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# Cellular and Molecular Mechanisms Underlying Epilepsy: An Overview with Our Findings

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## 1. Introduction

Epilepsy affects more than 50 million people worldwide. It is foreseen that around 50 million people in the world have epilepsy, or about 1% of the population. (<http://www.epilepsyfoundation.org>; <http://epilepsy.med.nyu.edu/epilepsy/frequently-asked-questions>: NYU Langone Medical Center, 2011). At the global level, it is estimated that there are nearly 50 million persons suffering from epilepsy of which three-fourths, i.e. 35 million, are in developing countries (<http://www.searo.who.int>). It is the most common serious neurological condition. It can affect all age groups and it may be the result of an acute or chronic cerebral illness. Epileptic seizures begin simultaneously and several histopathological changes occur in both cerebral hemispheres. Epilepsy is a disorder of the central nervous system characterized by recurrent and sudden increase in electrical activity. Metabolic studies have shown that oxygen availability, glucose utilization, and blood flow all increase dramatically during epileptic seizures. It is also known that epileptic activity may induce some molecular and structural changes in the different brain regions (Ingvar & Siejo, 1983; Siesjo et al., 1986; Oztas et al., 2001).

Enolase is glycolytic enzyme that converts 2-phosphoglycerate to phosphoenol pyruvate. It has three immunologically distinct subunits;  $\alpha$ ,  $\beta$ , and  $\gamma$ . The  $\gamma$  form is found primarily in the cytoplasm and process of neurons, which is referred to as neuron-specific enolase (NSE). NSE is a sensitive marker of neuronal damage in several central nervous system (CNS) diseases including epilepsy (Schmechel et al., 1978; Nogami et al., 1998a; Nogami et al., 1998b; Rodriguez-Nunez et al., 2000). Changes in membrane integrity as a result of neuronal injury can cause leakage of protein such as NSE from cytosol into extracellular space. Increased NSE in serum (sNSE) and in cerebrospinal fluid (cNSE) have been observed in animal model of traumatic and ischemic brain injury, cerebral hypoxia, and epileptic seizures (Hay et al., 1984; Persson et al., 1988; Hatfield & McKernan 1992; Barone et al., 1993; Brandel et al., 1999; Steinhoff et al., 1999). sNSE levels are also reported to increase in epileptic activities due to increased blood-brain barrier (BBB) permeability. Elevation of sNSE after SE correlated with overall histologic evidence for damage (Jacobi & Reiber, 1988; DeGiorgio et al., 1996; Sankar et al., 1997; Correale et al., 1998; Buttner et al., 1999; DeGiorgio et al., 1999; Schreiber et al., 1999). Although sNSE is not sensitive enough to detect neuronal damage, cNSE seems to be a reliable parameter for assessing neurological

insult in patients (Lima et al., 2004). Although multiple reports have documented elevation in NSE levels following neuronal injury in various neurological disorders, little is known about the localization of NSE in different brain regions after chemically induced acute and chronic seizures. Therefore, the present work was designed to investigate changes in NSE immunoreactivity in different brain regions including the cerebral cortex, thalamus, hypothalamus, and hippocampus in the single- and repeated PTZ-induced generalized tonic-clonic seizures in rats.

## 2. Epileptic seizures

In simple terms, our nervous system is a communication network that controls every thought, emotion, impression, memory, movement, and upmost defining who we are. Nerves, throughout the body, function like telephone lines enabling the brain to communicate with every part of the body via electrical signals. In epilepsy, brain's electrical rhythms have a tendency to become imbalanced resulting in recurrent seizures (Schachter, 2006). Normally, the brain continuously generates tiny electrical impulses in an orderly pattern. These impulses travel along the network of nerve cells, called neurons, in the brain and throughout the whole body via chemical messengers called neurotransmitters. A seizure occurs when the brain's nerve cells misfire and generate a sudden, uncontrolled surge of an electrical activity in the brain. Another concept important to epilepsy is that different areas of the brain control different functions.

The International League Against Epilepsy (ILAE) Commission on Classification and Terminology has revised concepts, terminology, and approaches for classifying seizures and forms of epilepsy. Generalized and focal are redefined for seizures as occurring in and rapidly engaging bilaterally distributed networks (generalized) and within networks limited to one hemisphere and either discretely localized or more widely distributed (focal). Classification of generalized seizures is simplified. No natural classification for focal seizures exists; focal seizures should be described according to their manifestations (e.g., dyscognitive, focal motor). The concepts of generalized and focal do not apply to electroclinical syndromes. Genetic, structural-metabolic, and unknown represent modified concepts to replace idiopathic, symptomatic, and cryptogenic. Not all epilepsies are recognized as electroclinical syndromes. Organization of forms of epilepsy is first by specificity: electroclinical syndromes, nonsyndromic epilepsies with structural-metabolic causes, and epilepsies of unknown cause. Further organization within these divisions can be accomplished in a flexible manner depending on purpose. Natural classes (e.g., specific underlying cause, age at onset, associated seizure type), or pragmatic groupings (e.g., epileptic encephalopathies, self-limited electroclinical syndromes) may serve as the basis for organizing knowledge about recognized forms of epilepsy and facilitate identification of new forms (Berg, 2010).

Concepts and terminology for classifying seizures and epilepsies have, until recently, rested on ideas developed nearly a century ago. In order for clinical epilepsy and practice to benefit fully from the major technological and scientific advances of the last several years, advances that are revolutionizing our understanding and treatment of the epilepsies, it is necessary to break with the older vocabulary and approaches to classifying epilepsies and seizures. The Commission on Classification and Terminology made specific recommendations to move this process along and ensure that classification will reflect the best knowledge, will not be arbitrary, and will ultimately serve the purpose of improving clinical practice as well as

research on many levels. The recommendations include new terms and concepts for etiology and seizure types as well as abandoning the 1989 classification structure and replacing it instead with a flexible multidimensional approach in which the most relevant features for a specific purpose can be emphasized. This is not a finished product and will take yet more time to achieve. Waiting any longer, however, would be a disservice to patient care and will continue the longstanding frustrations with the earlier system which, at this point in time, can be viewed as both antiquated and arbitrary (Berg et al., 2011). There are so many kinds of seizures that neurologists who specialize in epilepsy are still updating their thinking about how to classify them. Usually, they classify seizures into two types, primary generalized seizures and partial seizures. The difference between these types is in how they begin: Primary generalized seizures begin with a widespread electrical discharge that involves both sides of the brain at once. Hereditary factors are important in many of these seizures (Schachter, 2006; MedicineNet, Inc.). Partial seizures begin with an electrical discharge in one limited area of the brain. Some are related to head injury, brain infection, stroke, or tumor, but in most cases the cause is unknown (Steven C. Schachter, 2006; MedicineNet, Inc.). Identifying certain seizure types and other characteristics of a person's epilepsy like the age at which it begins, for instance, allows doctors to classify some cases into epilepsy syndromes. This kind of classification helps us to know how long the epilepsy will last and the best way to treat it.

**Primary generalized seizures:** Absence seizures are brief episodes of staring. During the seizure, awareness and responsiveness are impaired. People who have them usually do not realize when they have had one. There is no warning before a seizure, and the person is completely alert immediately afterwards (Schachter, 2006)

Simple absence seizures are just stares. Many absence seizures are considered *complex* absence seizures meaning they include a change in muscle activity. The most common movements are eye blinking. Other movements include slight tasting movements of the mouth, hand movements such as rubbing the fingers together, and contraction or relaxation of the muscles. Complex absence seizures are often more than 10 seconds long (Schachter, 2006). Atypical (a-TIP-i-kul) means unusual or not typical. The person will stare (as they would in any absence seizure) but often is somewhat responsive. Eye blinking or slight jerking movements of the lips may occur. This behavior can be hard to distinguish from the person's usual behavior, especially in those with cognitive impairment. Unlike other absence seizures, rapid breathing cannot produce them.

Myoclonic (MY-o-KLON-ik) seizures are brief, shock-like jerks of a muscle or a group of muscles. "Myo" means muscle and "clonus" (KLOH-nus) means rapidly alternating contraction and relaxation—jerking or twitching—of a muscle (Schachter, 2006). Even people without epilepsy can experience myoclonus in hiccups or in a sudden jerk that may wake you up as you are just falling asleep. These things are normal.

Muscle "tone" is the muscle's normal tension. "Atonic" (a-TON-ik) means "without tone," so in an atonic seizure, muscles suddenly lose strength. The eyelids may droop, the head may nod, and the person may drop things and often falls to the ground. These seizures are also called "drop attacks" or "drop seizures." The person usually remains conscious.

