groups 1mg BEP BS; 10 mg BEP BS; 1 mg BEP DS; 0,1 mg P1075 DS ; 0,5mg P1075 DS; 1 mg P1075 DS; 5HD BS; MR 1098 DS; HMR 1098 BS groups between 120-125 minutes time interval are significantly smaller than the control group ($p < 0,05$) (Table.3.60., Fig.3.77.).

Table 3.60. Spike wave amplitude (mV) obtained from 120 to 125 minute recordings and P values for all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	2,69	$\pm$	0,82	
0,1mg BEP BS	6	1,87	$\pm$	0,39	0,20
1mg BEP BS	6	1,44	$\pm$	0,44*	0,05
10 mg BEP BS	8	1,21	$\pm$	0,17*	0,01
0,1mg BEP DS	6	2,00	$\pm$	0,48	0,28
1 mg BEP DS	6	0,75	$\pm$	0,36*	0,03
10 mg BEP DS	8	1,98	$\pm$	0,45	0,23
0,1 mg P1075 BS	6	0,94	$\pm$	0,23	0,07
0,5 mg P1075 BS	6	1,71	$\pm$	0,14	0,12
1 mg P1075 BS	6	1,55	$\pm$	0,42	0,07
0,1 mg P1075 DS	8	1,40	$\pm$	0,46*	0,03
0,5mg P1075 DS	6	1,14	$\pm$	0,12*	0,01
1 mg P1075 DS	8	1,73	$\pm$	0,40*	0,10
5HD BS	8	1,37	$\pm$	0,43*	0,02
5HD DS	10	2,07	$\pm$	0,60	0,26
HMR 1098 DS	8	0,98	$\pm$	0,09*	0,04
HMR 1098 BS	8	1,00	$\pm$	0,20*	0,05

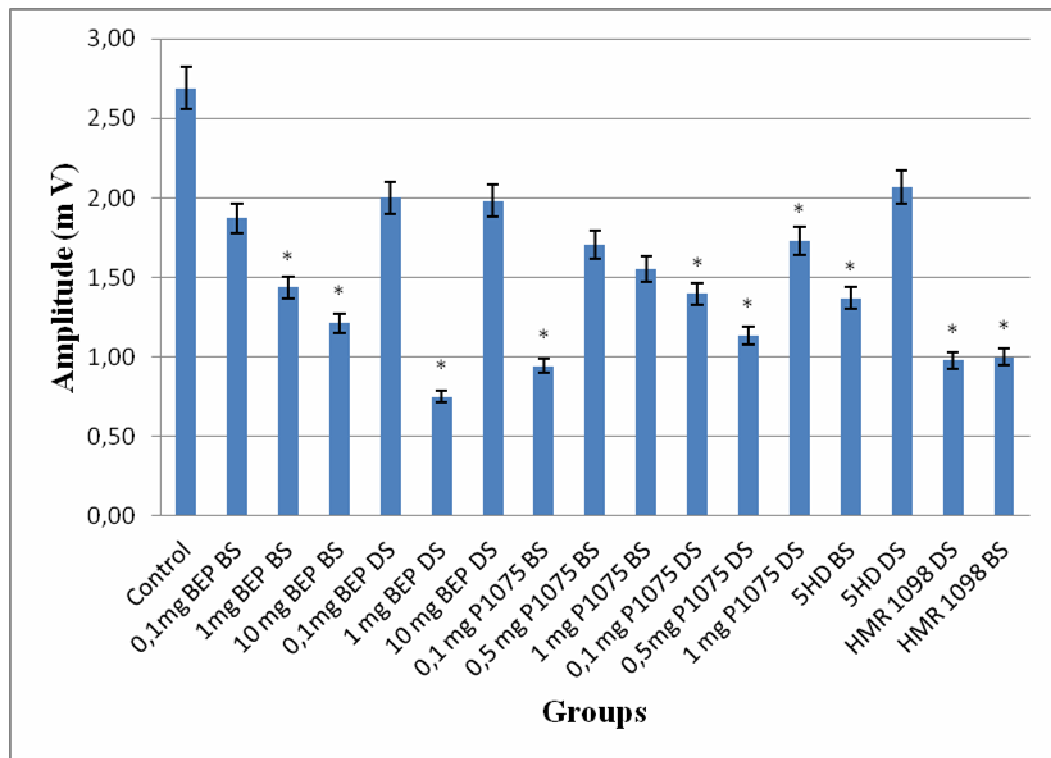


Figure 3.77. Spike wave amplitudes in mV obtained from 120 to 125 minutes recordings (Period 25). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.26. The amplitude of spike wave between 125 to 130 minutes in all groups
(Period 26)**

The spike wave amplitudes in groups 10 mg BEP BS; 1 mg BEP DS ;0,1 mg P1075 BS; 0,1 mg P1075 DS; 0,5mg P1075 DS;5HD BS; HMR 1098 BS between 120- 125 minutes time interval are significantly smaller than the control group ($p<0,05$) (Table.3.61, Fig.3.78.).

Table 3.61. Spike wave amplitude (mV) obtained from 125 to 130 minute recordings and P values for all groups. (Data are means $\pm$ SE * $P<0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	2,61	$\pm$	0,80	
0,1mg BEP BS	6	2,00	$\pm$	0,39	0,33
1mg BEP BS	6	1,56	$\pm$	0,38	0,10
10 mg BEP BS	8	1,21	$\pm$	0,16*	0,01
0,1mg BEP DS	6	2,13	$\pm$	0,43	0,45
1 mg BEP DS	6	0,73	$\pm$	0,35*	0,04
10 mg BEP DS	8	1,92	$\pm$	0,44	0,24
0,1 mg P1075 BS	6	0,96	$\pm$	0,22*	0,01
0,5 mg P1075 BS	6	1,68	$\pm$	0,19	0,14
1 mg P1075 BS	6	1,70	$\pm$	0,48	0,15
0,1 mg P1075 DS	8	1,38	$\pm$	0,46*	0,03
0,5mg P1075 DS	6	1,13	$\pm$	0,12*	0,02
1 mg P1075 DS	8	1,73	$\pm$	0,44	0,13
5HD BS	8	1,33	$\pm$	0,37*	0,03
5HD DS	10	2,03	$\pm$	0,62	0,29
HMR 1098 DS	8	0,99	$\pm$	0,10	0,07
HMR 1098 BS	8	0,94	$\pm$	0,22*	0,05

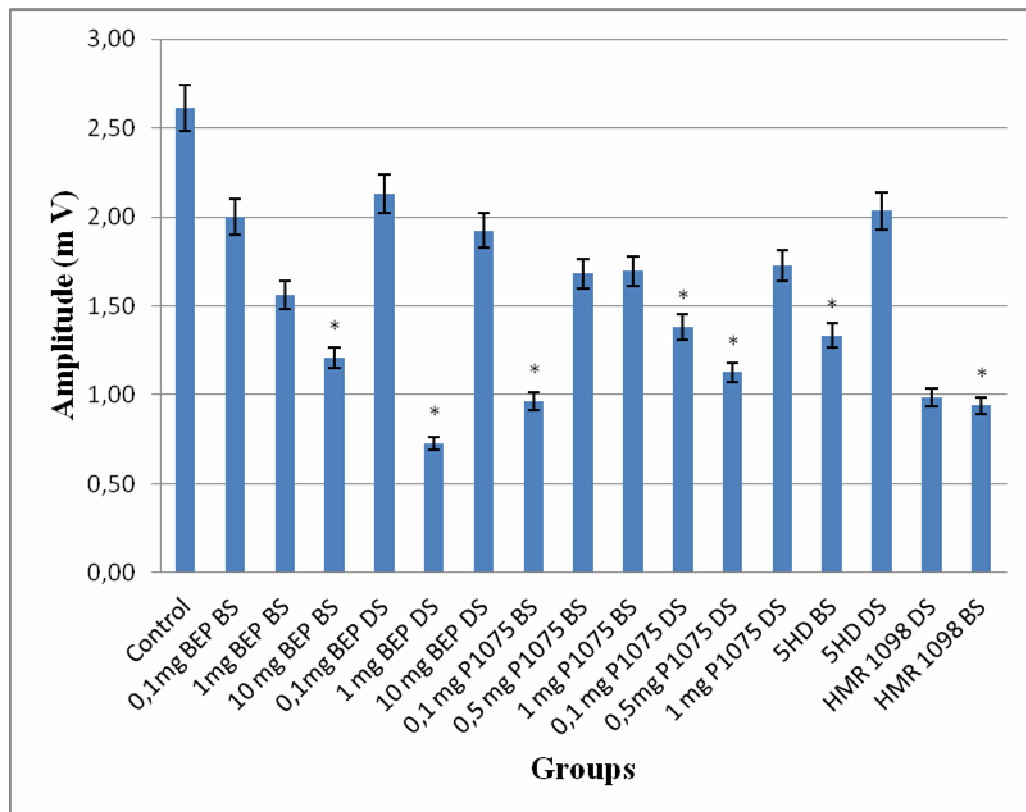


Figure 3.78. Spike wave amplitudes in mV obtained from 125 to 130 minutes recordings (Period 26). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.27. The amplitude of spike wave between 130 to 135 minutes in all groups
(Period 27)**

The spike wave amplitudes in groups 10 mg BEP BS; 1 mg BEP DS; 0,1 mg P1075 DS; 0,5mg P1075 DS; 5HD BS between 130 – 135 minutes time interval are significantly smaller than the control group ($p < 0,05$) (Table.3.62, Fig.3.79.).

Table 3.62. Spike wave amplitude (mV) obtained from 130 to 135 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	2,56	$\pm$	0,80	
0,1mg BEP BS	6	2,07	$\pm$	0,41	0,42
1mg BEP BS	6	1,56	$\pm$	0,38	0,11
10 mg BEP BS	8	1,05	$\pm$	0,20*	0,01
0,1mg BEP DS	6	2,09	$\pm$	0,45	0,45
1 mg BEP DS	6	0,19	$\pm$	0,07*	0,00
10 mg BEP DS	8	1,89	$\pm$	0,44	0,24
0,1 mg P1075 BS	6	0,89	$\pm$	0,21	0,09
0,5 mg P1075 BS	6	1,57	$\pm$	0,15	0,11
1 mg P1075 BS	6	1,60	$\pm$	0,41	0,12
0,1 mg P1075 DS	8	1,36	$\pm$	0,43*	0,03
0,5mg P1075 DS	6	1,04	$\pm$	0,14*	0,01
1 mg P1075 DS	8	1,76	$\pm$	0,44	0,16
5HD BS	8	1,29	$\pm$	0,36*	0,02
5HD DS	10	1,98	$\pm$	0,63	0,29
HMR 1098 DS	8	0,99	$\pm$	0,14	0,08
HMR 1098 BS	8	0,94	$\pm$	0,21	0,06

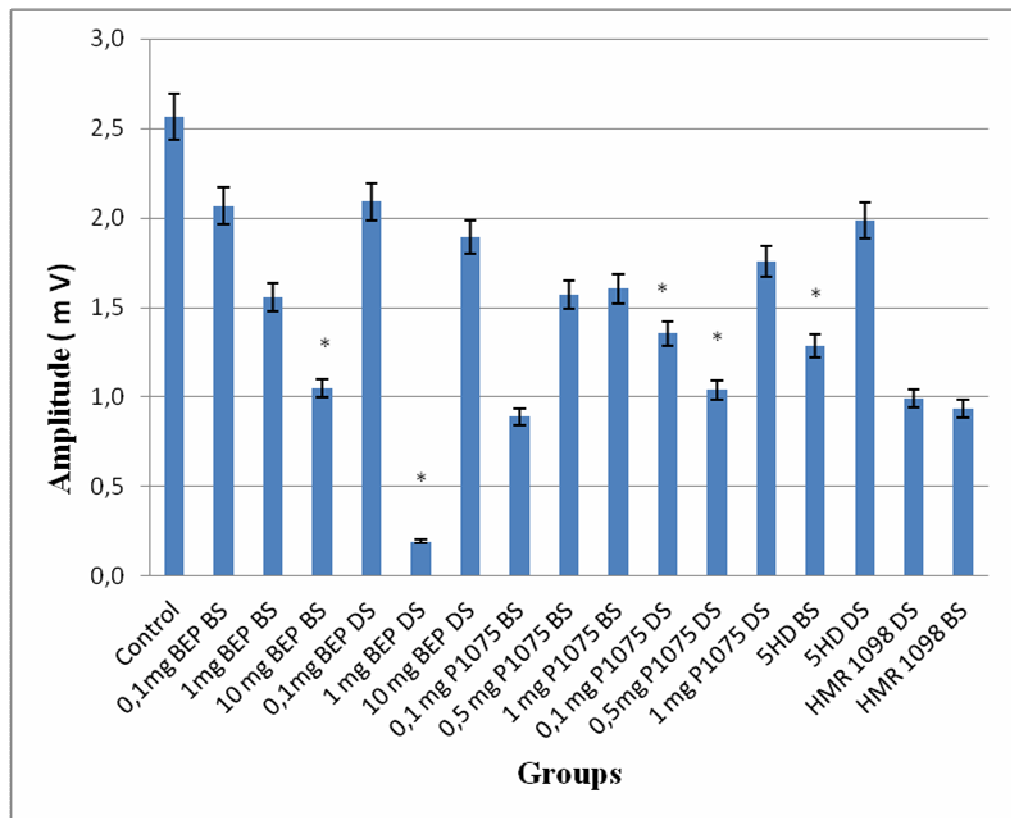


Figure 3.79. Spike wave amplitudes in mV obtained from 130 to 135 minutes recordings (Period 27). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.28. The amplitude of spike wave between 135 to 140 minutes in all groups
(Period 28)**

The spike wave amplitudes in groups 1 mg Bepridil DS between 135–140 minutes time interval are significantly smaller than the control group ($p < 0,05$) (Table.3.63, Fig.3.80.).

Table 3.63. Spike wave amplitude (mV) obtained from 135 to 140 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	1,54	$\pm$	0,29	
0,1mg BEP BS	6	2,07	$\pm$	0,38	0,34
1mg BEP BS	6	1,50	$\pm$	0,38	0,93
10 mg BEP BS	8	1,09	$\pm$	0,21	0,38
0,1mg BEP DS	6	2,12	$\pm$	0,48	0,30
1 mg BEP DS	6	0,21	$\pm$	0,07*	0,02
10 mg BEP DS	8	1,86	$\pm$	0,45	0,53
0,1 mg P1075 BS	6	0,87	$\pm$	0,19	0,23
0,5 mg P1075 BS	6	1,69	$\pm$	0,19	0,78
1 mg P1075 BS	6	1,60	$\pm$	0,39	0,91
0,1 mg P1075 DS	8	1,38	$\pm$	0,43	0,75
0,5mg P1075 DS	6	0,92	$\pm$	0,21	0,27
1 mg P1075 DS	8	1,87	$\pm$	0,56	0,52
5HD BS	8	1,07	$\pm$	0,36	0,36
5HD DS	10	2,00	$\pm$	0,64	0,35
HMR 1098 DS	8	0,96	$\pm$	0,16	0,26
HMR 1098 BS	8	0,90	$\pm$	0,22	0,22

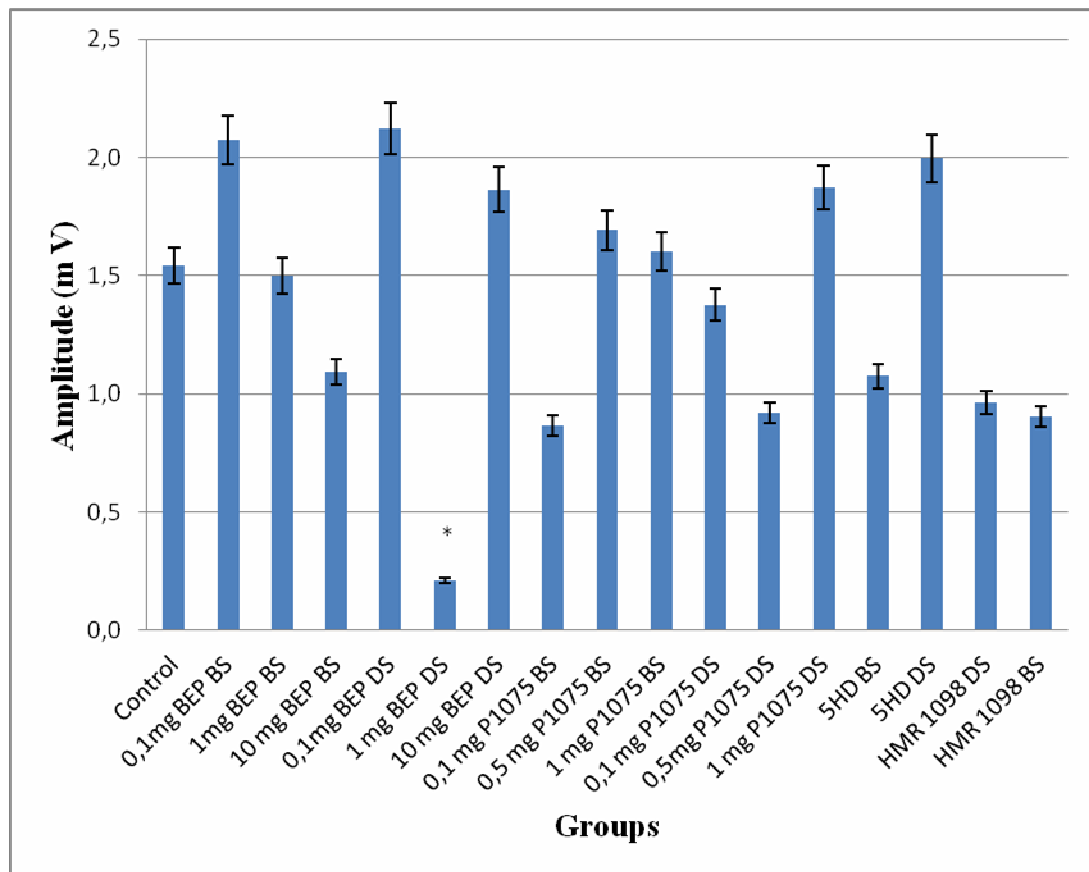


Figure.3.80. Spike wave amplitudes in mV obtained from 135 to 140 minutes recordings (Periyod 28) (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.29. The amplitude of spike wave between 140 to 145 minutes in all groups
(Period 29)**

The spike wave amplitudes in groups 1 mg bepridil DS between 140- 145 minutes time interval are significantly smaller than the control group ($p < 0,05$) (Table.3.64, Fig.3.81.).