Muscle "tone" is the muscle's normal tension at rest. In a "tonic" seizure, the tone is greatly increased and the body, arms, or legs make sudden stiffening movements. Consciousness is

usually preserved. Tonic seizures most often occur during sleep and usually involve all or most of the brain, affecting both sides of the body. If the person is standing when the seizure starts, he or she often will fall.

"Clonus" (KLOH-nus) means rapidly alternating contraction and relaxation of a muscle -- in other words, repeated jerking. The movements cannot be stopped by restraining or repositioning the arms or legs. Clonic (KLON-ik) seizures are rare, however. Much more common are tonic-clonic seizures, in which the jerking is preceded by stiffening (the "tonic" part). Sometimes tonic-clonic seizures start with jerking alone. These are called clonic-tonic-clonic seizures! This type is what most people think of when they hear the word "seizure." An older term for them is "grand mal." As implied by the name, they combine the characteristics of tonic seizures and clonic seizures. The tonic phase comes first: All the muscles stiffen. Air being forced past the vocal cords causes a cry or groan. The person loses consciousness and falls to the floor. The tongue or cheek may be bitten, so bloody saliva may come from the mouth. The person may turn a bit blue in the face. After the tonic phase comes the clonic phase: The arms and usually the legs begin to jerk rapidly and rhythmically, bending and relaxing at the elbows, hips, and knees. After a few minutes, the jerking slows and stops. Bladder or bowel control sometimes is lost as the body relaxes. Consciousness returns slowly, and the person may be drowsy, confused, agitated, or depressed.

## 2.1 Motor seizures

These cause a change in muscle activity. For example, a person may have abnormal movements such as jerking of a finger or stiffening of part of the body. These movements may spread, either staying on one side of the body (opposite the affected area of the brain) or extending to both sides. Other examples are weakness, which can even affect speech, and coordinated actions such as laughter or automatic hand movements. The person may or may not be aware of these movements (Schachter, 2006).

## 2.2 Sensory seizures

These cause changes in any one of the senses. People with sensory seizures may smell or taste things that are not there, may hear clicking, ringing, or a person's voice when there is no actual sound, or may feel a sensation of "pins and needles" or numbness. Seizures may even be painful for some patients. They may feel as if they are floating or spinning in space. They may have visual hallucinations, seeing things that are not there (a spot of light, a scene with people). They also may experience illusions—distortions of true sensations. For instance, they may believe that a parked car is moving farther away, or that a person's voice is muffled when it has actually clear (Schachter, 2006).

**Autonomic seizures** These cause changes in the part of the nervous system that automatically controls bodily functions. These common seizures may include strange or unpleasant sensations in the stomach, chest, or head; changes in the heart rate or breathing; sweating; or goose bumps.

## 2.3 Psychic seizures

These seizures change how people think, feel, or experience things. They may have problems with memory, garbled speech, ability to find the right word, or understanding



spoken or written language. They may suddenly feel emotions like fear, depression, or happiness with no apparent reason. Some may feel as though they are outside their body or may have déjà vu. These seizures usually start in a small area of the temporal lobe or frontal lobe of the brain. They quickly involve other areas of the brain that affect alertness and awareness. Thus, even though the person's eyes are open and they may move that seem to have a purpose, in reality "nobody's home." If the symptoms are subtle, other people may think the person is just daydreaming (Schachter, 2006). Some people can have seizures of this kind without realizing that anything has happened. Because the seizure can wipe out memories of events just before or after it, however, memory lapses can be a problem (Schachter, 2006).

Some of these seizures (usually ones beginning in the temporal lobe) start with a simple partial seizure. Also called an aura, this warning seizure often includes an odd feeling in the stomach. Then the person loses awareness and stares blankly. Most people move their mouth, pick at the air or their clothing, or perform other purposeless actions. These movements are called "automatisms" (aw-TOM-ah-TIZ-ums). Less often, people may repeat words or phrases, laugh, scream, or cry. Some people do things that can be dangerous or embarrassing, such as walking into traffic or taking their clothes off. These people need to take precautions in advance (Schachter, 2006). Complex partial seizures starting in the frontal lobe tend to be shorter than the ones from the temporal lobe. The seizures that start in the frontal lobe are also more likely to include automatisms like bicycling movements of the legs or pelvic thrusting (Schachter, 2006).

These seizures are called "secondarily generalized" because they only become generalized (spread to both sides of the brain) after the initial or "primary" event, a partial seizure, has already begun. They happen when a burst of electrical activity in a limited area (the partial seizure) spreads throughout the brain. Sometimes the person does not recall the first part of the seizure. These seizures occur in more than 30% of people with partial epilepsy (Schachter, 2006).

The concepts of generalized and focal when used to characterize seizures now explicitly reference networks, an increasingly accepted construct in neuroscience where networks are studied directly through the use of techniques such as functional magnetic resonance imaging (MRI). Berg and colleagues (2011) explicitly acknowledged the group called "idiopathic generalized" epilepsies, although with a different name. For etiology, the terms idiopathic, symptomatic, and cryptogenic had become unworkable as descriptors of etiology and had, over time, taken on connotations of "good" and "bad" outcome. Epilepsies that later were recognized as monogenic syndromes such as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) were classified as "cryptogenic" meaning "presumed symptomatic," as in secondary to a brain lesion. Current developments in molecular genetics and neuroimaging and other areas will, Berg and colleagues (2011) predict, lead to a rational system for characterizing and classifying causes based on mechanisms. In moving forward to the next phase, Berg and colleagues (2011) suggested the following terms and concepts:

**Genetic:** The epilepsy is a direct result of a genetic cause. Ideally, a gene and the mechanisms should be identified; however, this term would also apply to electroclinical syndromes for which twin or family segregation studies reproducibly show clinical evidence of a genetic basis (e.g., in the case of the genetic generalized epilepsies). At this time, channelopathies are the best example of genetic epilepsies (Berg et al., 2011).

**Structural-Metabolic:** The epilepsy is the secondary result of a separate structural or metabolic condition. Structural and metabolic were combined to separate the concept from genetic and also because the two are often inseparable (Berg et al., 2011).

**Unknown:** Plain and direct, this label simply and accurately indicates ignorance and that further investigation is needed to identify the cause of the epilepsy. Unlike cryptogenic (presumed symptomatic), it makes no presumptions and requires no explanation or reinterpretation (Berg et al., 2011).

## 2.4 Models of chemically induced epileptic seizures

A systemic administration of pentylenetetrazol (PTZ), an antagonist for the GABA (gamma-aminobutyric acid) receptor ion channel binding site was shown to cause generalized epilepsy in an animal model (Ahmed et al., 2005). Kindling is a model of epilepsy and epileptogenesis. Repeated application of subconvulsive doses of central nervous system (CNS) stimulants like PTZ (Corda et al., 1992) once every 24 to 48 hours over a period of time is also known to induce a permanent change in the epileptogenic sensitivity of the forebrain structures (Khanna et al., 2000). PTZ-induced seizure in rats, a relevant model of human absence and of generalized tonic-clonic epilepsy (ILE, 1989; Brevard et al., 2006).

In a single dose PTZ-treated group, rats were injected intraperitoneally (i.p.) with 55 mg/kg PTZ (Sigma Chemical Co) and observed for behavioral epileptic activity in our study. The animals in the repeated doses of PTZ-treated group were given 55 mg/kg PTZ i.p. on alternate days for six times and then the seizure activity was observed during each seizure period. After the last injection on the sixth day, similar procedure was applied as in the single dose PTZ-treated group. For the control group, saline solution was applied instead of PTZ. So, in our study, we also planned to examine hippocampal neurons in rat brain after the PTZ-induced epileptic seizures light and electron microscopically.

## 3. Histopathological changes of neurones in epilepsy

The extent that prolonged seizure activity, i.e. SE, and repeated, brief seizures affect neuronal structure and function in both the immature and mature brain has been the subject of increasing clinical and experimental research. The main emphasis is put on studies carried out in experimental animals, and the focus of interest is the hippocampus, the brain area of great vulnerability in epilepsy. Collectively, recent studies suggest that the deleterious effects of seizures may not solely be a consequence of neuronal damage and loss per se, but could be due to the fact that seizures interfere with the highly regulated developmental processes in the immature brain (Holopainen, 2008).

Holopainen (2008), provides not only up-to-date information of some of the processes involved in the complex reorganization cascade activated by seizures, but the aim is also to highlight the importance of the developing brain as a unique, dynamic structure within the field of neurochemistry and epilepsy research, and to awaken the interest for further new, innovative ways to approach this fascinating research field.

In epilepsy, several pathological changes typically occur in the brain, including neuronal loss, gliosis (Penfield, 1929; Steward et al., 1991), dendritic spine degeneration (Isokowa, 1998), and abnormal synaptic reorganization (Babb et al., 1991; Mello et al., 1993;

Leite et al., 1996; Xiang-ming Zha et al., 2005). These changes lead to abnormally increased excitability and synchronization, and eventually to the occurrence of spontaneous seizures (Cavalheiro et al., 1991; Isokawa & Mello, 1991; Bothwell et al., 2001).

It has been studied the effect of kainic acid (KA), a potent neuroexcitatory and neurotoxic analogue of glutamate, in the rat using a variety of light- and electron-microscopic techniques. The commonly affected areas include the olfactory cortex, amygdaloid complex, hippocampus, and related parts of the thalamus and neocortex (Schwob et al., 1980). Acute treatment with 30mg/kg KA did not produce major death of mouse hippocampal neurons, indicating that concentrations were not cytotoxic. Taken together, investigators' results provide new insights in the activation of several kinase-pathways implicated in cytoskeletal alterations that are a common feature of neurodegenerative diseases (Crespo-Biel et al., 2006).

Sankar et al. (2002) evaluated of the type of cell injury resulting from lithium-pilocarpine (LiPC) status epilepticus (SE) ultrastructurally. Limbic system comprises of the brain which are important for memory, emotions, and cognitive functions (Wen et al., 1999).

Hippocampus is an important component of this system and it is widely accepted that it plays an essential role in memory. The hippocampus is a part of the brain located inside the temporal lobe. It forms a part of the limbic system and plays a part in memory and spatial navigation. It is known that the damage to the hippocampus can also result from oxygen starvation (anoxia) and encephalitis. Reductions in neuronal cell number were indicative of an abnormal development. The developmental structural abnormalities in the hippocampus may contribute to the cognitive impairments which result from isolation rearing in rats (Bianchi et al., 2006). However, our understanding of the cellular and molecular mechanisms underlying epilepsy remains incomplete.

#### **4. Staining methods for neuronal damage localization of: Our findings**

In our study, brainsections were stained with Cresyl Fast Violet (CFV) for Nissl staining and then these sections were examined under a light microscope (BX50F-3; Olympus, Tokyo, Japan). CFV binds very strongly to the RNA in the neuron's rough endoplasmic reticulum (Chan & Lowe, 2002).

NSE is a major neuronal protein that catalyzes the interconversion of 2 phosphoglycerate and phosphopyruvate. Immunocytochemistry was performed using the avidinbiotin-peroxidase method. The sections were incubated with anti-NSE primary antibodies (Zymed, Carlton Court, San Francisco) for 24 h at 4°C in a humidified chamber. Following washing in PBS-Tx, biotinylated anti IgG secondary antibodies were applied for 15 min at room temperature. Samples were washed with PBS-Tx and Streptavidin-peroxidase conjugate was applied to the sections for 15 min at room temperature. Following washing in Tris, 0.6% hydrogen peroxide and 0.02% diaminobenzidine (DAB) was applied 5 min at room temp. As control, the primary antibody was omitted and replaced with non-immune serum. Immunoreactivity of NSE was examined under a light microscope (BX50F-3; Olympus, Tokyo, Japan).

After perfusion, hippocampi were microdissected from each rat and were post-fixed in 2% osmium tetroxide at 0.1 M, pH 7.4 phosphate buffer at 48C° for 1 hour, and stained with



uranyl acetate during 2 hour. Later the sections were flatembedded in Durcupan. Semi-thin (1 $\mu$ m) sections were first stained with CFV and screened. Hippocampal regions were selected, and ultrathin sections were cut and placed on singlehole grids. After staining with uranyl acetate and lead citrate, the sections were examined by EM (Zeiss EM-9S).

The number of cells was quantified in 765x102  $\mu$ m<sup>2</sup> fields (counting frame) of hippocampal regions of rat brains with the X40 objective (Olympus) using a grid for determination of the sampling volume via the Cavalieri method (Michel RP & Cruz-Orive,1988). In the seven slices through hippocampus, number of neurons were examined among the acute-PTZ treated, chronic-PTZ treated and the control brains according to unbiased counting methods. The number of neurons were counted in CA1, CA3 and gyrus dentatus (GD) regions. The mean value and S.D. were calculated in the control and PTZ-induced groups. The data were statistically analyzed using the SPSS statistical software package. All groups were compared using ANOVA. Values were expressed as the mean  $\pm$  standard error (SE).

Fifty-five mg/kg PTZ induced generalized tonic-clonic seizures in all animals. Following i.p. injections, generalized seizures started with the clonus of the facial and the forelimbmuscles, and continued with the neck and tail extensions, loss of straightening reflex with tonic flexion-extention, wild running and usually with extended clonic activities.

Different brain regions were examined for neuronal rER and NSE immunoreactivity in the control and PTZ-treated groups using light microscopy in our study. In the control brains, the observed morphology was as follow; nuclei of the neurons were huge in comparison with those of surrounding glial cells; DNA in the nucleus and nucleoli had similar staining properties; dispersed chromatin and prominent nucleoli reflect a high level of protein synthesis. The extensive cytoplasm was basophilic due to extensive rRNA damage. Nissl substance was stained with CFV to evaluate the morphology of neurons. Normal neuronal view was observed in the hippocampal regions from the control group by a light microscope; the nucleus was large with dispersed chromatin and prominent nucleoli and neuroplasm was basophilic due to extensive rRNA damage. CFV, for identifying the Nissl substance (GER) as dark blue material, revealed a granular appearance; nuclear DNA had a similar staining properties. Nissl method stained RNA, identifying the rER (Nissl substance) as purple blue (violet) material giving the neuronal cytoplasm a granular appearance (Figure 1. 1A, D, G, J). Aslight increase in Nissl stainingwas observed in the neurons of the cortex, thalamus, hypothalamus, and hippocampus of the single dose PTZ group rat brains comparing to the control group (Figure 1. 1B, E, H, K). However, slight decrease in the amount of nissl staining was noticed in III-VI layer of the cortex in the repeated dose PTZ-treated group (Figure 1. 1C). The NSE immunoreactivity was largely expressed in the brains of the control and seizing animals. This immunoreactivity was observed to be robust in the neuronal perikarya and dendrites. Representative coronal sections of NSE (+) cells depicting the cortex, thalamus, hypothalamus, and the hippocampus of the control, single and repeated dose PTZ-treated group are shown in Figure 1.2. The number of NSE (+) cells from the cortex, thalamus, hypothalamus, and hippocampus of all groups are shown in Table 1. In the cerebral cortex, no statistical significant difference was observed in the number of NSE (+) neurons in the single (B, E, H, K) and repeated (C, F, I, L) dose PTZ-treated groups compared to the control group (A, D, G, J), respectively. On the other hand, although a slight decrease in the NSE (+) immunoreactivity in the cortex of the repeated doses PTZ-treated group was noticed compared to the control group (Figure 1. 2A-C; Table 1.),