Table 3.64. Spike wave amplitude (mV) obtained from 140 to 145 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	1,48	$\pm$	0,33	
0,1mg BEP BS	6	2,10	$\pm$	0,24	0,28
1mg BEP BS	6	1,49	$\pm$	0,39	0,98
10 mg BEP BS	8	1,13	$\pm$	0,25	0,49
0,1mg BEP DS	6	1,69	$\pm$	0,19	0,71
1 mg BEP DS	6	0,19	$\pm$	0,07*	0,02
10 mg BEP DS	8	1,88	$\pm$	0,46	0,44
0,1 mg P1075 BS	6	0,78	$\pm$	0,16	0,21
0,5 mg P1075 BS	6	1,63	$\pm$	0,18	0,79
1 mg P1075 BS	6	1,62	$\pm$	0,38	0,81
0,1 mg P1075 DS	8	1,53	$\pm$	0,55	0,93
0,5mg P1075 DS	6	0,83	$\pm$	0,21	0,24
1 mg P1075 DS	8	1,74	$\pm$	0,58	0,62
5HD BS	8	0,96	$\pm$	0,38	0,32
5HD DS	10	1,98	$\pm$	0,63	0,31
HMR 1098 DS	8	1,20	$\pm$	0,19	0,58
HMR 1098 BS	8	0,84	$\pm$	0,19	0,21

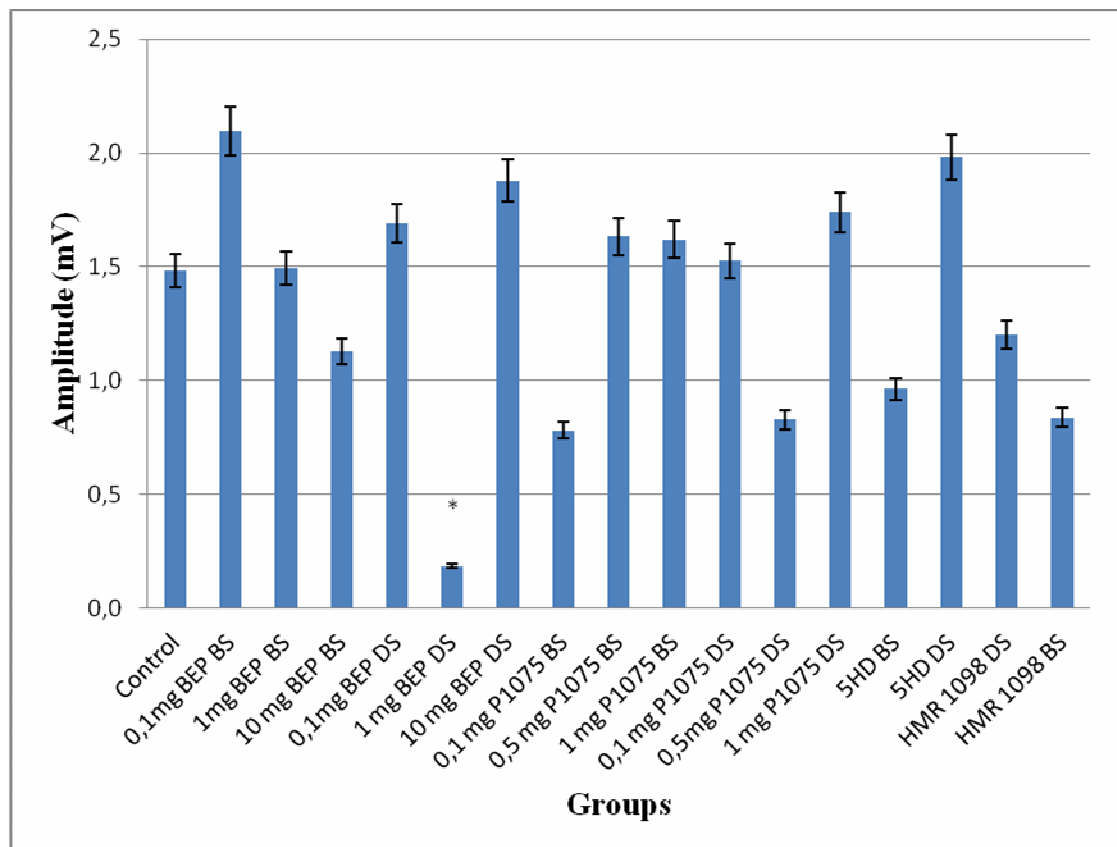


Figure 3.81. Spike wave amplitudes in mV obtained from 140 to 145 minutes recordings (Periyod 29). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.30. The amplitude of spike wave between 145 to 150 minutes in all groups
(Period 30)**

The spike wave amplitudes in groups 1 mg Bepridil DS; 0,1 mg P1075 BS; between 145- 150 minutes time interval are significantly smaller than the control group ($p<0,05$) (Table.3.65, Fig.3.81).

Table 3.65. Spike wave amplitude (mV) obtained from 145 to 150 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P<0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	1,78	$\pm$	0,32	
0,1mg BEP BS	6	1,91	$\pm$	0,33	0,82
1mg BEP BS	6	1,48	$\pm$	0,38	0,60
10 mg BEP BS	8	1,00	$\pm$	0,22	0,13
0,1mg BEP DS	6	1,74	$\pm$	0,19	0,94
1 mg BEP DS	6	0,22	$\pm$	0,08*	0,07
10 mg BEP DS	8	1,83	$\pm$	0,48	0,92
0,1 mg P1075 BS	6	0,53	$\pm$	0,11*	0,03
0,5 mg P1075 BS	6	1,49	$\pm$	0,19	0,61
1 mg P1075 BS	6	1,63	$\pm$	0,39	0,79
0,1 mg P1075 DS	8	1,57	$\pm$	0,55	0,68
0,5mg P1075 DS	6	0,77	$\pm$	0,19	0,08
1 mg P1075 DS	8	1,47	$\pm$	0,60	0,55
5HD BS	8	1,02	$\pm$	0,38	0,14
5HD DS	10	2,00	$\pm$	0,63	0,65
HMR 1098 DS	8	1,21	$\pm$	0,19	0,28
HMR 1098 BS	8	0,87	$\pm$	0,18	0,08

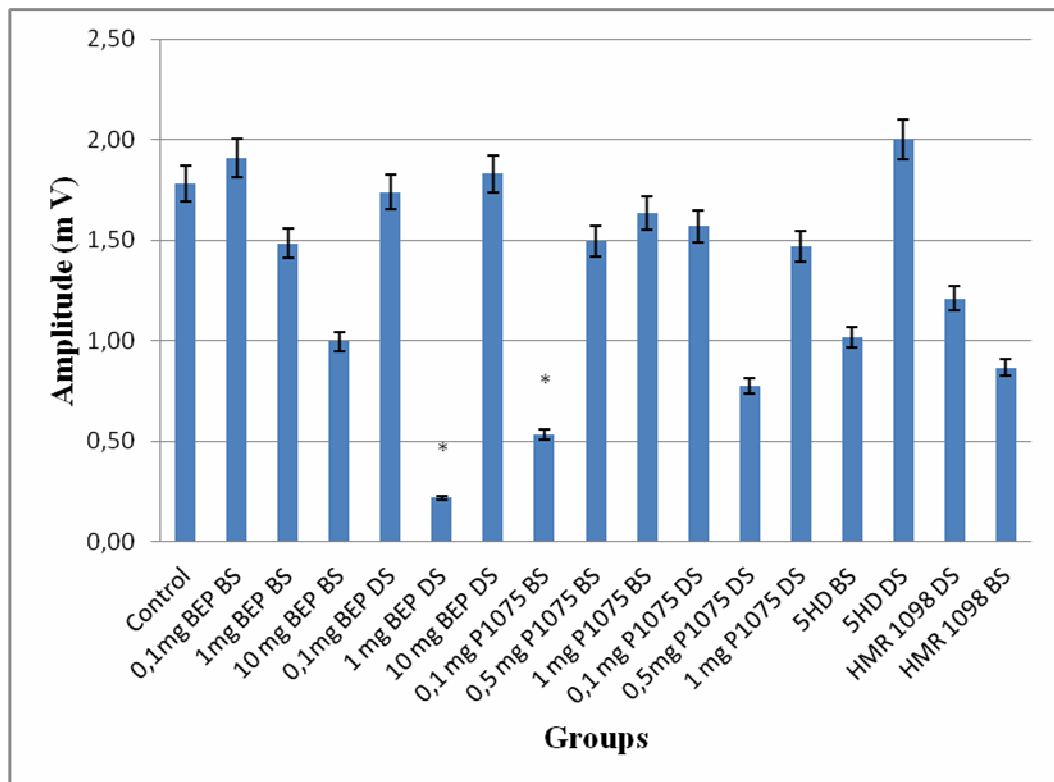


Figure 3.82. Spike wave amplitudes in mV obtained from 145 to 150 minutes recordings (Period 30). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.31. The amplitude of spike wave between 150 to 155 minutes in all groups
(Period 31)**

The spike wave amplitudes in groups 1 mg BEP DS; 0,1 mg P1075 BS between 150-155 minutes time interval are significantly smaller than the control group ($p < 0,05$) (Table.3.66, Fig.3.82).

Table 3.66. Spike wave amplitude (mV) obtained from 150 to 155 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	1,68	$\pm$	0,26	
0,1mg BEP BS	6	1,89	$\pm$	0,25	0,70
1mg BEP BS	6	1,47	$\pm$	0,38	0,71
10 mg BEP BS	8	1,19	$\pm$	0,17	0,34
0,1mg BEP DS	6	1,81	$\pm$	0,26	0,81
1 mg BEP DS	6	0,21	$\pm$	0,07*	0,01
10 mg BEP DS	8	1,71	$\pm$	0,45	0,95
0,1 mg P1075 BS	6	0,49	$\pm$	0,09*	0,03
0,5 mg P1075 BS	6	1,52	$\pm$	0,18	0,78
1 mg P1075 BS	6	1,58	$\pm$	0,33	0,85
0,1 mg P1075 DS	8	1,56	$\pm$	0,55	0,82
0,5mg P1075 DS	6	0,76	$\pm$	0,20	0,10
1 mg P1075 DS	8	1,40	$\pm$	0,61	0,58
5HD BS	8	1,07	$\pm$	0,34	0,24
5HD DS	10	2,07	$\pm$	0,65	0,42
HMR 1098 DS	8	1,21	$\pm$	0,21	0,37
HMR 1098 BS	8	1,04	$\pm$	0,24	0,21

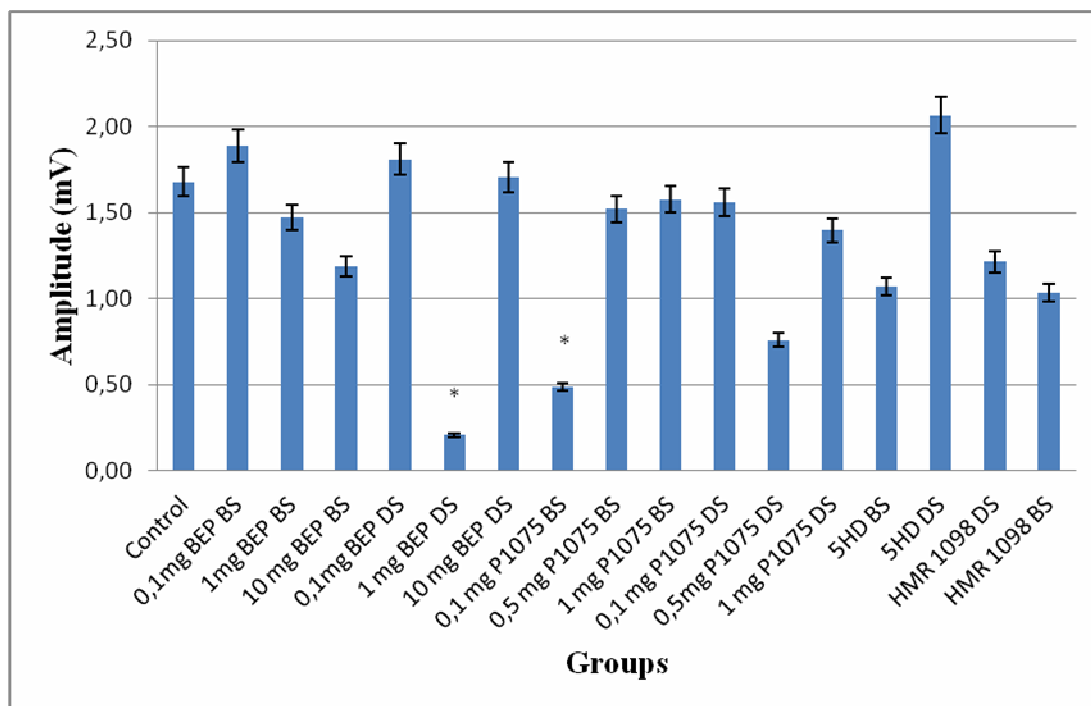


Figure 3.83. Spike wave amplitudes in mV obtained from 150 to 155 minutes recordings (Period 31). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.32. The amplitude of spike wave between 155 to 160 minutes in all groups
(Period 32)**

The spike wave amplitudes in groups 1 mg BEP DS; 0,1 mg P1075 BS; 0,5mg P1075 DS between 155-160 minutes time interval are significantly smaller than the control group ($p < 0,05$) (Table.3.67, Fig.3.83).

Table 3.67. Spike wave amplitude (mV) obtained from 155 to 160 minute recordings and P values in all groups (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	1,69	$\pm$	0,28	
0,1mg BEP BS	6	1,93	$\pm$	0,34	0,62
1mg BEP BS	6	1,41	$\pm$	0,35	0,58
10 mg BEP BS	8	1,13	$\pm$	0,22	0,22
0,1mg BEP DS	6	1,82	$\pm$	0,36	0,78
1 mg BEP DS	6	0,21	$\pm$	0,07*	0,03
10 mg BEP DS	8	1,74	$\pm$	0,43	0,91
0,1 mg P1075 BS	6	0,48	$\pm$	0,09*	0,01
0,5 mg P1075 BS	6	1,47	$\pm$	0,21	0,65
1 mg P1075 BS	6	1,55	$\pm$	0,33	0,78
0,1 mg P1075 DS	8	1,60	$\pm$	0,56	0,84
0,5mg P1075 DS	6	0,69	$\pm$	0,18*	0,04
1 mg P1075 DS	8	1,25	$\pm$	0,58	0,34
5HD BS	8	1,03	$\pm$	0,35	0,15
5HD DS	10	1,44	$\pm$	0,29	0,56
HMR 1098 DS	8	1,32	$\pm$	0,20	0,42
HMR 1098 BS	8	0,97	$\pm$	0,24	0,11

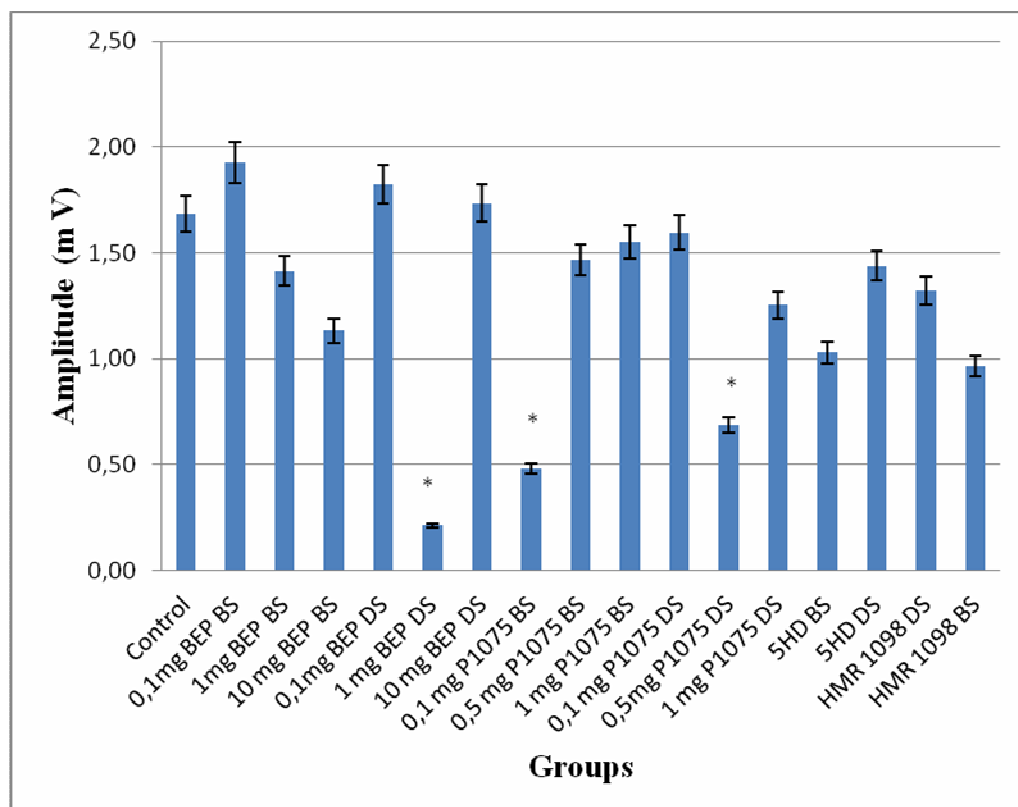


Figure 3.84. Spike wave amplitudes in mV obtained from 155 to 160 minutes recordings (Period 32). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.33. The amplitude of spike wave between 160 to 165 minutes in all groups
(Period 33)**

The spike wave amplitudes in groups 0,1mg P 1075 bs; 0,5 mg P1075 ds between 160-165 minutes time interval are significantly smaller than the control group ($p<0,05$) (Table 3.68, Fig 3.84).