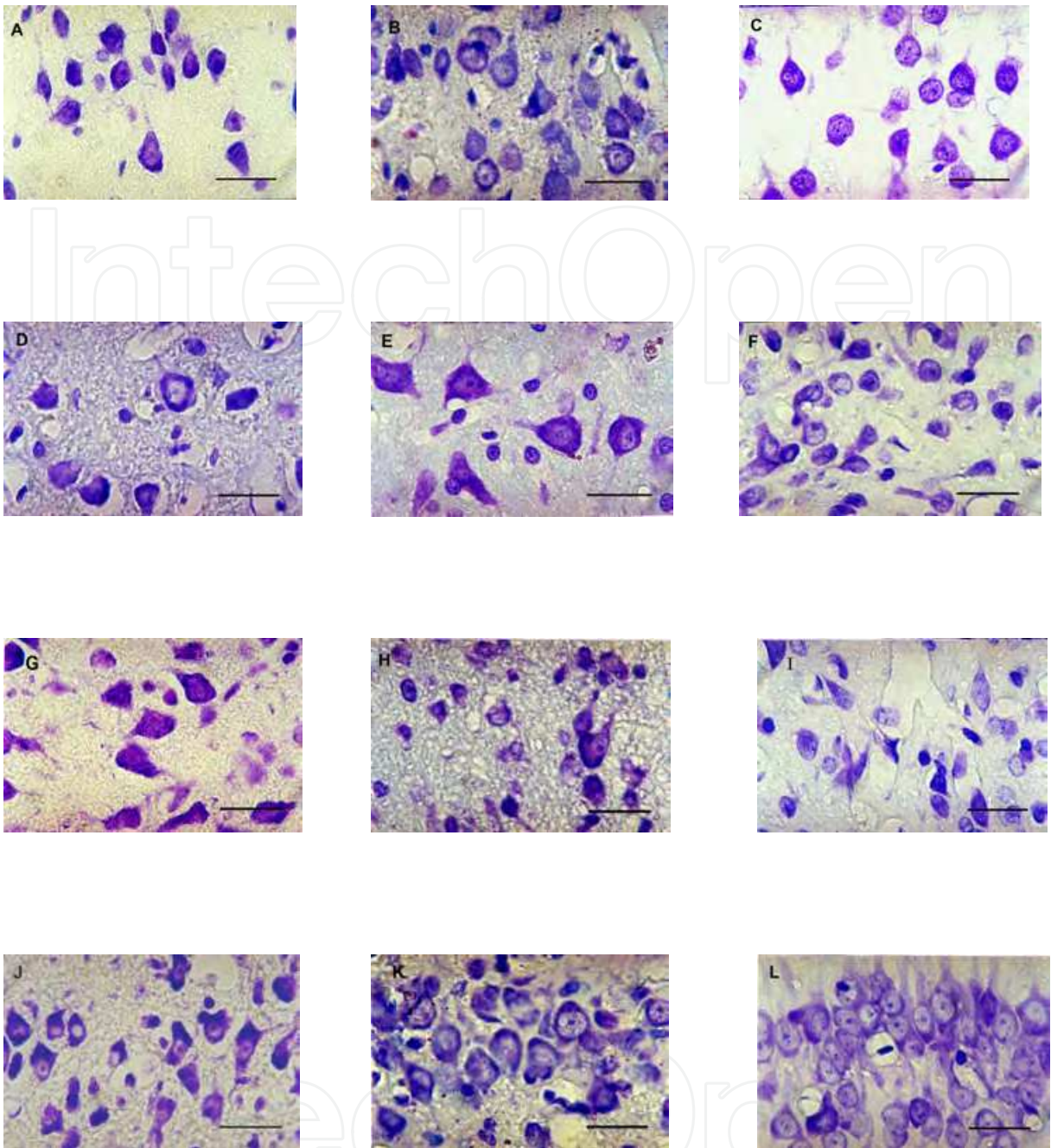


Fig. 1.1. Nissl staining of cerebral cortex (A, B, C), thalamus (D, E, F), hypothalamus (G, H, I), and hippocampus (J, K, L) of the control (A, D, G, J), single dose (B, E, H, K) and repeated doses (C, F, I, L) PTZ-treated group, respectively. Bar, 25  $\mu$ m. Although there was a significant ( $F = 13.05$ ;  $df = 2$ ;  $p < .001$ ) increase in the number of NSE (+) hypothalamic neurons of the single dose PTZ-treated group (Figure 1. 2H) compared to the control group (Figure 1. 2G), a significant ( $p = .001$ ) decrease in the number of NSE (+) hypothalamic neurons was detected in the repeated doses PTZ-treated group compared to the single dose PTZ-treated group (Figure 1. 2H, I and Table 1.). In the hippocampus, no statistical significant difference was observed in the number of NSE (+) neurons in the single and repeated PTZ-treated groups. A slight increase of NSE immunoreactivity was seen in the hippocampus of the single dose PTZ-treated group (Figure 1. 2K) compared to the control (Figure 1. 2J) and repeated doses PTZ-treated group (Figure 1. 2L) rats.

a significant increase in the number of NSE (+) cortical neurons was observed in the single dose PTZ-treated group (Figure 1. 2B) compared to the repeated doses PTZ-treated group (Figure 1. 2C) ( $F = 2.57$ ;  $df = 2$ ;  $p < .05$ ). In the thalamus, the number of the neuron showing NSE immunoreactivity was significantly ( $F = 4.68$ ;  $df = 2$ ;  $p < .05$ ) increased in the repeated doses PTZ-treated group compared to the control group (Figure 1. 2 D, F and Table 1.).

Brain regions	Cortex <sup>a</sup>	Thalamus <sup>b</sup>	Hypothalamus <sup>c</sup>	Hippocampus <sup>d</sup>
Groups	Mean $\pm$ SE			
Control group	414.00 $\pm$ 51.41	224.00 $\pm$ 14.86	124.50 $\pm$ 6.91	231.30 $\pm$ 23.14
Single dose PTZ-treated group	480.10 $\pm$ 32.01 *	315.70 $\pm$ 33.13	251.70 $\pm$ 28.42**	263.30 $\pm$ 10.97
Repeated doses PTZ-treated group	359.70 $\pm$ 23.76	362.20 $\pm$ 43.00**	144.66 $\pm$ 14.52***	235.10 $\pm$ 29.30

\*  $p < .05$  , compared with the repeted doses PTZ-treated group;  
\*\*  $p < .05$  compared with the control group;  
\*\*\*  $p < .05$  compared with the single dose PTZ-treated group.

Table 1. Number of NSE (+) neurons in the cortex, thalamus, hypothalamus, and hippocampus in the control and epileptic brains following single dose and repeated doses PTZ-induced seizures

Neurons of CA1, CA3 and GD regions from the control group appeared to be normal (Fig 2 1a, b, c). A few necrotic neurons from the acute-PTZ group were seen in CA1 and CA3 regions (Fig. 2. 2a, b). There was not significant difference between the number of CA1 and CA3 neurons in the acute-PTZ group and control group (Table 2.). Necrotic neurons were seen extensively in the GD region of the acute-PTZ group (Fig. 2. 2c). There was significant difference between the number of GD neurons in the acute-PTZ group and that of control group ( $p < 0.001$ ; Table 2.). CFV showed a decreased Nissl of hippocampal neurons in the chronic-PTZ group compared to the control group. There was a characteristic view of neuronal damage in light microscopic analysis of hippocampus in the chronic-PTZ groups. In this group, both necrotic and apoptotic neurons were observed in the CA1 region (Fig. 2. 3a). Necrotic histological changes were as follows; perikaryal swelling, chromatolysis and decreasing of Nissl. Apoptotic histological changes were perikaryal shrinking and dark nucleus. There was significant difference between the numbers of CA1 neurons in the chronic-PTZ group and that of control group ( $p < 0.001$ ; Table 2.). Neuronal loss were observed with a resultant narrowing, sparse staining and a breach of continuity of staining in the CA1 region in the chronic-PTZ group (Fig. 2. 3b). In the CA3 region of the chronic-PTZ group, both few necrotic and apoptotic neurons were observed (Fig. 2. 3c). There was no significant difference between the numbers of CA3 neurons from the experimental groups and control group (Table 2.). In the chronic-PTZ group, both necrotic and apoptotic neurons were observed extensively in the GD region (Fig. 2. 3d). There was significant difference between the number of GD neurons in the chronic-PTZ group and control group ( $p < 0.001$ ; Table 2.). Hippocampal CA1 sections were examined to evaluate transmission EM in all groups. The ultrastructural appearance of the cytoplasmic organelles and nuclear components of CA1 neurons was normal in the control group (Fig. 2. 4a). Necrotic neurons were seen rarely in the CA1 region of the acute-PTZ group at a lower magnification. The



necrotic degenerative changes were deformation of nuclear and perikaryal outlines, dilatation of the cisternae of endoplasmic reticulum at a higher magnification (Fig. 2. 4b). In the chronic-PTZ group both necrotic and apoptotic neurons were observed in the CA1 region at lower magnification. EM revealed that dying neurons at the CA1 region showed an apoptotic cells with the regularly shaped, round clumps of condensed chromatin

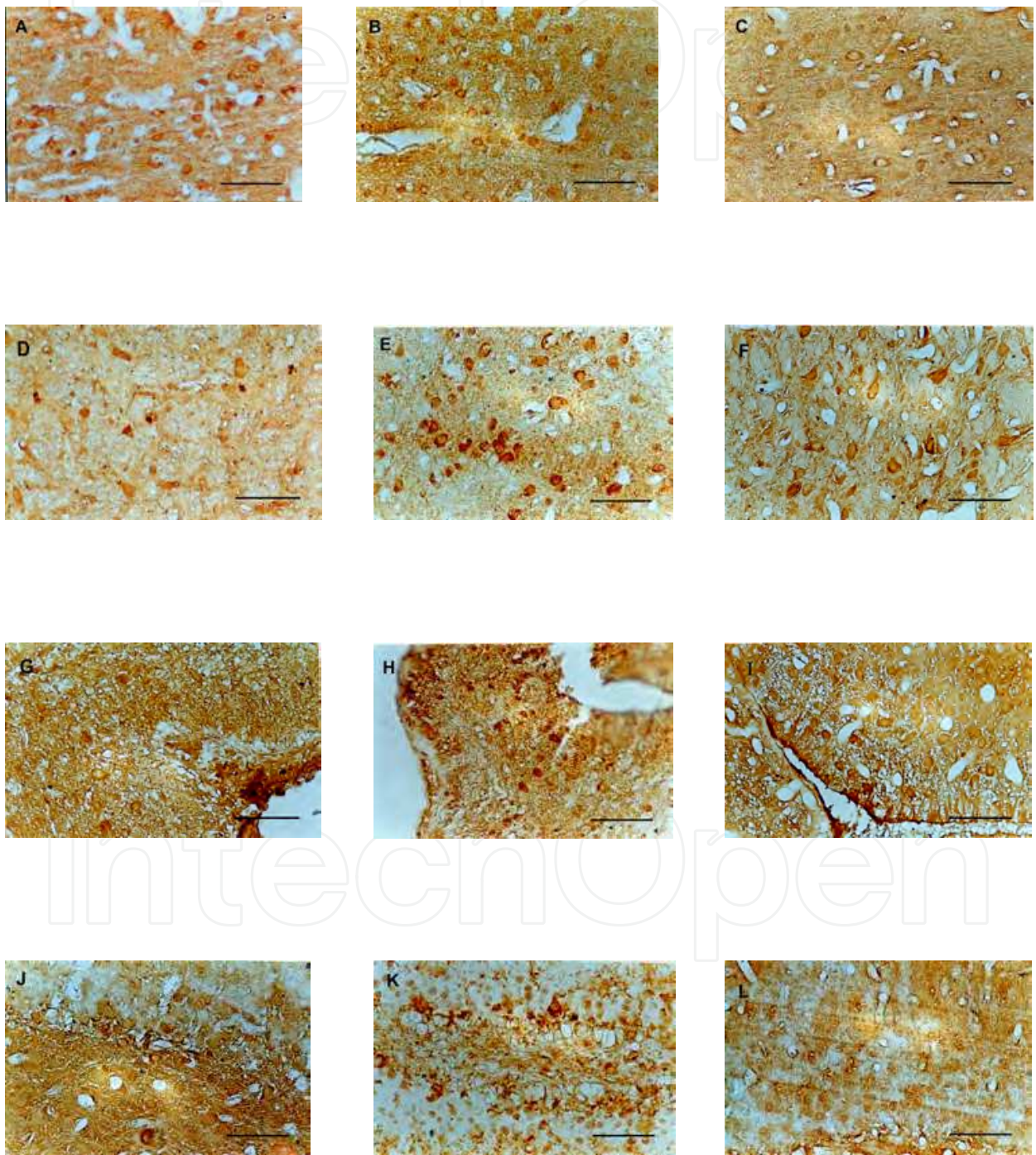
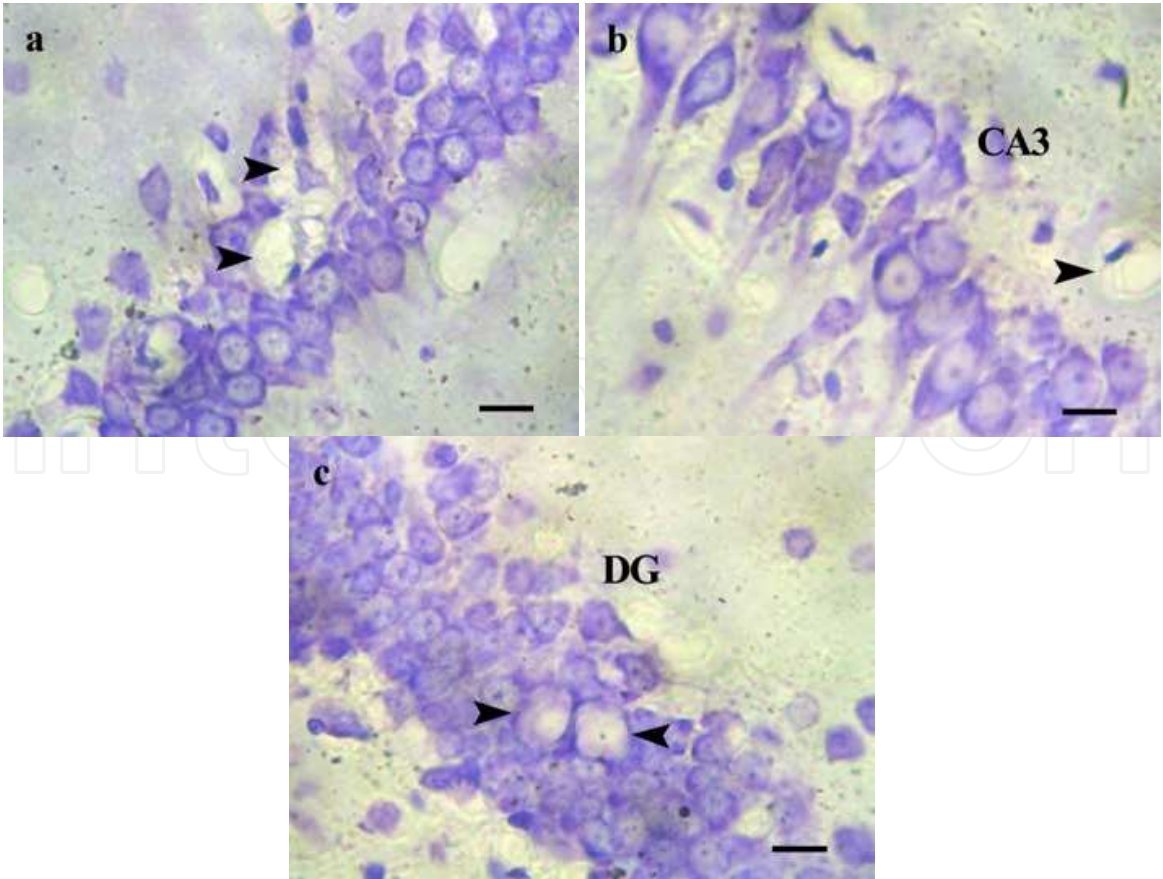
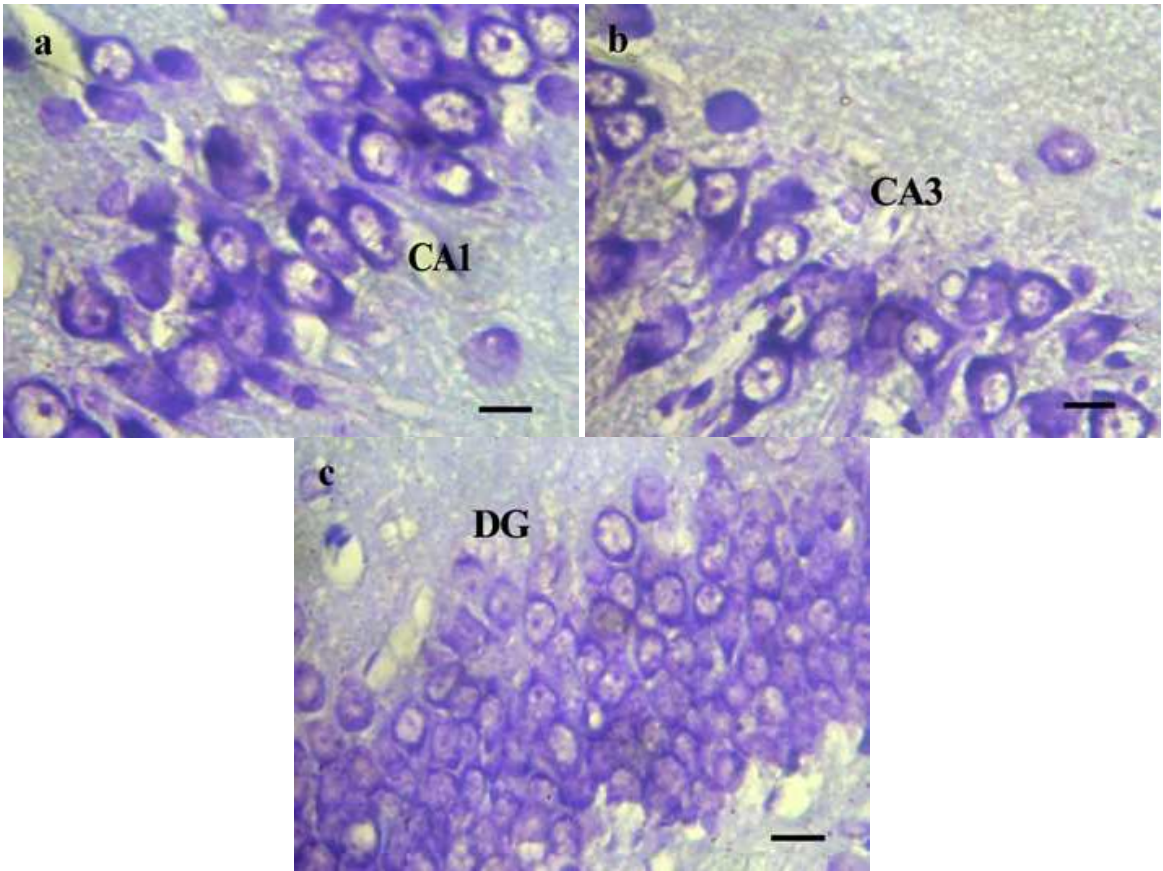