Table 3.68. Spike wave amplitude (mV) obtained from 160 to 165 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P<0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	1,74	$\pm$	0,31	
0,1mg BEP BS	6	1,84	$\pm$	0,29	0,84
1mg BEP BS	6	1,17	$\pm$	0,38	0,26
10 mg BEP BS	8	1,14	$\pm$	0,22	0,20
0,1mg BEP DS	6	1,83	$\pm$	0,39	0,86
1 mg BEP DS	6	0,20	$\pm$	0,07*	0,03
10 mg BEP DS	8	1,78	$\pm$	0,45	0,92
0,1 mg P1075 BS	6	0,48	$\pm$	0,09*	0,01
0,5 mg P1075 BS	6	1,49	$\pm$	0,23	0,63
1 mg P1075 BS	6	1,57	$\pm$	0,32	0,74
0,1 mg P1075 DS	8	1,58	$\pm$	0,57	0,74
0,5mg P1075 DS	6	0,72	$\pm$	0,20*	0,04
1 mg P1075 DS	8	1,21	$\pm$	0,60	0,26
5HD BS	8	0,96	$\pm$	0,36	0,10
5HD DS	10	1,42	$\pm$	0,29	0,47
HMR 1098 DS	8	1,29	$\pm$	0,21	0,33
HMR 1098 BS	8	0,96	$\pm$	0,25	0,09

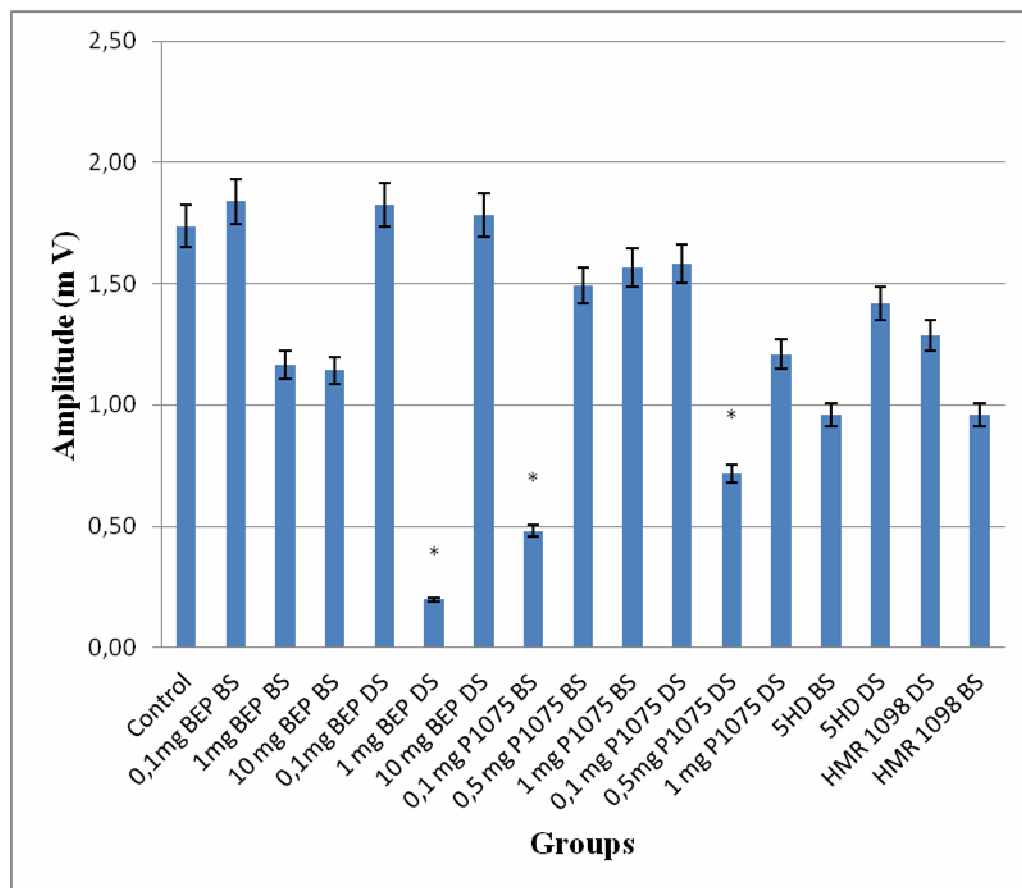


Figure 3.85. Spike wave amplitudes in mV obtained from 160 to 165 minutes recordings (Period 33). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.34. The amplitude of spike wave between 165 to 170 minutes in all groups
(Period 34)**

The spike wave amplitudes in groups 0,1 mg P 1075 bs between 165-170 minutes time interval are significantly smaller than the control group ($p < 0,05$) (Table 3.69, Fig. 3.85).

Table 3.69. Spike wave amplitude (mV) obtained from 165 to 170 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P < 0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	1,73	$\pm$	0,29	
0,1mg BEP BS	6	1,82	$\pm$	0,30	0,87
1mg BEP BS	6	1,06	$\pm$	0,34	0,20
10 mg BEP BS	8	1,19	$\pm$	0,22	0,26
0,1mg BEP DS	6	1,63	$\pm$	0,41	0,85
1 mg BEP DS	6	0,75	$\pm$	0,36	0,06
10 mg BEP DS	8	1,71	$\pm$	0,45	0,96
0,1 mg P1075 BS	6	0,47	$\pm$	0,08*	0,01
0,5 mg P1075 BS	6	1,18	$\pm$	0,18	0,30
1 mg P1075 BS	6	1,55	$\pm$	0,31	0,73
0,1 mg P1075 DS	8	1,62	$\pm$	0,58	0,83
0,5mg P1075 DS	6	0,82	$\pm$	0,17	0,08
1 mg P1075 DS	8	1,29	$\pm$	0,68	0,37
5HD BS	8	1,07	$\pm$	0,41	0,18
5HD DS	10	1,40	$\pm$	0,30	0,48
HMR 1098 DS	8	1,30	$\pm$	0,20	0,38
HMR 1098 BS	8	0,92	$\pm$	0,21	0,09

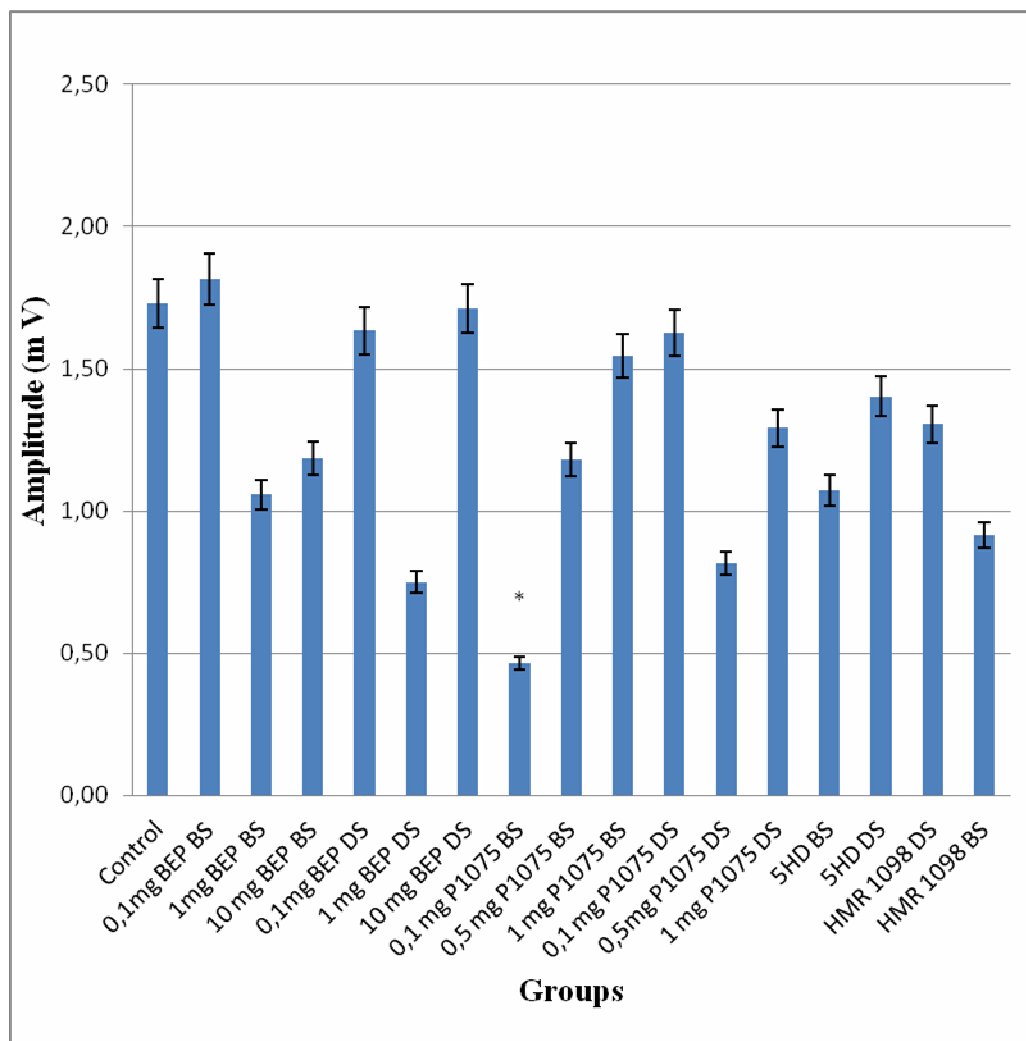


Figure 3.86. Spike wave amplitudes in mV obtained from 165 to 170 minutes recordings (Period 34). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.35. The amplitude of spike wave between 170 to 175 minutes in all groups
(Period 35)**

The spike wave amplitudes in groups 1mg/kg Bepridil bs; 0,1mg P 1075 bs; between 170-175 minutes time interval are significantly smaller than the control group ($p<0,05$) (Table.3.70, Fig.3.86).

Table 3.70. Spike wave amplitude (mV) obtained from 170 to 175 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P<0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	1,55	$\pm$	0,29	
0,1mg BEP BS	6	1,75	$\pm$	0,26	0,71
1mg BEP BS	6	0,52	$\pm$	0,23*	0,05
10 mg BEP BS	8	1,23	$\pm$	0,20	0,50
0,1mg BEP DS	6	1,66	$\pm$	0,49	0,83
1 mg BEP DS	6	0,74	$\pm$	0,35	0,12
10 mg BEP DS	8	1,77	$\pm$	0,45	0,66
0,1 mg P1075 BS	6	0,42	$\pm$	0,08*	0,03
0,5 mg P1075 BS	6	1,18	$\pm$	0,15	0,48
1 mg P1075 BS	6	1,51	$\pm$	0,31	0,93
0,1 mg P1075 DS	8	1,65	$\pm$	0,61	0,83
0,5mg P1075 DS	6	0,65	$\pm$	0,18	0,09
1 mg P1075 DS	8	1,26	$\pm$	0,70	0,55
5HD BS	8	1,10	$\pm$	0,37	0,36
5HD DS	10	1,45	$\pm$	0,30	0,82
HMR 1098 DS	8	1,31	$\pm$	0,23	0,61
HMR 1098 BS	8	1,00	$\pm$	0,17	0,25

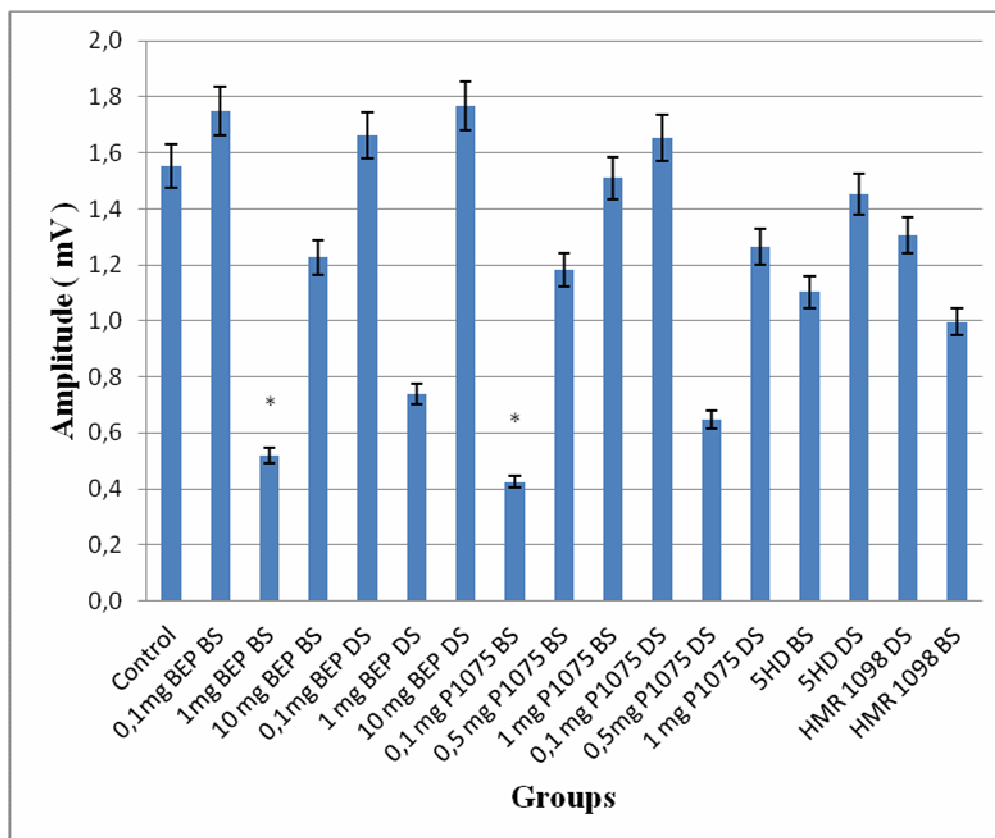


Figure 3.87. Spike wave amplitudes in mV obtained from 170 to 175 minutes recordings (Period 35). (Data are means $\pm$ SE *P<0.05: Compared to control).

**3.13.36. The amplitude of spike wave between 175 To 180 minutes in all groups
(Period 36)**

The spike wave amplitudes in groups 1mg/kg Bepridil bs ; 0,1mg P 1075 bs between 170-180 minutes time interval were significantly smaller than the control group ($p<0,05$) (Table.3.71, Fig.3.87).

Table 3.71. Spike wave amplitude (mV) obtained from 170 to 175 minute recordings and P values in all groups. (Data are means $\pm$ SE * $P<0.05$: Compared to control).

Groups	N	Mean $\pm$ SE			p Value
Control	9	1,66	$\pm$	0,30	
0,1mg BEP BS	6	1,88	$\pm$	0,27	0,67
1mg BEP BS	6	0,53	$\pm$	0,25*	0,03
10 mg BEP BS	8	1,23	$\pm$	0,19	0,38
0,1mg BEP DS	6	1,60	$\pm$	0,50	0,92
1 mg BEP DS	6	0,74	$\pm$	0,36	0,08
10 mg BEP DS	8	1,73	$\pm$	0,46	0,88
0,1 mg P1075 BS	6	0,41	$\pm$	0,07*	0,02
0,5 mg P1075 BS	6	1,15	$\pm$	0,18	0,34
1 mg P1075 BS	6	1,54	$\pm$	0,29	0,82
0,1 mg P1075 DS	8	1,54	$\pm$	0,56	0,81
0,5mg P1075 DS	6	0,65	$\pm$	0,18	0,06
1 mg P1075 DS	8	1,25	$\pm$	0,69	0,40
5HD BS	8	0,99	$\pm$	0,38	0,17
5HD DS	10	1,44	$\pm$	0,31	0,63
HMR 1098 DS	8	1,19	$\pm$	0,26	0,33
HMR 1098 BS	8	1,04	$\pm$	0,17	0,21

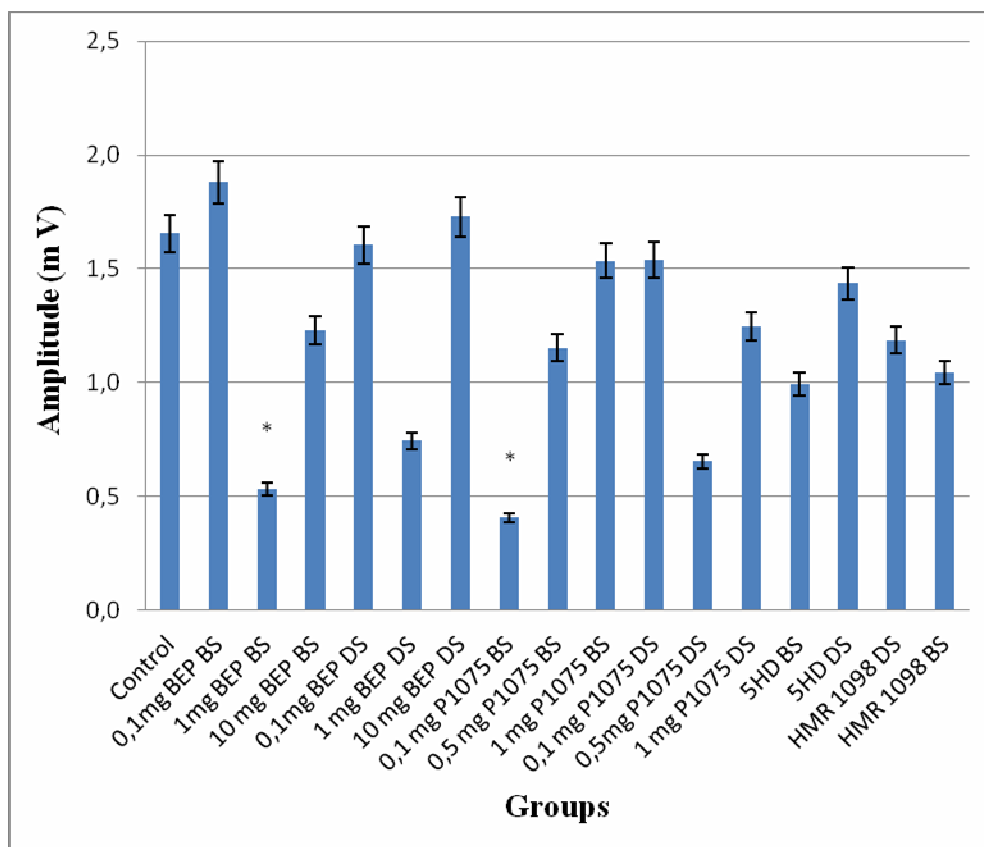


Figure 3.88. Spike wave amplitudes in mV obtained from 175 to 180 minutes recordings (Period 36) (Data are means $\pm$ SE *P<0.05: Compared to control).

4. DISCUSSION

ATP dependent potassium channel blocker used in this study increased the frequency of spike activity, otherwise opener decreased the seizure activity during epileptic seizure. In the literature, the effect of glybenclamide (K_{ATP} channel blocker) and pinacidil (K_{ATP} channel opener) on the epileptic seizure were researched (213). Although not identical drug were used, the result of this study had similarities to the previous studies in that P1075, ATP dependent potassium channel opener, decreased the duration and frequency of the epileptic activity, otherwise HMR1098, ATP dependent K channel blocker, increased the duration and frequency of epileptic activity (213).

Bepridil used in this study has a dual effect as a $mitoK_{ATP}$ channel opener and a $sarK_{ATP}$ channel blocker. Since dose of bepridil was not clear in the literature, it was studied in three different doses of bepridil and results were compared with the control. Bepridil applied before epileptic seizure was effective on spike wave frequency in all doses. Especially it was more effective at lower doses. Bepridil applied during epileptic seizure was only effective in doses of 0,1 and 1 mg/kg. Since there were no study found indicating the effect of bepridil on the seizure, the result related with bepridil could not be compared. But it was known that bepridil closes sarcolemmal K_{ATP} channel and opens mitochondrial K_{ATP} channel (214). It was found very effective to decrease arrhythmia induced by ischemia and reperfusion. In

this study bepridil was found to be effective to decrease the spike wave frequency during epileptic seizure. The effect of bepridil might be derives from its effect on to the K_{ATP} channel in neurons. Since bepridil is known to be effective on the ATP dependent potassium channel, possibly the spike occuring during epileptic seizure are related with the ATP dependent potassium channel modulation. It has been reported that bepridil is an antianginal agent having vasodilator and direct cardiac effects, including negative chronotropic and inotropic effects (215). Bepridil, in animal models, has robust anti-arrhythmic activities. It has been demonstrated by electrophysiological studies that bepridil action potential duration (216). Studies showed that bepridil has a protective effect and prolong the action potential duration in myocardial cell (216-217). Scientist have studied physiological and pathophysiological roles of K_{ATP} channels primarily using K_{ATP} channel blockers and K^+ channel openers, but there is no direct evidence on the role of the K_{ATP} channels (218, 219, 220, 221, 222). In the previous studies, it was shown that K_{ATP} channels couple with the intracellular metabolic state and it is important in the control of neuronal excitability and seizure propagation (223, 224, 225). A key role in the induction and maintenance of kindling of the PTX-induced seizures may involve the changes in the K_{ATP} channels that observed in kindled rat brain (226).

Cytoprotective effect of bepridil can be explained by following possible mechansim. Due to the seizure, nerve cell become ischemic and get less blood flow. In that condition just as like ischemic myocardial cell, electrical potential change and heterogenicity increases. Nerve cell having continous discharge prolonge spike activity in seizure. Since blocker increases the ischemic damage in the nerve cell, seizure activity increases more, otherwise opener decreases this type of activity. Recently opening of sarcolemmal K_{ATP} channel and blockage of mitochondrial K_{ATP}

channel at the same time was found to be more protective against the arrhythmia induced by ischemia and reperfusion in heart (227, 228). In our study bepridil was found more protective against epileptic seizure in similar way. Mechanism of the protection in both cases might be similar, since in both study suggest that irregular senchronised activity decreases in the presence of both blockage of sarcolemmal K_{ATP} channel and opening of mitochondrial K^+ channel. Blockage of Potassium influx into the mitochondria leads to the osmotic swelling and finally leads to the ruptering the cell. Opening of mito K_{ATP} channel prevents this type of damage and preserve the cell. Otherwise, opening of sarcolemmal K_{ATP} channel decrease calcium overloading in the nerve cell and decrease action potential duration and shorten the continous discharge leading to seizure spike initiation.

CA1 decreases K^+ flux, depending on concentration in neurons (229). This result suggest that blockade of K currents by bepridil contributes to the protection of brain against ischemic damage (230). Also Bepridil provides its anti-arithmetic effect by opening mito K_{ATP} channels and closing sarcoplasmic channels (214). Thus K^+ in cytoplasm migrates to mitochondri and may lead to Ca^{++} channel blocakage (215). Further studies should be need to perform to understand the precise role of K inflow on the blockage of Ca cahannel. Bepridil is used in clinical studies as a calcium channel blocker (214). It was also observed by patch clamp techniques that bepridil was effective to decrease K outflux (231).

Sarc K_{ATP} channels are found in the cell membrane and controls electrical activity of the brain (219, 222, 225, 229). Mito K_{ATP} channels, are found in inner mitochondrial membrane and regulates mitochondrial volume and also have a role in protection of cell (232, 233). Both two types of K_{ATP} channels are normally closed state. Under

abnormal conditions, K_{ATP} channels in cell have tendency to open under metabolical stress (hypoclycemia, hypoxia, ischemia etc.).

In the experimental epilepsy studies done with PTZ and kainic acid it has been observed that K_{ATP} channel blockers (glibenclamide, 4-aminopyridine) trigger the seizure and shorten the latency, on the other hand openers (cromakalim) prevent seizure and prolong the latency (219-220, 223, 234, 235, 236, 237, 238, 229).

Ischemic brain damage induced by carotid ligation is prevented by Bepridil. In these conditions it was suggested that the membrane hyperpolarization is induced by hypoxia and anoxia, and extracellular K^+ concentration increases by activation of K^+ channels. Sarcolemmal blockage and mitochondrial opening of ATP dependent potassium channel induced by bepridil was shown to decrease brain injury induced by the ligation of arteria carotis (239, 240, 241). Similar event might be effective in this study. Bepridil might decrease the electrical discharge induced by pencillin induced seizure and result in less frequency of spike during seizure.

P1075, a derivative of pinacidil, is a cytoplasmic K_{ATP} channel agonist. Up to date P1075 was used in ischemia / reperfusion studies done on heart (242-243). Effective doses and effects on brain and epilepsy was not clear in the literature. P1075 was thought to be effective in epilepsy as a hypothesis of this study. But it was not found to be effective to decrease the frequency of epileptic spike in all doses. P 1075 in 0.1 mg/kg, 0.5 mg/kg, 1mg/kg of doses and the effect of timing of application were first tested in this study. P 1075 in a 0.1 mg/kg dose applied before seizure increased latency compared to control. In 0.1 mg/kg dose of P1075 both before seizure and during seizure groups was observed to have decreased spike frequency compared to control group. In this group the seizure have ended early. In the group that P1075 applied in 1 mg/kg dose, it was not effective as like in its lower doses on the

reducing spike frequency. P1075 open the K_{ATP} channels, cell become hyperpolarized and repolarized rapidly. The start of the seizure delayed and spike frequency decreased. According to these results it could be said that, 0.1 mg/kg dose of P1075 applied before seizure has protective effect against to the epileptic seizure. Since there are no comparable study found in the literature related with the effect of P1075 on the epileptic seizure, these results could not be compared.

In many studies performed before, it was shown that ischemic preconditioning decrease ischemic and hypoxic damage in brain and heart (244-245). In this study, openers might be showing preconditioning effect when they are given before seizure. Both P1075 and bepridil decreased the frequency of spike and their duration when they are given before seizure.

On metabolic conditions as hypoxia or ischemia, intracellular ATP/ADP level decreases, sarc K_{ATP} channels open and K^+ outfluxes, as a result, cell hyperpolarizes in which voltage gated Ca^{++} channels close and Ca^{++} influx decreases. Anaerobic respiration occurs in the cell and lactic acid accumulate intracellularly. As lactic acid increases also H^+ ion concentration resulting in decreased pH and inhibition of anaerobic respiration. Since ATP amount is declined Na/K ATPase pump does not work. Na^+ gets into the cell via Na^+-H^+ and Na^+-Ca^+ exchangers. There are openings in the K_{ATP} channels by the blockage of Ca^{++} influx, which are also called Ca^{++} channel antagonists (246-247)

HMR 1098 is specific for the heart (239). However Zhang and his friends, in their studies conducted in 2011, suggest that HMR 1098 was not specific to SUR isotype in heart (249, 250). In this study, it was found that HMR 1098 application during and before seizure increased spike wave frequency significantly. This means that HMR 1098 was also effective to the K_{ATP} channel in nerve cell. K_{ATP} channel

antagonist, HMR 1098 has a prolongation effect on seizure. In addition studies in heart showed that HMR 1098 shorten action potential duration (251-252). Plasma membrane sarcolemmal K_{ATP} channel is blocked by this drug, but mito K_{ATP} channels are not blocked (253). Since HMR 1098 is a sarcolemmal channel blocker, by closing K_{ATP} channels that open during seizure and it blocks K efflux and leads to Ca^{++} overload which means intracellular Ca^{++} amount increases and seizure gets more severe. When it is applied before seizure, it decreases seizure threshold because of stimulation of Ca^{++} overload. In our study, HMR1098 increased the spike frequency when it is applied both during and before seizure are coincident with the above mentioned electrophysiologic effect.

When Sarcolemmal K_{ATP} channels are closed, K^+ can not leave out of the cell and Ca^{++} influx increases. High amount of intracellular Ca^{++} level activates degradative enzymes and cell goes to lysis. In this study, increase in intracellular Ca^{++} concentration makes the cell more positive (depolarization) which leads to easy stimulation. While increases in intracellular Ca^{++} concentration causes over excitation of neurons, it also damages the cell irreversibly by activating many degradative enzymes including apoptotic pathway (224-254-255).

The results obtained from statistical evaluations states that sarcolemmal K_{ATP} openers, decreases spike wave frequency and seizure initiation times more successfully than mitochondrial channel openers. Another valuable information obtained from these results is that sarcolemmal channel blockers increases spike wave frequency and decreases seizure initiation times much more than mitochondrial channel blockers. According to data obtained in this study, it can be said that sarcolemmal channels are more effective in decreasing epileptic seizure.

5HD in 10mg/kg dose were used in different experimental epilepsy models (237, 256, 257) and it was applied before seizure and during seizure in the same dose as like in the present study. In the above study, it was found that 5HD increased spike wave frequency similarly as like in our present study. While spike wave frequency was lower than the control group in between 1 to 15 periods, in later time it was same with the control group. 5HD is the commonly used mitochondrial blocker and selectively block $\text{mitoK}_{\text{ATP}}$ channels. In intact cells, 5-HD fails to inhibit $\text{sarcK}_{\text{ATP}}$ channels, suggesting that mitochondria are the targets of 5-Hydroxydecanoate (5-HD) that it inhibits the protective effect of ischemic preconditioning, and it is assumed to be a selective inhibitor of mitochondrial ATP-sensitive K^+ ($\text{mitoK}_{\text{ATP}}$) channels (257, 258, 259, 260). 5-HD is also a substrate for mitochondrial outer membrane acyl-CoA synthetase, which catalyzes the reaction: $5\text{HD} + \text{CoA} + \text{ATP} \rightarrow 5\text{-HD-CoA (5-hydroxydecanoyl-CoA)} + \text{AMP} + \text{pyrophosphate}$. $\text{SarcK}_{\text{ATP}}$ channels are inhibited by 5-HD in the absence of ATP and CoA but insensitive to 5-HD-CoA. As a result of above study it was suggested that 5HD is not a specific blocker, it effects both mitochondrial and cytoplasmic K_{ATP} channels.

5HD is a selective mitochondrial blocker and protect the nerve cell against seizure induced damage. During the epileptic seizure, nerve cell get less blood flow and become ischemic. Blockage of mitochondrial channel by 5HD in normal condition, leads to the calcium loading in mitochondria. Increasing in mitochondrial calcium leads to activation of degradative enzymes that result in the stop of aerobic respiration and decreasing ATP production. By this way 5HD may increase cellular damage and the severity of epileptic discharges.

Most of potassium channel inhibitors and activators interact both $\text{mitoK}_{\text{ATP}}$ and sarcoplasmic K_{ATP} channels (245) The influx of K^+ could be involved in changes in

mitochondrial membrane potential, mitochondrial volume homeostasis, or respiration and pH gradient (246). Additionally, reactive oxygen species synthesis is regulated by the influx of K^+ ions across the inner mitochondrial membrane (247).

Cytoprotective effect of potassium channel openers were observed both in cardiac and neural tissue cell (251). In this study, cytoprotective effect of opener was not measured or evaluated. But the decreased latency of seizure in P1075 and bepridil treated rats might be derived from this kind of cytoprotective effect.

Epilepsy is a disease occurring because of extreme activation of nervous system. Increased glutamate and Ca^{++} in brain is another reason of epilepsy and it has been shown in many studies that it triggers neuronal cell death. It has been long-confirmed by experimental models and clinical studies that a prolonged seizure or status epilepticus (SE) can cause neuronal death in the brain (243,257). But, the detailed effect of K_{ATP} channel openers and blockers on neuronal death and apoptosis in cerebral ischemia–reperfusion-induced injury has not been fully understood, and whether mito K_{ATP} channels play a more important protective role than sarc K_{ATP} channels in the brain is unclear.

Epileptic seizures caused by ischemia and trauma lead to formation of excitotoxicity, free radicals, inflammation and cell apoptosis. Today antiepileptic drugs used in the treatment inhibits one or more of these destructive mechanisms which results in decrease or stop of cell damage and epilepsy. It is estimated that K_{ATP} openers used in this study, might decrease the cell damage by stopping one or more of these destructive mechanism (258).

K_{ATP} channel openers and blocker have been used in epileptic studies induced by pilokarpine, pentilentetrazol and kainic acid, but the effect of sarcoplasmic openers and blockers on the seizure activity have not fully determined (224). In these studies

it was found that K_{ATP} channel openers increase seizure threshold and decrease spike wave frequency, while blockers conversely decrease seizure threshold and increase spike wave frequency.

In this study the effects of special drugs on penicillin induced epilepsy was researched. Results obtained in this study was confirmed the result of previous study so that K_{ATP} channel openers increased seizure threshold and decreased spike wave frequency (9-10). In addition to the previous research, in this study it was investigated the effects of bepridil that is both mitochondrial opener and sarcoplasmic K_{ATP} channel blocker, and selective sarcoplasmic opener, P1075 on the seizure activity. According to these results sarcoplasmic K_{ATP} channel openers had more positive effect on spike wave frequency, amplitude and seizure initiation time than mitochondrial K_{ATP} channels openers. In addition it has been found that selective mitochondrial blocker, 5HD increased seizure activity. Selective opening of mitoK_{ATP} channels had neuroprotective effects against ischemia–reperfusion injury in the brain, neurons could be protected against death and injury by activation of mitoK_{ATP} channels (244).