Fig. 2.2. NSE immunostaining of cerebral cortex (A, B, C), thalamus (D, E, F), hypothalamus (G, H, I), and hippocampus (J, K, L) of the control, single dose, and repeated doses PTZ-treated group, respectively. Bar, 100  $\mu$ m.





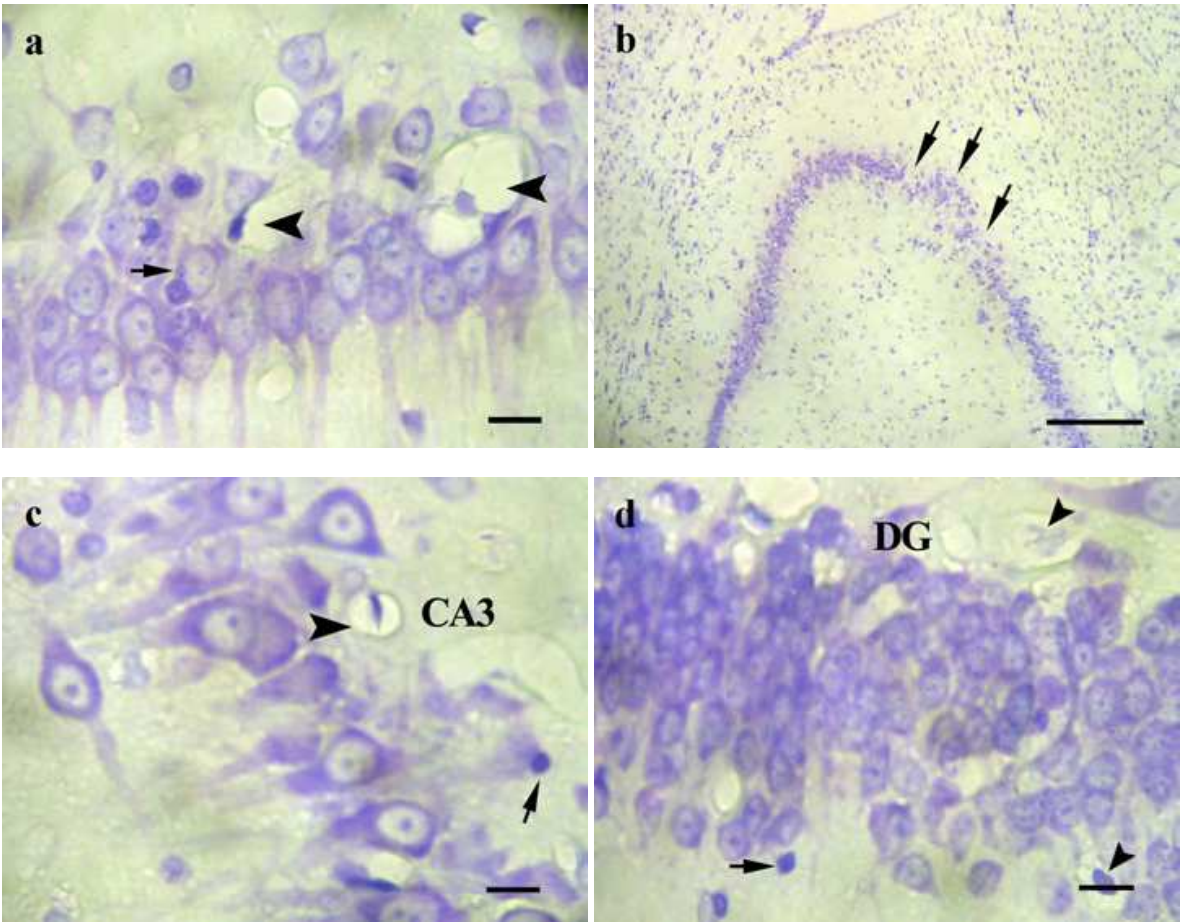


Fig. 2.1-3. Photomicrographs of Nissl-stained hippocampal regions, CA1(a), CA3 (b) and DG (c) in the control group (Fig.2. 1), acute-PTZ group (Fig. 2. 2) and the chronic-PTZ group (Fig.2. 3). Neuronal loss were seen Fig. 2. 2 and 2. 3. In the sections through hippocampus of the acute and chronic-PTZ groups showed a thinned, sparsely staining and a breach of staining in the CA3 pyramidal cell layer (arrows in).

with preservation of nuclear membrane continuity, and cell body shrinkage (Fig. 2. 4c). This feature could be distinguished from the signs of necrosis in CA1, including over swelling, cytolysis, and pyknotic nucleus with irregular contour of the chromatin (Fig. 2. 4b). These types of necrotic cells were observed in hippocampus of the chronic-PTZ group.

Groups/Hippocampal regions	CA1	CA3	DG
Control group	126.43±19.321	70.571±48.938	208.14±14.276
Acute-PTZ group	120±18.556	66.714±46.804	192.43±19.025*
Chronic-PTZ group	84.162±7.7766*	58.286±40.211	121.43±12.843*

\* p< 0.001

Table 2. Number of neurons in the hippocampal regions of the brain from the control, acute- and chronic-PTZ groups. Neurons were counted in the 765×10<sup>2</sup> μm<sup>2</sup> fields of coronal sections.