In this study differently from other studies, drugs were applied in two different time; before and during seizure and it is found that drugs had different effects according to application time of drug. For example Bepridil and P1075 application during seizure shorten the length of seizure activity having spike wave. Otherwise application of HMR 1098 and 5HD before seizure increased spike wave frequency

K_{ATP} channel blockers; tolbutamine, glibencilimide and 5HD were used in various research studying experimental epilepsy model (261, 262). Their effects on spike wave frequency were not studied in that research. However the effect of K_{ATP}

channel blockers on the threshold of seizure and the duration of seizure activity were observed in that study.

5. CONCLUSION

The modulation of K_{ATP} channel is important in the seizure activity. K_{ATP} blocker increases seizure activity, but opener has opposite effect. Since HMR1098 increased seizure activity more than 5HD, sarcolemmal blockage instead of mitochondrial blockage can be said to be more effective in the prolongation of seizure activity. P1075 was most effective drug in respect to bepridil in decreasing epileptic seizure activity. This means that sarcolemmal K_{ATP} blocking and mitochondrial K_{ATP} opening at the same time are effective to decrease epileptic activity. Dose dependent effect of P1075 and bepridil shows that the epileptic activity might be related with level of opened sarcolemmal K_{ATP} channel.

6. FUTURE PROSPECTIVES

This study showed that K_{ATP} channel are related with generation of epileptic activity. Since both mitochondrial and sarcolemmal K_{ATP} channel modulator are involved in this activity, more study should be performed to understand selective role of these channel using by selective drug. Although the dual effect of both sarcolemmal and mitochondrial K_{ATP} channel was investigated in myocardial injury and arrhythmia, although same lacking were there in ischemia and reperfusion induced arrhythmia. There are still so less studies researching the dual or selective effect of mitochondrial and sarcoplasmic channel opener or blocker on the generation of seizure activity. Since there are ischemic and hypoglycemic effect of K_{ATP} channel blocker, the relation of hypoglycemia and hyperglycemia together with the selective K_{ATP} channel modulator should be evaluated in further research. HMR1098 initiate the epileptic seizure early and lead to the long lasting seizure activity. Possible reason of this might be depend on its ischemic effect due to the calcium overloading. But the calcium overloading or ischemic damage were not determined in this study. In further research, the underlying mechanism of early initiation and longer seizure activity induced by HMR1098 should be studied. Bepridil decreased seizure activity. Possible reason of this effect might be depends on its effect on blocking of sarcolemmal channel and opening of mitochondrial channel together. But still there are no clarity in the mechanism of bepridil on seizure activity occurring in

experimentally induced epilepsy. The mitochondrial or sarcolemmal channel blockage or opening are more predominant in this effect are open to study. We found that P1075 is more effective to decrease epileptic activity. This might be due to the opening of sarcolemmal K_{ATP} channel. But this should be supported by further studies. We did not measure blood glucose, insulin and apoptosis, necrosis and the level of ischemia in control and drug treated group. In further research, only the effect of K_{ATP} channel blocker in the induction of epileptic seizure and its relation with hypoglycemia and ischemic level can be evaluated. Especially the role of K_{ATP} channel modulator in the ischemia induced epilepsy model might be researched. Since there are genetic basis of epilepsy, and the number of K_{ATP} channel are determined by the genetic inheritance, the epileptic activity should be researched in K_{ATP} knockout rats or the number of K_{ATP} channel in rats that are very prone to epilepsy should be studied.

7. REFERENCES

1. Bagirici F, Gokce FM, Marangoz C. Depressive effect of nicardipine on penicillin-induced epileptiform activity in rats. *Neuroscience Research Communications*; 24: 149–154. 1999.
2. Banarjee PN, Filippi D, Hauser WA. The descriptive epidemiology of epilepsy: A review. *Epilepsy Research*; 85: 31-34. 2009.
3. Cook DL, Satin LS, Ashford ML, Hales CN. ATP-sensitive K⁺ channels in pancreatic beta-cells, spare channel hypothesis. *Diabetes*; 37: 495–498. 1988.
4. Mannhold R. KATP channel openers: structure–activity relationships and therapeutic potential. *Medical Research Review*; 24:213–66. 2004
5. Jahangir A, Terzic A. KATP channel therapeutics at the bedside. *Journal of Molecular and Cellular Cardiology*; 39: 99-112. 2005.
6. Hernandez SC, Basile AS, Fedorova I, Arima H, Stannard B, Fernandez AM. Mice transgenically overexpressing sulfonylurea receptor 1 in forebrain resist seizure induction and excitotoxic neuron death. *Proceeding of the National Academy of Science*; 98: 3549–54. 2001.
7. Yamada K, Inagaki N. Neuroprotection by KATP channels. *Journal of molecular and cellular cardiology*; 38: 945-949. 2005.

8. Ghasemi M, Shafaroodi H, Karimollah AR, Gholipour T, Nezami BG, Ebrahimi F, Dehpour AR. ATP sensitive potassium channels contribute to the time –dependent alteration. *Seizure*; 19: 53 –58. 2010.
9. Sarantopoulos C, McCallum B, Sapunar D, Kwok WM, Hogan Q. ATP-sensitive potassium channels in rat primary afferent neurons: the effect of neuropathic injury and gabapentin. *Neuroscience Letter*; 343: 185-189. 2003.
10. Kobayashi K, Nishizawa Y, Sawada K, Ogura H, Miyabe M. K⁺-channel openers suppress epileptiform activities induced by 4- Aminopyridine in cultured rat hippocampal neurons. *Journal of Pharmacological Science*; 108: 517-528. 2008.
11. Shafaroodi H, Asadi S, Sadeghipour H, Ghasemia M, Ebrahimi F, Tavakoli S, Hajrasouliha AR, Dehpour AR. Role of ATP- sensitive potassium channels in the biphasic effects of morphine on pentylenetetrazole-induced seizure threshold in mice. *Epilepsy Research*; 75: 63-69. 2007.
12. Zupec-Kania BA, Spellman E. An overview of the ketogenic diet for pediatric epilepsy. *Nutrition in Clinical Practice*; 23: 589-596. 2009.
13. Shneker BF, Fountain NB. *Epilepsy. Disease a month*; 49: 426-78. 2003.
14. Fisher RS, Emde BW, Blume W. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsy*; 46 : 470-472. 2005.
15. Baykan B, Gürses C, Gökyiğit A. *Nöroloji*. Ed: Öge EA. *Epilepsi*. 2.Basım. Istanbul: Nobel Tıp Kitabevleri; 279-308. 2004.
16. Stafstrom CE. Epilepsy: a review of selected clinical syndromes and advances in basic science. *Journal of Cereb Blood Flow& Metabolism*; 26: 983-1004. 2006.
17. Sánchez AR, Sanmartí FX, Serratosa JM. Genetic causes of epilepsy. *Neurologist*; 13: 47-51.2007.

18. Kang JQ, Macdonald RL. Making sense of nonsense GABA(A) receptor mutations associated with genetic epilepsies. *Trends in Molecular Medicine*; 15: 430-438. 2009

19. Dibbens LM, Harkin LA, Richards M. The role of neuronal GABA(A) receptor subunit mutations in idiopathic generalized epilepsies. *Neuroscience Letter*; 453: 162-165. 2009.

20. Wallace R. Mutations in GABA-receptor genes cause human epilepsy. *The Lancet Neurology*; 1: 212. 2002.

21. Alexander GM, Godwin DW. Metabotropic glutamate receptors as a strategic target for the treatment of epilepsy. *Epilepsy Research*; 71: 1–22. 2006.

22. Moldrich RX, Chapman AG, De Sarro G, Meldrum BS. Glutamate metabotropic receptors as targets for drug therapy in epilepsy. *European Journal of Pharmacology*; 476: 3-16. 2003.

23. Aroniadou AV, Fritsch B, Qashu F, Braga MF. Pathology and pathophysiology of the amygdala in epileptogenesis and epilepsy. *Epilepsy Research*; 78: 102-116. 2008.

24. Roshan MS, Ferrigan L, Khoshnood MJ, Davies CH, Cobb SR. Regulation of epileptiform activity in hippocampus by nicotinic acetylcholine receptor activation. *Epilepsy Research*; 56: 51-65. 2003.

25. Zimmerman G, Njunting M, Ivens S. Acetylcholine-induced seizure-like activity and modified cholinergic gene expression in chronically epileptic rats. *European Journal of Pharmacology*; 27: 965-975. 2008.

26. Zaidel DW, Esiri M, Oxbury JM. Regional differentiation of cell densities in the left and right hippocampi of epileptic patients. *Journal of Neurology*; 240: 5: 322-325. 1993.

27. Alberch J, Arenas E, Arroyos AR, Marsal J. Excitatory amino acids release endogenous acetylcholine from rat striatal slices: Regulation by Gammaaminobutyric acid. *Neurochem International*; 17: 107-116. 1990.

28. Chanuta E, Benoît B, Lacroixa L, Nodab A, Gasdeblayc S, Bondierd JR. Botterid CV. Variations of dopamine, serotonin, and amino acid concentrations in Noda epileptic rat (NER) *Retina Brain Research*; 1: 56 – 64. 2006.

29. Chapman AG, Meldum BS, Siesjo BK. Cerebral metabolic changes during prolonged seizures in rats. *Journal of Neurochemistry*; 28: 1025-1035. 1977.

30. Cain DH, Boon P, Bevan M. Failure of Aspartame to Affect Seizure susceptibility in kindled rats. *Neuropharmacology*; 28: 433-435. 1989.

31. Guilarte TR. Regional changes in the concentrations of Glutamate, Glycine, Taurine and GABA in the Vitamin B6 Deficient developing rat brain: Association with neonatal seizures. *Neurochemical Research*; 14: 889-897. 1989.

32. Durlach JP, Rouhani S, Bara S, Guet BM. The control of central neuronal Hyperexcitability in Magnesium Deficiency, Nutrients and Brain Function. *Central neuronal Excitability and magnesium Deficiency*; 48-71. 1987.

33. Fisher RS. Animal models of the epilepsies. *Brain Research*; 14: 245- 278. 1989.

34. Engel JJ, Kuhl DE, Phelps ME, Chandall PH. Comparative localization of epileptic foci in partial epilepsy by PCT and EEG. *Annals of Neurology*; 12: 529-537. 1982.

35. Elmer E, Kokaia M, McIntyre DC, Londavall O. Epileptogenesis induced by rapidly recurring seizures in genetically fast-but not slow-kindling rats. *Brain Research*; 789: 111- 117. 1998.

36. Mason CR, Cooper RM. A permanent change in convulsive threshold in normal and braindamaged rats with repeated small doses of pentylenetetrazol. *Epilepsia*; 13: 663-674. 1972.
37. Mc Namara JO. Kindling: an animal model of complex partial epilepsy. *Annals of neurology*; 168: 72-76. 1984.
38. Seino M. Classification criteria of epileptic seizures and syndromes. *Epilepsy Research*; 70: 27-33. 2006.
39. Coppola G, Arcieri S, D'Aniello A. Levetiracetam in submaximal subcutaneous pentylenetetrazol-induced seizures in rats. *Seizure*; 19: 296-299. 2010.
40. Pitkanen A, Schwartzkroin PA, Moshé SL. Models of seizures and epilepsy. Elsevier Academic Press; 345-350. 2006.
41. Fisher RS, and Prince DA. Spike wave rhythms in cat cortex induced by parenteral penicillin. II. Cellular features. *Electroencephalography and clinical Neurophysiology*; 42: 625- 639.1977.
42. Gloor P. Generalized Epilepsy with Spike-and-Wave Discharge: A Reinterpretation of its Electrographic and Clinical Manifestations. *Epilepsia*; 20: 571–588. 1979.
43. Guberman A, Gloor P, Sherwin AL. Response of generalized penicillin epilepsy in the cat to ethosuximide and diphenylhydantoin. *Neurology*; 25:758-764. 1975.
44. Yıldırım M, Ayyıldız M, Agar E. Endothelial nitric oxide synthase activity involves in the protective effect of ascorbic acid against penicillin-induced epileptiform activity. *Seizure: European Journal of Epilepsy*; 19: 102-108. 2010.
45. Matsumoto H, Ajmone MC. Cortical cellular phenomena in experimental epilepsy: interictal manifestations. *Experimental Neurology*; 9: 286-304. 1964.

46. Johnston D, Brown TH. Mechanisms of neuronal burst generation. In Schwartzkroin PA, Wheal H. Electrophysiology of Epilepsy. London Academic Press; 277-301. 1984.
47. Noebels JL, Pedley TA. Anatomic localization of topically applied penicillin during experimental focal epilepsy in cat neocortex. Brain Research; 125:293-303.1977.
48. Prince DA, Wilder BJ. Control mechanisms in cortical epileptogenic foci. Archives of Neurology; 16: 194-20.1967.
49. Mac Donald RL, Barker JL. Pentilenetetrazol and penicillin are selective antagonists of GABA-mediated post-synaptic inhibition in cultured mammalian neurons. Nature; 267; 720-721. 1977.
50. Hill RG, Simmonds MA, Straughn DW. A Comparative study of some convulsant substances as gamma-aminobutyric acid antagonists in the feline cerebral cortex. British Journal of Pharmacology; 49: 37-51. 1973.
51. Dingledine R, Gjerstad L. Reduced inhibition during epileptiform activity in the in vitro hippocampal slice. Journal of Physiology London; 305: 297-313. 1980.
52. Ayala GF, Vasconsetto C. Penicillin as an epileptogenic agent: its effect on an isolated neuron. Science; 167: 1257-1260. 1970.
53. Marangoz C, Karatoy M. Penisilin epilepsisi odağında inhibitör sistemler üzerine deneysel bir çalışma. Atatürk Üniversitesi Fen Fakültesi Dergisi. Özel Sayı 1; 1: 112-122. 1982.
54. Marangoz C, Ayyıldız M, Ağar E. Evidence that sodium nitroprusside possesses anticonvulsant effects mediated through nitric oxide. Neuro Report; 5: 2454 - 2456.1994.
55. Prince DA, Farrell D. "Centerencephalic" spike -wave discharges following parenteral penicillin injection in the rat. Neurology; 19: 309-310. 1969.

56. Triggle DJ. Calcium antagonist history and perspective. *Stroke*; 21: 49-58. 1990.

57. Speckmann EJ, Traub H, Köhling R. Contribution of calcium ions to the generation of epileptic activity and antiepileptic calcium antagonism. *Neuropsychobiology*; 27: 122- 126. 1993

58. Carter DS, Haider SN, Blair RE, Deshpande LS, Sombati S, DeLorenzo RJ. Altered Calcium/Calmodulin Kinase II Activity Changes Calcium Homeostasis That Underlies Epileptiform Activity in Hippocampal Neurons in Culture. *The Journal Of Pharmacology and Experimental Therapeutics*; 319: 1021-102. 2006.

59. Shin C, Mc Namara JO. Mechanism of epilepsy. *Annual Review of Medicine*; 45: 379–389. 1994.

60. Delorenzo RJ, Sun DA, Deshpande LS. Cellular mechanisms underlying acquired epilepsy: the calcium hypothesis of the induction and maintenance of epilepsy. *Pharmacology of Therapeutics*; 105: 229–266. 2005.

61. Delorenzo RJ, Pal S, Sombati S. Prolonged activation of the N-methyl-D-aspartate receptor-Ca²⁺ transduction pathway causes spontaneous recurrent epileptiform discharges in hippocampal neurons in culture. *Proceeding of the National Academy Of Sciences*; 95: 14482–14487. 1998.

62. Raza M, Pal S, Rafiq A, DeLorenzo RJ. Long-term alteration of calcium homeostatic mechanisms in the pilocarpine model of temporal lobe epilepsy. *Brain Research*; 903: 1–10. 2001.

63. Raza M, Blair RE, Sombati S, Carter DS, Deshpande LS. and DeLorenzo RJ Evidence that injury-induced changes in hippocampal neuronal calcium dynamics during epileptogenesis cause acquired epilepsy. *Proceeding of the National Academy Of Sciences*; 101: 17522–17527. 2004.

64. Pal S, Sun D, Limbrick D, Rafiq A, DeLorenzo RJ. Epileptogenesis induces long-term alterations in intracellular calcium release and sequestration mechanisms in the hippocampal neuronal culture model of epilepsy. *Cell Calcium*; 30: 285–289. 2001.

65. Sun DA, Sombati S, Blair RE, DeLorenzo RJ. Long-lasting alterations in neuronal calcium homeostasis in an in vitro model of stroke-induced epilepsy. *Cell Calcium*; 35: 155– 156. 2004.
66. Palomero GE, Cuchillo I, García AG, Renart J, Albillos A, Montiel C. Greater diversity than previously thought of chromaffin cell Ca²⁺ channels. derived from mRNA identification studies. *FEBS Letters*; 48: 1235–1239. 2000.
67. García AG, García-De-Diego AM, Gandía L, Borges R, García-Sancho J. Calcium signalling and exocytosis in adrenal chromaffin cells. *Physiological Review*; 86: 1093–1131. 2006.
68. Carbone E, Marcantoni A, Giaccipoli A, Guido D, Carabelli V. T-type channels-secretion coupling: evidence for a fast low-threshold exocytosis. *Pflügers Archiv*; 453: 373–383. 2006.
69. Mahapatra S, Calorio C, Vandael DHF, Marcantoni A, Carabelli V, Carbone E. Calcium channel types contributing to chromaffin cell excitability, exocytosis and Endocytosis. *Cell Calcium*; 51: 321– 333. 2012.
70. Chandy K G, Gutman G A, Grissmer S. Physiological role, molecular structure and evolutionary relationships of voltage-gated potassium channels in T lymphocytes. *Seminars in Neuroscience*; 5: 125–134.1993.
71. Storm J F. Functional diversity of K⁺ currents in hippocampal pyramidal neurons. *Neuroscience*; 5: 79–92. 1993
72. Marangoz C. Sinir fizyolojisiine giriş-I. Beyin korteksi. EEG ve Epilepsi. Samsun: 19 Mayıs Üniversitesi Matbaası baskısı; 120-131. 2001.
73. Bordey A, Lyons A, Hablitz JJ, Sontheimer H. Electrophysiological characteristics of reactive astrocytes in experimental cortical dysplasia. *Journal of Neurophysiology*; 85: 1719– 1731. 2001.

74. Grady MS, Charleston JS, Maris. D., Witgen. B. M., & Lifshitz. J. Neuronal and glial cell number in the hippocampus after experimental traumatic brain injury: analysis by stereological estimation. *Journal of Neurotrauma*; 20: 929–941. 2003.
75. Noma A. ATP-regulated K⁺ channels in cardiac muscle. *Nature*; 305: 147–148. 1983.
76. Ascroft FM. ATP sensitive K⁺ Channels and disease: from molecule to malady. *American Journal Of Physiology, Endocrinology and Metabolism*; 293: 880-889. 2007.
77. Yokoshiki H, Sunagawa M, Seki T, Sperelakis N. Antisense oligodeoxynucleotides of sulfonylurea receptors inhibit ATP-sensitive K⁺ channels in cultured neonatal rat ventricular cells. *Pflügers Archiv* January; 437: 400-408. 1999.
78. Cook DL, Satin LS, Ashford ML, Hales CN. ATP-sensitive K⁺ channels in pancreatic beta-cells; Spare Channel hypothesis. *Diabetes*; 37: 495-498. 1988.
79. Boyth AE. Sulfonylurea receptors, ion channels, and fruit flies. *Diabetes*; 37: 847-850. 1988.
80. Bozdoğan Ö, Suveren E, Gonca E. Anestezi Altındaki Sıçanlarda Reperfüzyon Aritmileri Üzerine Thimerosalin Etkisi ve Bu Etkide ATP Bağımlı Potasyum Kanallarının Rolü. *Düzce Tıp Fakültesi Dergisi*; 4 : 5-9. 2002.
81. Bozdoğan Ö, ATP-dependent Potassium Channel Openers and Blockers: Proarrhythmic and Antiarrhythmic Effects Following Myocardial Ischemia and Reperfusion. *Kafkas Üniversitesi Veteriner Fakültesi Dergisi*; 3: 127-133. 1998.
82. Fujita A, Kurachi Y. Molecular aspects of ATP- sensitive K⁺ channels in the cardiovascular system an K⁺ channel openers. *Pharmacology & Therapeutics*; 85: 39-53. 2000.

83. Fujimura N, Tanaka E, Yamamoto S, Shigemori M, Higashi H.. Contribution of ATP-sensitive potassium channels to hypoxic hyperpolarization in rat hippocampal CA1 neurons in vitro. *Journal of Neurophysiology*; 77: 378–385. 1997.

84. Zawar C, Plant TD, Schirra C, Konnerth A, Neumcke B,. Cell-type specific expression of ATP-sensitive potassium channels in the rat hippocampus. *Journal of Physiology*; 514: 327–341. 1999.

85. Trapp S, Ballanyi K. KATP channel mediation of anoxia-induced outward current in rat dorsal vagal neurons in vitro. *Journal of Physiology*; 487: 37–50. 1995.

86. Ashford ML, Boden PR, Treherne JM. Glucose-induced excitation of hypothalamic neurones is mediated by ATP-sensitive K⁺ channels. *Pflugers Archive*; 415: 479–483. 1990.

87. Ashford ML, Boden PR, Treherne JM. Tolbutamide excites rat glucoreceptive ventromedial hypothalamic neurones by indirect inhibition of ATP-K⁺ channels. *British Journal of Pharmacology*; 101: 531–540. 1990.

88. Dunn Meynell AA, Routh VH, McArdle JJ, Levin BE. Low-affinity sulfonylurea binding sites reside on neuronal cell bodies in the brain. *Brain Research*; 745: 1–9. 1997.

89. Liss B, Bruns, R Roeper J. Alternative sulfonylurea receptor expression defines metabolic sensitivity of KATP channels in dopaminergic midbrain neurons. *Embo journal*; 18: 833–846. 1999.

90. Heurteaux C, Lauritzen I, Widmann C, Lazdunski M. Essential role of adenosine, adenosine A1 receptors, and ATP-sensitive K⁺ channels in cerebral ischemic preconditioning. *Proceedings of the National Academy of Sciences. USA*; 92: 4666–4670. 1995.

91. Blondeau N, Plamondon H, Richelme C, Heurteaux C, Lazdunski M.. KATP channel openers, adenosine agonists and epileptic preconditioning are stress signals inducing hippocampal neuroprotection. *Neuroscience*; 100: 465–474. 2000.
92. Yamada M, Isomoto S, Matsumoto S, Kondo C, Shindo T, Horio Y, Kurachi Y. Sulphonylurea receptor 2B and Kir6.1 form a sulphonylurea-sensitive but ATP-insensitive K⁺ channel. *Journal of Physiology*; 499: 715–720. 1997.
93. Aguilar-Bryan L, Bryan J. Molecular biology of adenosine triphosphate-sensitive potassium channels. *Endocrinology Review*; 20: 101–135. 1999.
94. Ashcroft FM, Gribble FM. Correlating structure and function in ATP-sensitive K⁺ channels. *Trends Neurosciences*; 21: 288–294. 1998.
95. Seino S. ATP-sensitive potassium channels: a model of heteromultimeric potassium channel/receptor assemblies. *Annual Review of Physiology*; 61: 337–362. 1999.
96. Higgins CF. ABC transporters: from microorganisms to man. *Annual Review of Cell Biology*; 8: 67–113. 1992.
97. Conti LR, Radeke CM., Shyng SL, Vandenberg CA. Transmembrane topology of the sulfonylurea receptor SUR1. *The Journal of Biological Chemistry*; 276: 41270–41278. 2001.
98. Tusnady GE, Bakos E, Varadi A, Sarkadi B. Membrane topology distinguishes a subfamily of the ATP-binding cassette (ABC) transporters. *FEBS Lett*; 402: 1–3. 1997.
99. Isomoto S, Kondo C, Yamada M, Matsumoto S, Higashiguchi O, Horio Y, Matsuzawa Y, Kurachi Y. A novel sulfonylurea receptor forms with BIR (Kir6.2) a smooth muscle type ATP-sensitive K⁺ channel. *The Journal of Biological Chemistry*; 271 : 24321–24324. 1996.

100. Chutkow WA, Makielski JC, Nelson DJ, Burant CF, Fan Z.. Alternative splicing of Sur2 Exon 17 regulates nucleotide sensitivity of the ATP-sensitive potassium channel. *The Journal of Biological of Chemistry*; 274: 13656–13665. 1999.

101. Inagaki N, Gono T, Clement JP, Wang CZ, Aguilar-Bryan L, Bryan J, Seino S. A family of sulfonylurea receptors determines the pharmacological properties of ATP-sensitive K⁺ channels. *Neuron*; 16: 1011–1017. 1996.

102. Clement JP, Kunjilwar K, Gonzalez G, Schwanstecher M, Panten U, Aguilar-Bryan L, Bryan J.. Association and stoichiometry of KATP channel subunits. *Neuron*; 18: 827–838. 1997.

103. Shyng S, Ferrigni T, Nichols CG. Regulation of KATP channel activity by diazoxide and MgADP. Distinct functions of the two nucleotide binding folds of the sulfonylurea receptor. *The Journal of General Physiology*; 110: 643–654. 1997.

104. Sakura H, Trapp S, Liss B, Ashcroft FM. Altered functional properties of KATP channel conferred by a novel splice variant of SUR1. *The Journal of Physiology*; 521: 337–350. 1999.

105. Tucker, SJ, Gribble, F.M., Zhao, C., Trapp, S., Ashcroft, F.M.,. Truncation of Kir6.2 produces ATP-sensitive K⁺ channels in the absence of the sulphonylurea receptor. *Nature*; 387: 179. 1997.

106. Sharma N, Crane A, Clement JP, Gonzalez G, Babenko AP, Bryan J, Aguilar-Bryan L. The C terminus of SUR1 is required for trafficking of KATP channels. *The Journal of Biological of Chemistry*; 274: 20628–20632. 1999.

107. Sakura H, Trapp S, Liss B, Ashcroft FM. Altered functional properties of KATP channel conferred by a novel splice variant of SUR1. *The Journal of Physiology*; 521: 337–350. 1999.

108. Zingman LV, Alekseev AE, Bienengraeber M, Hodgson D, Karger AB, Dzeja PP, Terzic, A. Signaling in channel/enzyme multimers: ATPase transitions in SUR module gate ATP-sensitive K⁺ conductance. *Neuron*; 31 :233–245. 2001.
109. Clement JP, Kunjilwar K, Gonzalez G, Schwanstecher M, Panten U, Aguilar-Bryan L, Bryan J. Association and stoichiometry of KATP channel subunits. *Neuron*; 18: 827–838. 1997.
110. Babenko AP, Gonzalez G, Bryan J. Pharmacology of sulfonylurea receptors. Separate domains of the regulatory subunits of KATP channel isoforms are required for selective interaction with K⁺ channel openers. *The Journal of Biological Chemistry*; 275: 717–720. 2000.
111. Mikhailov MV, Proks P, Ashcroft FM, Ashcroft SJ. Expression of functionally active ATP-sensitive K-channels in insect cells using baculovirus. *FEBS Lett*; 429 : 390–394. 1998.
112. John SA, Monck JR, Weiss JN, Ribalet B. The sulphonylurea receptor SUR1 regulates ATP-sensitive mouse Kir6.2 K⁺ channels linked to the green fluorescent protein in human embryonic kidney cells (HEK 293). *The Journal of Physiology*; 510 : 333–345. 1998.
113. Tucker SJ, Gribble FM, Proks P, Trapp S, Ryder TJ, Haug T, Reimann F, Ashcroft FM. Molecular determinants of KATP channel inhibition by ATP. *EMBO Journal*; 17: 3290–3296. 1998.
114. Drain P, Li L, Wang J. KATP channel inhibition by ATP requires distinct functional domains of the cytoplasmic C terminus of the pore-forming subunit. *Proceedings of the National Academy of Sciences USA*; 95 : 13953– 13958. 1998.
115. Tanabe K, Tucker SJ, Ashcroft FM, Proks P, Kioka N, Amachi T, Ueda K. Direct photoaffinity labeling of Kir6.2 by [γ -(32)P]ATP-[γ]4-azidoanilide. *Biochemical and Biophysical Research Communication*; 272 : 316–319. 2000.

116. Matsuo M, Kioka N, Amachi T, Ueda K. ATP binding properties of the nucleotide-binding folds of SUR1. *The Journal of Biological Chemistry*; 274: 37479–37482. 1999.
117. Ueda K, Komine J, Matsuo M, Seino S, Amachi T. Cooperative binding of ATP and MgADP in the sulfonylurea receptor is modulated by glibenclamide. *Proceedings of the National Academy of Sciences*; 96 : 1268–1272. 1999.
118. Ueda K, Matsuo M, Tanabe K, Morita K, Kioka N, Amachi T, Comparative aspects of the function and mechanism of SUR1 and MDR1 proteins. *Biochemical and Biophysical Research Communication*; 1461 : 305–313. 1999.
119. Bienengraeber M, Alekseev AE, Abraham MR, Carrasco A J, Moreau C, Vivaudou M, Dzeja PP, Terzic A. ATPase activity of the sulfonylurea receptor: a catalytic function for the KATP channel complex. *The FASEB Journal*; 14: 1943–1952. 2000.
120. Bear CE, Li C, Galley K, Wang Y, Garami E, Ramjeesingh M,. Coupling of ATP hydrolysis with channel gating by pur reconstituted CFTR. *Journal of Bioenergetics and Biomembranes*; 29 : 465–473. 1997.
121. Ribalet B, Ciani S, Eddlestone GT. ATP mediates both activation and inhibition of KATP channel activity via cAMP-dependent protein kinase in insulin-secreting cell lines. *The Journal of General Physiology*; 94: 693–717. 1989.
122. Beguin P, Nagashima K, Nishimura M, Gono T, Seino S. PKA-mediated phosphorylation of the human KATP channel: separate roles of KIR6.2 and SUR1 subunit phosphorylation. *EMBO Journal*; 18: 4722–4732. 1999.
123. Shyng SL, Nichols CG. Membrane phospholipid control of nucleotide sensitivity of KATP channels. *Science*; 282 : 1138–1141. 1998.
124. Gloyn AL. Relapsing diabetes can result from moderately activating mutations in KCNJ11. *Human Molecular Genetics*; 14: 925–934. 2005.

125. Sakura H, Ammala C, Smith PA, Gribble FM, Ashcroft FM. Cloning and functional expression of the cDNA encoding a novel ATP-sensitive potassium channel subunit expressed in pancreatic beta-cells, brain, heart and skeletal muscle. *FEBS Letters*; 377: 338–344. 1995.

126. Chutkow WA, Simon MC, Le Beau MM, Burant CF. Cloning, tissue expression, and chromosomal localization of SUR2, the putative drug-binding subunit of cardiac, skeletal muscle, and vascular KATP channels. *Diabetes*; 45: 1439–1445. 1996.

127. Isomoto S, Kondo C, Yamada M, Matsumoto S, Higashiguchi O, Horio Y, Matsuzawa Y, Kurachi Y. A novel sulfonylurea receptor forms with BIR (Kir6.2) a smooth muscle type ATP-sensitive K⁺ channel. *The Journal of Biological Chemistry*; 271: 24321–24324. 1996.

128. Aguilar-Bryan L, Nichols CG, Wechsler SW, Clement JPt, Boyd AE, 3rd, Gonzalez G, Herrera-Sosa H, Nguy K, Bryan J, Nelson DA. Cloning of the beta cell high-affinity sulfonylurea receptor: a regulator of insulin secretion. *Science*; 268: 423–426. 1995.

129. Levin BE, Dunn-Meynell AA, Routh VH.. Brain glucose sensing and body energy homeostasis: role in obesity and diabetes. *American Journal of Physiology*; 276: 1223- 1231. 1999.

130. Erecinska M, Dagan F. Relationships between the neuronal sodium/potassium pump and energy metabolism, Effects of K⁺, Na⁺, and adenosine triphosphate in isolated brain synaptosomes. *Journal of Genetic Physiology*; 9: 591-616. 1990.

131. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature*; 402 : 656–660. 1999.

132. Woods SC, Seeley RJ, Porte J D, Schwartz MW. Signals that regulate food intake and energy homeostasis. *Science*; 280: 1378–1383. 1998.

133. Tusnady GE, Bakos E, Varadi A, Sarkadi B. Membrane topology distinguishes a subfamily of the ATP-binding cassette (ABC) transporters. *FEBS Letters*; 402 : 1–3. 1997.

134. Isomoto S, Kondo C, Yamada M, Matsumoto S, Higashiguchi O, Horio Y, Matsuzawa Y, Kurachi Y. A novel sulfonylurea receptor forms with BIR (Kir6.2) a smooth muscle type ATP-sensitive K⁺ channel. *The Journal of Biological Chemistry*; 271 : 24321–24324. 1996.

135. Chutkow WA, Makielski JC, Nelson DJ, Burant CF, Fan Z. Alternative splicing of Sur2 Exon 17 regulates nucleotide sensitivity of the ATP-sensitive potassium channel. *The Journal of Biological Chemistry*; 274: 13656–13665. 1999.

136. Sakura H, Trapp S, Liss B, Ashcroft FM. Altered functional properties of KATP channel conferred by a novel splice variant of SUR1. *The Journal of Physiology*; 521: 337–350. 1999.

137. Clement J P, Kunjilwar K, Gonzalez G, Schwanstecher M, Panten U, Aguilar-Bryan L, Bryan J. Association and stoichiometry of KATP channel subunits. *Neuron*; 18: 827–838. 1997.

138. Inagaki N, Gono T, Seino S. Subunit stoichiometry of the pancreatic beta-cell ATP-sensitive K⁺ channel. *FEBS Lett*; 409 : 232–236. 1997.

139. Shyng S, Ferrigni T, Nichols CG. Regulation of KATP channel activity by diazoxide and MgADP. Distinct functions of the two nucleotide binding folds of the sulfonylurea receptor. *The Journal of General Physiology*; 110: 643–654. 1997.