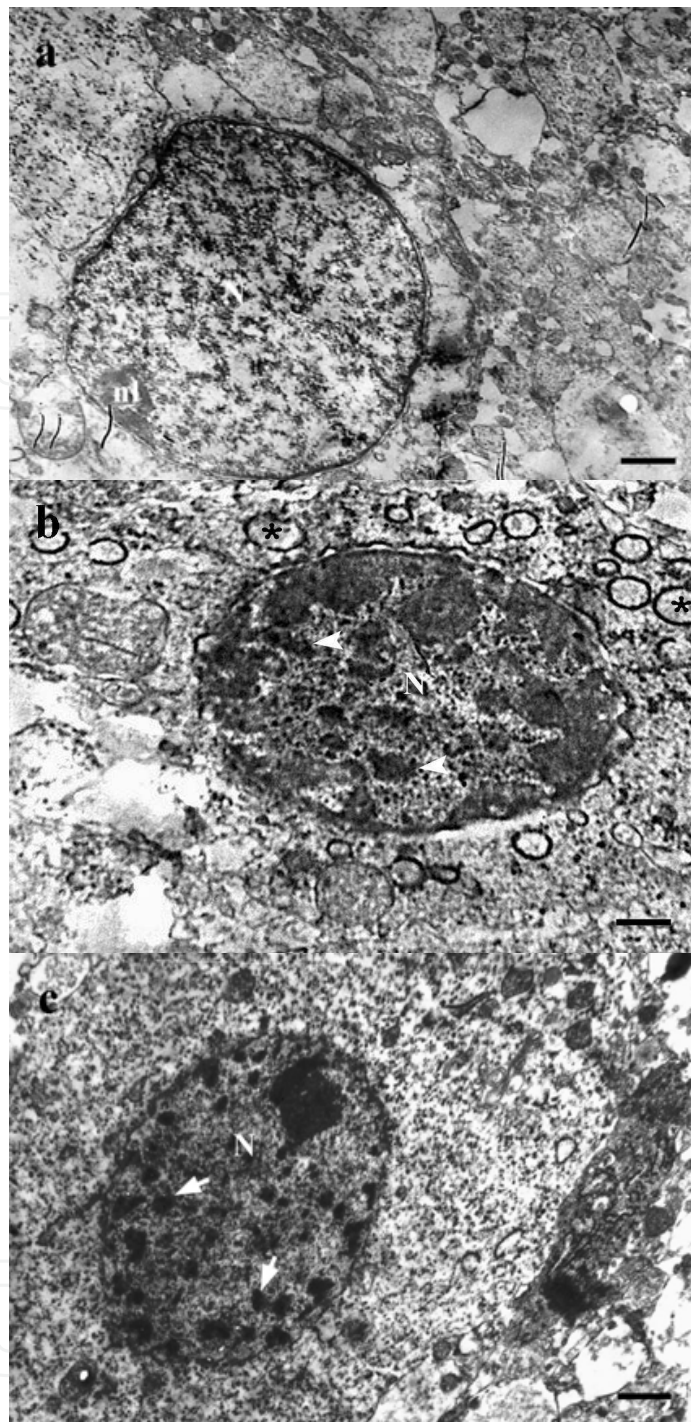


Fig. 2.4. Electron micrographs of hippocampal neurons in the control (a), acute- (b) and chronic-PTZ (c) groups. In a normal CA1 pyramidal neuron of control group, Nucleus (N) is euchromatic and exhibiting normal cytoplasmic features (a). Necrotic features (b), i.e., numerous small vacuoles throughout the cytoplasm as well as disruption of plasma membrane and a pyknotic nucleus with irregular contour of the chromatin clumps (arrowheads in ) were seen the acute-PTZ group (b). In the chronic-PTZ group, CA1 neuron displayed apoptotic-like features such as chromatin condensation into a few round clumps (arrows in) and condensation of a relatively intact cytoplasm with preservation of plasma membrane (c)



## 5. Discussion

In this study, systemic injections of 55 mg/kg PTZ produced a high incidence of convulsions, and wild running. Yonekawa et al. (1980) have studied relationship between PTZ-induced seizures and brain PTZ levels in mice. PTZ is often used in experimental models of epilepsy. In their study examined this relationship and determined how different routes of PTZ administration affected brain PTZ uptake and seizure development. The critical brain PTZ level for onset of clonus ranged from 20 to 50 microg/g. This dose of PTZ was same with our experimental porcesses. Seizures activity is associated with neuronal damage.

The results of the present study demonstrated the presence of NSE immunoreactivity and Nissl staining in neurons of the different brain regions after PTZ-induced seizures. Although NSE (+) neurons significantly increased in the hypothalamic regions of the single dose PTZ-treated group, NSE (+) neurons were found to be increased only in the thalamic region of the repeated doses PTZ-treated group compared to the control group. In addition, NSE (+) neurons were found to be slightly increased in the cortex, thalamus and hippocampus in the single dose PTZ-treated group compared to the control group.

Several studies have demonstrated that seizure-associated brain damage was initiated by the release of excitatory amino acid neurotransmitters from excessively firing presynaptic terminals in ultimately neurotoxic concentrations. Additionally, pannecrosis through excessive focal tissue acidosis may also contribute to the neurotoxicity processes (Sloviter & Dempster, 1985; Auer & Siej̄o, 1988). Interictal energetic deficiency in the epileptogenic hippocampus could contribute to impaired glutamate reuptake and glutamate-glutamine cycling that resulting in persistently increased extracellular glutamate. Increased lactate production together with poor lactate and glucose utilization were the cause of worsening of energy metabolism, which then produced a glial and neuronal toxicity. It has been reported that in the epileptogenic hippocampus of patients with temporal lobe epilepsy the level of glutamate were increased (Cavus et al., 2005) and glial glutamine synthetase is down regulated (vander Hel et al., 2005). In this study, the number of NSE (+) neurons that was observed to be increased in investigated brain regions after single dose PTZ-induced seizure indicates that these regions become more active metabolically. These regions seems to be compatible with those that shown to have increased metabolic activity during epileptic seizures in previous studies (Siesjo et al., 1986; Rasmussen et al., 1994). NSE immunostaining in the brain is useful for evaluating brain damage from various cases. This also supports the notion that NSE immunoreactivity is spared in less necrotic neurons (Nogami et al., 1998a). The present findings, which showed an increase in NSE immunoreactivity and nissl staining in the single dose PTZ-treated group, were correlated with the results of Nogami et al. (1998a). In another study that quantified NSE (+) neurons in the frontal cortex and hippocampus of the rat brain after systemic administration of kainic acid, while the concentrations of NSE remained unaffected in the frontal cortex, NSE levels were found to be significantly decreased in the hippocampus (Ding et al., 2000). These results are in accordance with the present findings. In the present study, although the number of NSE (+) neurons in the cortex and hippocampus increased in the single dose PTZ-treated group, it was found to be decreased in the repeated doses PTZ-treated group. Neuronal damage from epileptic insults occurs predominantly in cortical lamina III and IV where thalamocortical afferents terminate, suggesting a transneuronal effect in producing cortical neuronal

necrosis in SE (Auer & Siejō, 1988). In accordance with this study, in repeated doses PTZ-treated group, the present authors observed also a slight decrease in NSE (+) immunoreactivity and nissl amount in the cortical and hypothalamic neurons. It is well known that in comparison with the other brain regions, the hippocampal neurons appear to be more vulnerable to the excitatory damage caused by seizures (van Bogaert, 2001). In the present study, no statistically significant difference obtained in the hippocampus after repeated PTZ-induced seizures and number of NSE (+) neurons in these regions were close to the control values. Pavlova and colleagues (2005) stated that the rats developed tolerance to PTZ kindled seizures, showing oxidative stress and neurodegeneration in hippocampal region. On the other hand, in the present study, the intensity of NSE staining in the hippocampal neurons was found to be decreased after repeated PTZ-induced seizures. Considering to the results of both studies, it can be suggested that oxidative damage of neurons resulting in neurodegeneration in the hippocampus was not directly related to the recurrence of a convulsive activity.

It has been stated that the focus of interest is the hippocampus, the brain area of great vulnerability in epilepsy (Holopainen, 2008).

According to our results, anti-NSE immunostaining might reflect the cellular damage of neurons during the antemortem period and could add further information about the integrity of neurons, which could be helpful determining the injured brain areas besides the morphological change of neurons assessed by CFV. Nissl substance can usually be seen in neuronal bodies stained with basophilic dyes and consist of rER and associated ribosomes. The ribosomes contain RNA and are the sites of protein synthesis. It imparts a light violet color to the rER. This stain gives a diffused coloration when the rER is less and spread out and imparts a granular appearance when the rER is abundant (Young & Health, 2000). Although neurons metabolically are highly active, the Nissl substance is often very prominent (Crossman & Neary, 2000). In this study the Nissl bodies were especially abundant in the perikarya of the cortical, thalamic, hypothalamic, and hippocampal neurons in the control and single PTZ-treated group, but the severity of Nissl staining was less in the repeated PTZ-treated group. The results also indicated that a significant increase in the number of NSE (+) neurons in the thalamus after repeated PTZ seizures comparing to the control group. This may be related with increase metabolically activity of the thalamic neurons after epileptic seizures. The increase in the number of NSE (+) cells in the brain were in parallel to the other studies that reported an increase in the serum levels of NSE following epileptic seizures (Sankar et al., 1997). NSE is a good indicator of neuronal damage. The level of sNSE and cNSE are increased in brain diseases such as anoxic brain injury and stroke (Hasegawa et al., 2002). The sNSE levels are reported to reach maximum levels between 1 and 6 h postictally (Tumani et al., 1999). It appears that this enzyme located in the neurons passes to the serum with the destruction of the BBB and reaches peak levels for a certain amount of time. The reversible opening of the BBB has already been shown during the PTZ-induced epileptic seizure (Sahin et al., 2003). As a result, while the number of NSE (+) neuron were increased in all investigated brain region of the single dose PTZ-treated group, the same increase was noted only in the thalamic region of repeated dose PTZ. Additionally a low NSE immunoreactivity was seen in the cortex, hypothalamus, and hippocampus of the repeated doses PTZ-treated group. These findings suggest that some adaptive changes may develop in the CNS after repeated seizures. On the other hand, a low

immunoreactivity in the brain regions could reflect the lower metabolic state of damaged neurons (Nogami et al., 1998). Cellular and molecular mechanisms related with the metabolic changes that are observed following epileptic seizures may be responsible from the brain damage.