140. Zerangue N, Schwappach B, Jan YN, Jan LY. A new ER trafficking signal regulates the subunit stoichiometry of plasma membrane KATP channels. *Neuron*; 22: 537–548. 1999.

141. Tucker S J, Gribble FM, Zhao C, Trapp S, Ashcroft FM. Truncation of Kir6.2 produces ATP-sensitive K⁺ channels in the absence of the sulphonylurea receptor. *Nature*; 387: 179–183.1997.
142. Sharma N, Crane A, Clement JP, Gonzalez G, Babenko AP, Bryan J, Aguilar-Bryan L. The C terminus of SUR1 is requiredfor trafficking of KATP channels. *The Journal of Biological Chemistry*; 274: 20628–20632. 1999.
143. Sakura H, Trapp S, Liss B, Ashcroft FM. Altered functional properties of KATP channel conferred by a novel splice variant of SUR1. *The Journal of Physiology*; 521: 337–350.1999.
144. Baukrowitz T, Schulte U, Oliver D, Herlitz S, Krauter T, Tucker SJ, Ruppersberg J P, Fakler B. PIP₂ and PIP as determinants for ATP inhibition of KATP channels. *Science*; 282 : 1141–1144 . 1998.
145. Gribble FM, Tucker SJ, Ashcroft FM. The essential role of the Walker A motifs of SUR1 in KATP channel activation by Mg-ADP and diazoxide. *EMBO Journal*; 16: 1145–1152. 1997.
146. Szewczyk A, Pikula S, Wojcik G, Nalecz MJ. Glibenclamide inhibits mitochondrial K⁺ and Na⁺ uniports induced by magnesium depletion. *The International Journal of Biochemistry and Cell Biology*; 28: 863–971. 1996.
147. Comelli M, Metelli G, Mavelli I. Down modulation of mitochondrial F₀F₁ ATP synthase by diazoxide in cardiac myoblasts: a dual effect of the drug. *American Journal of Physiology Heart and Circulation*; 292: 820–829. 2007.
148. Schäfer G, Wegener C, Portenhauser R, Bojanovski D Diazoxide. An inhibitor of succinate oxidation. *Biochem Pharmacol*; 18: 2678–2681. 1969.
149. Hanley PJ, Mickel M, Löffler M, Brandt U, Daut J. K(ATP) channel-independent targets of diazoxide and 5-hydroxydecanoate in the heart. *Journal of Physiology*; 542: 735–741. 2002.

150. Garlid K D, Halestrap AP. The mitochondrial KATP channel—Fact or fiction? *Journal of Molecular and Cellular Cardiology*; 52: 578–583. 2012.
151. Holmuhamedov E L, Jahangir A, Oberlin A, Komarov A, Colombini M, Terzic A. Potassium channel openers are uncoupling protonophores: implication in cardioprotection. *FEBS Lett*; 568 :167–170. 2004.
152. Ashcroft FM, Harrison DE, Ashcroft SJH. Glucose induces closure of single potassium channels in isolated rat pancreatic b-cells. *Nature*; 312: 446–448. 1984.
153. Ashcroft FM. ATP-sensitive K channels and disease: from molecule to malady. *American Journal of Physiology Endocrinology and Metabolism*; 293: 880–889. 2007.
154. Cook DL, Satin LS, Ashford ML, Hales CN. ATP-sensitive K_p channels in pancreatic beta-cells. Spare-channel hypothesis. *Diabetes*; 37: 495–498. 1988.
155. Tarasov AI, Welters HJ, Senkel S, Ryffel GU, Hattersley AT, Morgan NG, Ashcroft FM. A Kir6.2 mutation causing neonatal diabetes impairs electrical activity and insulin secretion from INS-1 beta-cells. *Diabetes*; 55: 3075–3082. 2006.
156. Zhang Q, Galvanovskis J, Abdulkaderm F, Partridge CJ, Göpel SO, Eliasson L, Rorsman P. Cell coupling in mouse pancreatic beta-cells measured in intact islets of Langerhans. *Philosophical Transactions A: Mathematical. Physical & Engineering Sciences*; 366: 3503–3523. 2008.
157. Dunne MJ, Cosgrove KE, Shepherd RM, Aynsley G A, Lindley KJ. Hyperinsulinism in infancy: from basic science to clinical disease. *Physiological Reviews*; 84 : 239–275. 2004.
158. Ueda K, Matsuo M, Tanabe K, Morita K, Kioka N, Amachi T. Comparative aspects of the function and mechanism of SUR1 and MDR1 proteins. *Biochimica et Biophysica Acta*; 1461: 305–313. 1999.

159. Bienengraeber M, Alekseev AE, Abraham MR, Carrasco AJ, Moreau C, Vivaudou M, Dzeja PP, Terzic A, ATPase activity of the sulfonylurea receptor: a catalytic function for the KATP channel complex. *The FASEB Journal*; 14: 1943–1952. 2000.
160. Bear CE, Li C, Galley K, Wang Y, Garami E, Ramjeesingh M. Coupling of ATP hydrolysis with channel gating by purified, reconstituted, CFTR. *Journal of Bioenergetics and Biomembranes*; 29: 465–473. 1997.
161. Ribalet B, Ciani S, Eddlestone GT. ATP mediates both activation and inhibition of KATP channel activity via cAMP-dependent protein kinase in insulin-secreting cell lines. *The Journal of General Physiology*; 94: 693–717. 1989.
162. Beguin P, Nagashima K, Nishimura M, Gonoi T, Seino S. PKA-mediated phosphorylation of the human KATP channel: separate roles of KIR6.2 and SUR1 subunit phosphorylation. *EMBO Journal*; 18: 4722–4732. 1999.
163. Shyng S, Nichols CG. Membrane phospholipid control of nucleotide sensitivity of KATP channels. *Science*; 282 :1138–1141. 1998.
164. Koster JC, Sha Q, Nichols CG. Sulfonylurea and K⁺-channel opener sensitivity of KATP channels. Functional coupling of KIR6.2 and SUR1 subunits. *The Journal of General Physiology*; 114: 203–213. 1999.
165. Xie LH, Takano M, Kakei M, Okamura M, Noma A. Wortmannin, an inhibitor of phosphatidylinositol kinases, blocks the MgATP-dependent recovery of Kir6.2/SUR2A channels. *The Journal of Physiology*; 514: 655–665. 1999.
166. Sanchez JA, Gonoi T, Inagaki N, Katada T, Seino S. Modulation of reconstituted ATP-sensitive K⁺-channels by GTP-binding proteins in a mammalian cell line. *The Journal of Physiology*; 507: 315–324. 1998.
167. Isomoto S, Kondo C, Yamada M, Matsumoto S, Higashiguchi O, Horio Y, Matsuzawa Y, Kurachi Y. A novel sulfonylurea receptor forms with BIR (Kir6.2) a smooth muscle type ATP-sensitive K⁺ channel. *The Journal of Biological Chemistry*; 271 : 24321–24324. 1996

168. Gribble FM, Tucker SJ, Seino S, Ashcroft FM. Tissue specificity of sulfonylureas: studies on cloned cardiac and beta-cell KATP channels. *Diabetes*; 47 : 1412–1418. 1998.
169. Wellman GC, Quayle JM, Standen NB. ATP-sensitive K⁺ channel activation by calcitonin gene-related peptide and protein kinase A in pig coronary arterial smooth muscle. *The Journal of Physiology*; 507: 117–129. 1998.
170. Beguin P, Nagashima K, Nishimura M, Gonoi T, Seino S.. PKA-mediated phosphorylation of the human KATP channel: separate roles of KIR6.2 and SUR1 subunit phosphorylation. *EMBO Journal*; 18: 4722–4732. 1999.
171. Lin YF, Jan YN, Jan LY. Regulation of ATP-sensitive potassium channel function by protein kinase A-mediated phosphorylation in transfected HEK293 cells. *EMBO Journal*; 19: 942–955. 2000.
172. Shyng SL, Nichols CG. Membrane phospholipid control of nucleotide sensitivity of KATP channels. *Science*; 282 : 1138–1141. 1998.
173. Koster JC, Sha Q, Nichols CG. Sulfonylurea and K⁺-channel opener sensitivity of KATP channels. Functional coupling of KIR6.2 and SUR1 subunits. *The Journal of General Physiology*; 114: 203–213. 1999.
174. Xie LH, Takano M, Kakei M, Okamura M, Noma A. Wortmannin an inhibitor of phosphatidylinositol kinases. blocks the MgATP-dependent regulation of recovery of Kir6.2/SUR2A channels. *Journal of Physiology*; 514 :655-665. 1999.
175. Hopkins F, Fatherazi S, Peter-Riesch B, Corkey BE, Cook DL. Two sites for adenine- nucleotide regulation of ATP-sensitive potassium channels in mouse pancreatic beta-cells and HIT cells. *Journal of Membrane Biology*; 129: 287–295. 1992.
176. Frances M, Ashcroft. ATP-sensitive potassium channelopathies: focus on insulin secretion. *The Journal of Clinical Investigation*; 115: 2047–2058. 2005.

177. Seino S, Miki T. Physiological and pathophysiological roles of ATP-sensitive K⁺ channels. *Progress in Biophysics and Molecular Biology*; 81: 133-176. 2003.
178. Miki T. ATP-sensitive K⁺ channels in the hypothalamus are essential for the maintenance of glucose homeostasis. *Nature Neurosciences*; 4: 507–512. 2001.
179. Wang R. The regulation of glucose-excited neurons in the hypothalamic arcuate nucleus by glucose and feeding-relevant peptides. *Diabetes*; 53: 1959–1965. 2004.
180. Zingman LV. Kir6.2 is required for adaptation to stress. *Proceeding of the National Academy of Science USA*; 99: 13278–13283. 2002.
181. Suzuki M. Role of sarcolemmal KATP channels in cardioprotection against ischemia/reperfusion injury in mice. *Journal of Clinical Investigation*; 109: 509–516. 2002.
182. Liss B, Bruns R, Roeper J. Alternative sulfonylurea receptor expression defines metabolic sensitivity of KATP channels in dopaminergic midbrain neurons. *EMBO Journal*; 18: 833–846. 1999.
183. Gloyn AL. Activating mutations in the ATP-sensitive potassium channel subunit Kir6.2 gene are associated with permanent neonatal diabetes. *The New England Journal of Medicine*; 350: 1838–1849. 2004.
184. Sagen JV. Permanent neonatal diabetes due to mutations in KCNJ11 encoding Kir6.2: patient characteristics and initial response to sulfonylurea therapy. *Diabetes*; 53: 2713–2718. 2004.
185. Daut J, Klieber HG, Cyrys S, Noack T. KATP channels and basal coronary vascular tone. *Cardiovascular Research*; 28: 811–817. 1994.

186. Spanswick D, Smith MA, Mirshamsi S, Routh VH, Ashford ML. Insulin activates ATP-sensitive K⁺ channels in hypothalamic neurons of lean, but not obese rats. *Nature*; 3 : 757–758. 2000.
187. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ, Bauer T.L. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *The New England Journal of Medicine*; 334: 292–295. 1996.
188. Bagdade JD, Bierman EL, Porte D.. The significance of basal insulin levels in the evaluation of the insulin response to glucose in diabetic and nondiabetic subjects. *Journal of Clinical Investigation*; 46: 1549–1557. 1967.
189. Schwartz MW, Woods SC, Porte D, Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature*; 404 : 661–671. 2000.
190. Koster J C, Marshall BA, Ensor N, Corbett JA, Nichols CG Targeted overactivity of beta cell KATP channels induces profound neonatal diabetes. *Cell*; 100: 645–654. 2000.
191. Wickenden AD. Potassium channels as anti-epileptic drug targets. *Neuropharmacology*; 43:1055-1060. 2002.
192. Joshi S, Rajasekaran K, Kapur J. GABAergic transmission in temporal lobe epilepsy: The role of neurosteroids. *Experimental Neurology*; 244: 36-42. 2013.
193. Schuit FC, Huypens P, Heimberg H, Pipeleers DG. Glucose sensing in pancreatic beta-cells: A model for the study of other glucose-regulated cells in gut pancreas and hypothalamus. *Diabetes*; 50: 1- 11. 2001.
194. Ohtsuka T, Ishiwa D, Kamiya Y, Itoh H, Nagata I, Saito Y, Yamada Y, Sumitomo M, Andoh T. *Neuroscience*; 137:573-581. 2006.
195. Meldrum BS, Bruton CJ. Epilepsy. In: Greenfield's neuropathology (Adams JH. Duchon LW. eds). New York: Oxford University Press; 1246–83. 1992.

196. Briellmann RS, Berkovic SF, Syngeniotis A, King MA, Jackson GD. Seizure-associated hippocampal volume loss: a longitudinal magnetic resonance study of temporal lobe epilepsy. *Annals Neurology*; 51: 641–644. 2002.
197. Helmstaedter C, Kurthen M, Lux S, Reuber M, Elger CE. Chronic epilepsy and cognition: a longitudinal study in temporal lobe epilepsy. *Annals Neurology*; 54:425–32. 2003.
198. Liou AKF, Clark RS, Henshall DC, Yin XM, Chen J. To die or not to die for neurons in ischemia traumatic brain injury and epilepsy: a review on the stressactivated signaling pathways and apoptotic pathways. *Progress in Neurobiology*; 69: 103–42. 2003.
199. Marangoz C. Deneysel epilepsi modelleri. *O.M.Ü Tıp Dergisi*; 14: 147-186. 1997 .
200. Gregory RP, Oates T, Merry RTG. EEG epileptiform abnormalities in candidates for aircrew training. *Electroencephalogr Clin Neurophysiol* 1993; 86: 75–77. Crunelli V, Leresche N. Childhood Absence Epilepsy: Genes, Channels, Neurons and Networks. *Nature Review Neuroscience*; 3: 371-382. 2002.
201. Bağırıcı F. Penisilin modeli deneysel epilepside kalsiyum kanal blokerlerinin elektrokortikograma (ECoG) etkileri. Doktora Tezi; Ondokuz Mayıs Üniversitesi Sağlık Bilimleri Enstitüsü. Samsun. 1996.
202. Schmidt RF. Integrative functions of the central nervous system. In: *Human physiology*. Ed.(s), Schmidt RF, Thews G, 2nd Ed. Springer-Verlag, Berlin, Heidelberg; 124-165.1989 .
203. Miller JW, Snyder AZ, Coben LA, Prensky AL. Clinical electroencephalography and related techniques. In: *Clinical Neurology*, Ed, Joynt RJ, Lippincott, Philadelphia; 1: 5. 1992.

204. Timofeeva OA, Gordon CJ. Changes in EEG power spectra and behavioral states in rats exposed to acetylcholinesterase inhibitor chlorpyrifos and muscarinic agonist oxotremorine. *Brain Research*; 893: 165-177. 2001.
205. Keita MS, Frankel-Kohn L, Bertrand N, Lecanu L, Monmaur P. Acetylcholine release in the hippocampus of the urethane anaesthetized rat positively correlates with both theta frequency and relative power in theta band. *Brain Research*; 887: 323-334. 2000.
206. Başar E, Schürman M, Demiralp T, Başar-Eroğlu C, Ademoğlu, A. Event-related oscillations are “real brain responses”-Wavelet analysis and new strategies. *International Journal of Psychophysiology*; 39: 91-127. 2001.
207. Ferri R, Cosentino, FII, Elia M, Musumeci SA, Marinig R, Bergonzi P. Relationship between delta, sigma, beta and gamma EEG bands at REM sleep onset and REM sleep end. *Clinical Neurophysiology*; 112: 2046-2052. 2001.
208. Nayak A, Roy RJ, Sharma A. Time-frequency spectral representation of the EEG as an aid in the detection of depth of anesthesia. *Annals of Biomedical Engineering*; 22: 501-513. 1994.
209. Walker AE, and Johnson HC. Convulsive factor in commercial penicillin. *Archives of Surgery*; 50: 69-73. 1945.
210. Noebels JL, and Pedley TA. Anatomic localization of topically applied; penicillin during experimental focal epilepsy in cat neocortex. *Brain Research*; 125: 293-303. 1977.
211. Ankaralı S, Canan S. Merkezi Sinir Sistemi.. Başkent Üniversitesi. Ankara. 2004.
212. Bozdoğan Ö. Fizioloji . Palme yayıncılık. Ankara. 2012.

213. Seino S, Miki T. Physiological and pathophysiological roles of ATP – sensitive K channels. *Progress in Biophysics & Molecular Biology*; 81: 133-176. 2003.
214. Freiman T M. Modulation of K⁺-evoked [3H]-noradrenaline release from rat and human brain slices by gabapentin: involvement of KATP channels. *Naunyn-Schmiedeberg's archives of pharmacology*; 363: 537-54. 2001.
215. Varughese JF, Baxley T, Chalovich JM, Li Y. A Computational and Experimental Approach to Investigate Bepridil Binding with Cardiac Troponin. *The Journal of Physical Chemistry*; 115: 2392–2400. 2011.
216. Takanari H, Honjo H, Takemoto Y, Suzuki T, Kato S, Harada M, Okuno Y, Ashihara T, Opthof T, Sakuma I, Kamiya K, Kodama I. Bepridil facilitates early termination of spiral-wave reentry in two-dimensional cardiac muscle through an increase of intercellular electrical coupling. *Journal of Pharmacological Sciences*; 115: 15-26. 2011.
217. Chen LW, Jan CR Effect of the antianginal drug bepridil on intracellular Ca²⁺ release and extracellular Ca²⁺ influx in human neutrophils. *International Immunopharmacological*; 1: 945-53. 2001.
218. Sun HS and Feng ZP. Neuroprotective role of ATP-sensitive potassium channels in cerebral ischemia. *Acta Pharmacologica Sinica*; 34: 24–33. 2013.
219. Watts AE, Henderson G. Putative pre-and postsynaptic ATP–sensitive potassium channels in the rat substantia nigra in vitro. *The Journal of Neuroscience*; 15: 3065-3074. 1995.
220. Stanford I M, Lacey M G. Electrophysiological investigation of adenosine triphosphate-sensitive potassium channels in the rat substantia nigra pars reticulata. *Neuroscience*; 74: 499-509. 1996.
221. Blondeau N. KATP channel openers, adenosine agonist and epileptic preconditioning are stress signals inducing hippocampal neuroprotection. *Neuroscience*; 100: 465-474. 2000.

222. Leker RR, Neufeld MY. Anti Epileptic drugs as possible neuroprotectants in cerebral ischemia. *Brain Research Reviews*;42:187-203. 2003.
223. Bodenshtein T M, Vaidya KS, Ismail A, Beck BH, Diers AR, Edmonds MD, Kirsammer GT, Landar A, Welch DR. Subset of ATP sensitive potassium channel (KATP) inhibitors increase gap junctional intercellular communication in metastatic cancer cell lines independent of SUR expression. *FEBS Letter*; 586: 27-31. 2012.
224. Nichols CG. KATP channels as molecular sensors of cellular metabolism. *Nature*; 440: 470-476. 2006 .
225. Xuea Y, Xiea N, Lind Y, Xuc J, Hana Y, Wanga S, Jiang H, Chia Z. Role of PI3K/Akt in diazoxide preconditioning against rat hippocampal neuronal death in pilocarpine-induced seizures *Brain Research*; 1383: 135–140. 2011.
226. Yamada K. Protective role of ATP sensitive potassium channels in hypoxia-induced generalized seizure. *Science*; 292; 1543-1546. 2001.
227. Gonca E. The Effect of the sarcolemmal and mitochondrial ATP dependent potassium channels on the ischemia/reperfusion arrhythmias in male and female rats. The role of endogenous estrogen. *Abant İzzet Baysal Üniversitesi Fen edebiyat Fakültesi Doktora tezi*. Bolu. 2008.
228. Gonca E, Bozdoğan Ö. Both mitochondrial KATP channel opening and sarcolemmal KATP channel blockage confer protection against ischemia/reperfusion induced arrhythmia in anesthetized male rats. *Journal of Cardiovascular Pharmacology and Therapeutics*; 15: 403-11. 2010.
229. Wang J, Li Z, Feng M, Ren K, Shen G, Zhao C, Jin X, Jiang K. Opening of Astrocytic Mitochondrial ATP-Sensitive Potassium Channels Upregulates Electrical Coupling between Hippocampal Astrocytes in Rat. *Brain Slices*; 8 : 1-14. 2013.

230. Jazayeri A, Zolfaghari S, Ostadhad S. Anticonvulsant Effect of Diazoxide against Dichlorvos-Induced Seizures in Mice The Scientific World Journal; 1-4. 2013.
231. Heurteaux C, Bertaina V, Widmann C, Lazdunski M. K⁺ channel openers prevent global ischemia-induced expression of c-fos, c-jun, heat shock protein, and amyloid beta-protein precursor genes and neuronal death in rat hippocampus. Proceeding of the National Academy of Science USA; 90: 9431-9435. 1993.
232. Jianga K, Shuia Q, Xia Z, Yub Z. Changes in the gene and protein expression of KATP channel subunits in the hippocampus of rats subjected to picrotoxin-induced kindling. Progress in Biophysics & Molecular Biology; 81; 133-176. 2003.
233. Kong D, Vong L, Parton LE, Ye C, Tong Q, Hu X, Choi B, Bru ning C J, Lowell BB. Glucose stimulation of Hypothalamic MCH Neurons Involves KATP Channels, Is Modulated by UCP2 and Regulates Peripheral Glucose Homeostasis. Cell Metabolism; 12: 545-552. 2010.
234. Jiang K, Shuia Q, Xiaa Z, Yu Z. Changes in the gene and protein expression of KATP channel subunits in the hippocampus of rats subjected to picrotoxin-induced kindling. Molecular Brain Research; 128: 83–89. 2004.
235. Ghasemi M, Shafaroodi H, Karimollah A R, Gholipour T, Nezami BG Ebrahimi F, Dehpour A R. ATP-sensitive potassium channels contribute to the time-dependent alteration in the pentylenetetrazole-induced seizure threshold in diabetic mice. Seizure; 19: 53–58. 2010.
236. Shafaroodi H, Hashemi M, Dehpour AR. Role of ATP-sensitive potassium channels in the clonic seizure threshold inuced by pentylenetetrazole in mice with diabetes type I. Diabetes; 20: 22-27. 2010.
237. Xuea Y, Xiea N, Caoa L, Zhaoa X, Jiang H, Chia Z. Diazoxide preconditioning against seizure- induced oxidative injury is via teh PI3K/Akt pathway in epileptic rat. Neuroscience Letter; 495: 130-134. 2011.

238. Melena A, Buttiglione M, Cannoena G, Vitiello F. Camerinoa DC, Tricarico D. Opening/bloking action of pyruvate kinase antibodies on neuronal and muscular KATP channels. *Pharmacololical research*; 66 : 401-408. 2012.

239. Yamanaka R, Shindo Y, Hotta K, Suzuki K, Oka K. NO/ c GMP / PKG signaling pathway induces magnesium release mediated by mitoKATP channel opening in rat hippocampal neurons. *FEBS Letters*; 587: 2643-2648. 2013.

240. Sato T, Costa ADT, Saito T, Ogura T, Ishida H, Garlid KD, Nakaya H. Bepridil, an Antiarrhythmic Drug, Opens Mitochondrial KATP Channels, Blocks Sarcolemmal KATP Channels, and Confers Cardioprotection *The Journal of pharmacology and experimental therapeutics*; 316; 182–188. 2006.

241. Seino S, Miki T. Physiological and pathophysiological roles of ATP-sensitive K⁺ channels. *Progress in Biophysics and Molecular Biology*; 81: 133–176. 2003.

242. Jilkina O, Kuzio B, Grover GJ, Kupriyanov VV. Effects of K(ATP) channel openers, P-1075, pinacidil, and diazoxide, on energetics and contractile function in isolated rat hearts. *The Journal of Molecular and Cellular Cardiology*; 34: 427. 2002.

243. Jilkina O, Kuzio B, Grover GJ, Folmes CD, Kong HJ, Kupriyanov VV. Sarcolemmal and mitochondrial effects of a KATP opener, P-1075, in "polarized" and "depolarized" Langendorff-perfused rat hearts. *Biochimica et Biophysica Acta*; 1618: 39-50. 2003.

244. Toshiaki Sato, Norihito Sasaki, Jegatheesan Seharaseyon, Brian O'Rourke and Eduardo Marbán Selective Pharmacological Agents Implicate Mitochondrial but Not Sarcolemmal KATP Channels in Ischemic Cardioprotection *Circulation*; 101: 2418-2423. 2000.

245. Wang L, Zhua QL, Wang GZ, Deng TZ, Chena R, Liua MH, Wang SW. The protective roles of mitochondrial ATP-sensitive potassium channels during hypoxia–ischemia–reperfusion in brain. *Neuroscience Letters*; 491: 63–67. 2011.

246. Mahapatra S, Caloriol C, Vandael DHF, Marcantoni A, Carabelli V, Carbone E. Calcium channel types contributing to chromaffin cell excitability, exocytosis and endocytosis. *Cell Calcium*; 51: 321-330. 2012.
247. Ballanyi K. Protective role of neuronal KATP channels in brain hypoxia. *The journal of experimental Biology*; 207; 3201-3212. 2004.
248. Gögelein H et al. Effects of the cardioselective KATP channel blocker HMR 1098 on cardiac function in isolated perfused working rat hearts and in anesthetized rats during ischemia and reperfusion. *Naunyn Schmiedeberg's Archive of Pharmacology*; 36: 33-41. 2001.
249. Zhang HX et al. HMR 1098 is not an SUR isotype specific inhibitor of heterologous or sarcolemmal K ATP channels. *The Journal of Molecular and Cellular Cardiology*; 50: 552-560. 2011.
250. Wirth KJ, Uhde J, Rosenstein B, Englert HC, Gögelein H, Schölkens BA, Busch AE. K(ATP) channel blocker HMR 1883 reduces monophasic action potential shortening during coronary ischemia in anesthetised pigs. *Naunyn - Schmiedeberg's Archive of Pharmacol*; 3: 61-155. 2000.
251. Bancila V, Nikonenko I, Dunant Yves, Bloc A. Zinc inhibits glutamate release via activation of pre-synaptic KATP channels and reduces ischaemic damage in rat hippocampus *Journal of Neurochemistry*; 90: 1243–1250. 2004.
252. Gögelein H et al. Effects of the cardioselective KATP channel blocker HMR 1098 on cardiac function in isolated perfused working rat hearts and in anesthetized rats during ischemia and reperfusion. *Naunyn-Schmiedeberg's Archive of Pharmacology*; 364: 33-41. 2001.
253. HX ZHANG et al. HMR 1098 is not an SUR isotype specific inhibitor of heterologous or sarcolemmal K ATP channels. *The Journal of Molecular and Cellular Cardiology*; 50: 552-560. 2011.

254. Bancila V, Nikonenko I, Dunant Y, Bloc A. Zinc inhibits glutamate release via activation of pre-synaptic KATPchannels and reduces ischaemic damage in rat hippocampus. *Journal of Neurochemistry*; 90 : 1243–1250. 2004.
255. Yamada K, Inagaki N. Neuroprotection by KATP channels. *The Journal of Molecular and Cellular Cardiology*; 38: 945-949. 2005.
256. Sun HS, Feng ZP. Neuroprotective role of ATP-sensitive potassium channels in cerebral ischemia *Acta Pharmacologica Sinica*; 34: 24–32. 2013.
257. Fu Q, Sun Z, Zhang J, Gao N, Qi F, Che F, Guozhao M. Diazoxide preconditioning antagonizes cytotoxicity induced by epileptic seizures *Neural Regeneration Research*; 8 :1000-1100. 2013.
258. Liss B, Roeper J. A role for neuronal KATP channels in metabolic control of the seizure gate. *Trends in Pharmacological Science*; 12 -22. 2001.
259. Li X, Rapedius M, Baukowitz T, Liu GX, Srivastava DK, Daut J, Hanley PJ. 5-Hydroxydecanoate and coenzyme A are inhibitors of native sarcolemmal KATP channels in inside-out patches. *Biochimica et Biophysica Acta*; 1800: 385-91. 2010.
260. Foster DB, Rucker JJ, Marban E. Is Kir 6.1.a subunit of mitoK (ATP)? *Biochemical and Biophysical Research Communications*; 366: 649-656. 2008 .
261. Sahafaroodi H, Asadi S, Sadeghipour H, Ghasemi M, Ebrahimi F, Tavakoli S, Hajrasouliha AR, Dehpour AR. Role of ATP sensitive potassium Channels in the biphasic effects of morphine on penthylenetetrazole-induced seizure threshold in mice. *Epilepsy Research*; 7: 63-6. 2007.
262. Szewczyk A, Kajma A, Malinska D, Wrzosek A, Bednarczyk P, Zablocka B, Dolawy Krzysztof. Pharmacology of mitochondrial Potassium Channels: dark side of the field. *FEBS Letter*; 584: 2063-2069. 2010.

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- 1- Bozdoğan Ö, Kaya ST, Yaşar S, Orallar H. Effect of ATP-dependent channel modulators on ischemia-induced arrhythmia change depending on age and gender, Exp Biol Med, 238, 1170-1179, 2013.

Communications to national scientific meetings

- 1- Karakaş A, Pehlivan F, **Soytürk H**, Gündüz B. Suriye hamsterlarında hamilelik dönemi leptin profoli. Sözlü bildiri. 29. Ulusal Fizyoloji Kongresi, GATA Ankara 2003.
- 2- **Soytürk H**, Karakaş A, Gündüz B. Kafeinin yavru Suriye hamsterlarının gelişimi üzerine etkileri. Poster. 30. Ulusal Fizyoloji Kongresi, Selçuk Üniversitesi, Konya 2004.
- 3- Karakaş A, **Soytürk H**, Gündüz B. Kafeinin yetişkin erkek Suriye hamsterlarının motor aktivite ritmi üzerine etkileri. Poster 30. Ulusal Fizyoloji Kongresi, Selçuk Üniversitesi, Konya 2004.
- 4- Karakaş A, **Soytürk H**, Gündüz B. Moğolistan gerbilllerinde pineal bezin maternal transfer üzerine etkileri; 30. Ulusal Fizyoloji Kongresi, Selçuk Üniversitesi, Konya 2004.
- 5- **Orallar H**, Gökçe M F. Nöropeptid Y'nin penisilin modeli epilepsi üzerine etkileri. Poster 5. Ulusal sinir bilim kongresi Karaelmas Üniversitesi, Zonguldak 2006.
- 6- **Orallar H**, Kaya T, Yaşar S, Yılmaz Ş, Toklucu M, Çelebi H, Özarslan O, Güçlü R, Ateş T, Bozdoğan Ö. Yaşlı ve genç sıçanlarda kısa dönem besin kısıtlamasının iskemi aritmileri üzerine etkileri; 21.Ulusal Biyoloji Kongresi, Ege Üniversitesi, İzmir 2012.
- 7- **Orallar H**, Kaya T, Yaşar S, Özarslan O, Yılmaz Ş, Toklucu M, Bozdoğan Ö. Sıçanlarda Kısa dönem egzersizin iskemi reperfüzyon aritmileri üzerine etkileri; 21. Ulusal Biyoloji Kongresi, Ege Üniversitesi, İzmir 2012.

- 8- Öner F, **Orallar H**, Beyazçiçek E, Özarslan O, Demir Ş, Bozdoğan Ö. Adaçayı ekstraktının penisilin modeli deneysel epilepsi üzerine etkileri. Poster p106. 39. Ulusal Fizyoloji Kongresi Hacettepe Üniversitesi Ankara 2013.
- 9- **Orallar H** , Demir Ş, Bozdoğan Ö. Penisilin Modeli Deneysel Epilepside ATP Bağımlı Kanal Agonisti Bepridil ve P1075'in Doza Bağlı Antiepileptik Etkisi. Sözlü Bildiri S 19. 39. Ulusal Fizyoloji Kongresi Hacettepe Üniversitesi Ankara 2013.
- 10- Yaşar S, Bozdoğan Ö, Kaya ST, **Orallar H**. Sıçanlarda koroner arterin kısmi ve tam (LAD) tıkanması sonucu oluşan aritmiler üzerine ATP-bağımlı potasyum kanal düzenleyicilerinin etkisi, Sözlü bildiri. 39. Ulusal Fizyoloji Kongresi, Hacettepe Üniversitesi Ankara 2013.
- 11- **Orallar H**, Demir Ş, Bozdoğan Ö. Penisilin G ile oluşturulan deneysel epilepsi modelinde ATP bağımlı K (KATP) kanal agonist ve antagonistlerinin etkileri, S12. Sözlü bildiri. 40. Ulusal Fizyoloji Kongresi, Erciyes Üniversitesi Kayseri 2014.
- 12- Kayacan Y, Çetinkaya A, **Orallar H**, Çakır S, Beyazçiçek E, Önal AC, Yıldırım A. Mogolistan Gerbilllerinde Trabzon Hurması (Diospyros Kaki) ekstraktı ile uygulanan kosubandı egzersizinin penisilin g ile oluşturulan epilepsisi üzerindeki etkileri. 189 nolu Poster. 40. Ulusal Fizyoloji Kongresi, Erciyes Üniversitesi Kayseri 2014.
- 13- Çakır S, Çetinkaya A, Kayacan Y, **Orallar H**, Önal AC, Yıldırım A. Alıç (Crataegus Oxyacantha) ekstraktı ve kronik koşu egzersizinin penisilin G ile oluşturulan epilepsi üzerine etkileri. 192 nolu Poster. 40. Ulusal Fizyoloji Kongresi, Erciyes Üniversitesi Kayseri 2014.

Communications to international scientific meetings

- 1- **Orallar H**, Kaya ST, Yaşar S, Firdevs B, Bozdoğan Ö. Does the food restriction affect the ischemia induced arrhythmia and infarct size after coronary occlusion in rats? Abstract. Acta Physiologica, 203(Supplement 686): PC056, 2011
- 2- Yaşar S, Kaya ST, **Orallar H**, Bozdoğan Ö. The effect of adenosine and atropine combination on the arrhythmia that has occurred following coronary occlusion in rats. Abstract. Acta Physiologica, 203(Supplement 686): PC062, 2011.
- 3- Kaya ST, Yaşar S, **Orallar H**, Bozdoğan Ö. The effect of intermittened fasting and water restriction on ischemia and reperfusion induced arrhythmias in rats. Abstract. Acta Physiologica, 203(Supplement 686): PC046, 2011.