Both necrotic and apoptotic forms of cell death contribute to brain damage in the PTZ-induced epilepsy model. One of the most common stains used for nervous system tissues is CFV method, which binds very strongly to the RNA in the neuron's GER (rER), since it's a basic stain (Chan and Lowe, 2002; Damjanov, 1996). Therefore, CFV is a specific stain to show the GER in the neurons. It imparts a light violet color to the GER. This stain gives a diffused coloration when the GER is less and spread out and imparts a granular appearance when the GER is abundant (Young & Health, 2000). Perikaryal injury in cytoplasmic swelling and degranulation of ribosomes from the GER. This loss of RNA is seen as disappearance of cytoplasmic basophilia which is called chromatolysis. Necrotic and apoptotic neurons were observed in the chronic-PTZ treated group. Necrosis was observed extensively in the brains of the chronic-PTZ animals. Nadler and colleagues (1980a) have used intraventricular injections of KA to destroy the hippocampal CA3-CA4 cells, thus denervating the inner third of the molecular layer of the fascia dentata and stratum radiatum and stratum oriens of area CA1. Their results showed a preferential ordering in the reinnervation of dentate granule cells (DGCs) that was not readily explained by proximity to the degenerating fibers and also that removal of CA3-CA4-derived innervation more readily elicits translaminal growth in the fascia dentata than in area CA1. These results might be relevant to clinical situations in which neurons of the hippocampal end-blade were lost. Nadler and colleagues (1980b) have studied the degeneration of hippocampal CA3 pyramidal cells investigating by a light- and electron-microscopy after intraventricular injection of the potent convulsant, KA. EM revealed evidence of pyramidal cell degeneration within one hour. The earliest degenerative changes were confined to the cell body and proximal dendritic shafts. These included an increased incidence of lysosomal structures, deformation of the perikaryal and nuclear outlines, some increase in back ground electron density, and dilation of the cisternae of the endoplasmic reticulum accompanied by detachment of polyribosomes. Within the next few hours the pyramidal cells atrophied and became electron dense. Then these cells became electron lucent once more as ribosomes disappeared and their membranes and organelles broke up and disintegrated. The dendritic spines and the initial portion of the dendritic shaft became electron dense within four hours and degenerated rapidly, whereas the intermediate segment of the dendrites swelled moderately and became more electron lucent. We also a few necrotic neurons from the acute-PTZ group were seen in the CA3 regions. Our findings were similar to Nadler and colleagues (1980b). We also observed necrotic degenerative changes including the deformation of nuclear and perikaryal outlines, dilatation of the cisternae of endoplasmic reticulum in the acute-PTZ group. In the chronic-PTZ group, both a few necrotic and apoptotic neurons were observed in the CA3 regions. But we did not determined significant difference in the number of neurons in the CA3 region in the acute- and chronic-PTZ groups. Schwob and colleagues (1980) have studied the effect of systemic and intracerebral injections of KA, a potent neuroexcitatory and neurotoxic analogue of glutamate, in the rat using a variety of light- and electron-microscopic techniques. The initial neuropathological reactions include dendritic and glial dilatations in discrete areas of the neuropil; affected neuronal somata either appear swollen and pale, or are shrunken with dark cytoplasm. In



the most severely affected areas, the lesion progresses to severe disruption of the neuropil. The commonly affected areas include the olfactory cortex, amygdaloid complex, hippocampus, and related parts of the thalamus and neocortex. Intracerebral injections of 2–6 nmol produce extensive neuronal damage in distant structures, as well as at the injection site. The pattern of distant damage varies with the site of the injection and appears to reflect axonal connections between the affected areas near the injection and the distant areas of damage. Injections into the posterior part of the olfactory cortex which involve the entorhinal cortex (EC) tend to produce severe degeneration in field CA1 of the hippocampus, although field CA3 is more severely damaged following intraventricular, intrahippocampal or intrastriatal injections. Du and colleagues (1993) have obtained specimens EC during a surgical treatment of intractable partial seizures and were studied by light microscopy in Nissl-stained sections. A distinct loss of neurons was observed in the anterior portion of the medial EC in the absence of apparent damage to temporal neocortical gyri. These observations provided neuropathological evidence for an involvement of the EC in temporal lobe epilepsy (TLE). Since the EC occupies a pivotal position in gating hippocampal inputs and outputs, their results further support previous suggestions that dysfunction of this region may contribute, either independently or in concert with Ammon's horn sclerosis, to epileptogenesis in humans. Du and colleagues (1995) have examined the EC in three established rat models of epilepsy using Nissl staining. Adult male rats were either electrically stimulated in the ventral hippocampus for 90 minute or injected with KA or LiPC. At 24 hour, all animals that had exhibited a bout of acute SE showed a consistent pattern of neuronal loss in the EC in Nissl-stained sections. We also determined neuronal loss in hippocampal GD at 24 hours in Nissl stained sections of the acute-PTZ group. Du and colleagues (1995) have also seen an identical pattern of nerve cell loss in the EC of rats killed 4 weeks following the treatments. This lesion was completely prevented by an injection of diazepam and pentobarbital, given one hour after KA administration. Taken together, these experiments indicated that prolonged seizures caused a preferential neuronal loss in layer III of the medial EC and that this lesion might be related to a pathological elevation of intracellular calcium ion concentrations. Isokawa (1998) has determined that dendritic degeneration was a common pathology in TLE animal models. In a study of a rat pilocarpine model, visualization of dendrites of the hippocampal DGCs by biocytin revealed a generalized spine loss immediately after an acute seizure induced by pilocarpine. The present finding suggests that initial acute seizures do not cause permanent damages in dendrites and spines of DGCs; instead, dendritic spines were dynamically maintained in the course of the establishment and maintenance of spontaneous seizures. Local dendritic spine degeneration, detected later in the chronic phase of epilepsy, was likely to have a separate cause from initial acute insults. We also detected both apoptotic and necrotic neurons ultrastructurally. Eid and colleagues (1999) have been studied in the animals also develop hyperexcitability of the EC and the hippocampal region CA1. Pathologically swollen dendrites and electrondense neuronal profiles were present in the lesioned sector as well. The majority of the electron-dense profiles was identified as degenerating dendritic spines that were closely apposed to strongly glutamate-immunopositive axon terminals. These findings might be of relevance for the genesis and spread of temporal lobe seizures. Clinical, radiologic, and experimental evidence indicated that the EC region might be linked to the pathology of hippocampal sclerosis (HS) in patients with TLE (Du et al., 1993; Du &

Schwartz, 1992; Dawodu & Thom, 2005). Morphological analysis of hippocampal formation after pilocarpine-induced SE showed increased glucose utilization in most brain regions including the hippocampus during a period of continuous seizure activity (Clifford et al., 1987), an extensive loss of neurons within the hilar area of the GD (Mello et al., 1993; Cavaleiro, 1995), and loss of interneurons in the CA1, CA3, and hilus regions (Cavaleiro, 1995). In our study we also determined a significant neuronal loss in the CA1 region of the chronic-PTZ group compared with the control group. We determined significant difference between the numbers of CA1 neurons in the chronic-PTZ group and control group ( $p < 0.001$ ; Table 2). Chandler and colleagues (2003) have observed that loss of interneurons could undoubtedly contribute to a decrease in GABA release. Several neurotransmitters, also including GABA, modulate glutamate release at synapses between hippocampal mossy fibers (MFs) and CA3 pyramidal neurons. Hilar mossy cells loss directly resulted in granule cell hyperexcitability (Toth et al., 1997; Santhakumar et al., 2001).

Impaired GABAergic inhibition might contribute to the development of hyperexcitability in epilepsy. Thus, decrease GABA activities, which an inhibitory neurotransmitter, led to the removal of synaptic inhibition on epileptic neurons and to epilepsy seizures making neurons prone to more excitability. Heterotopic granule cells exhibit features often have been observed in epileptic tissue. Granule cell dispersion in the GD, similar to that seen in human epileptic hippocampi has also been observed in animal models of epilepsy, e.g., after KA injection into the dorsal hippocampus (Cavaleiro et al., 1982; Ben-Ari, 1985) and in the pilocarpine model. The distribution of granule cells in the GD of the hippocampal formation has been studied in control autopsy and TLE specimens. Results contributed to the altered circuitry of the hippocampal formation in TLE (Houser, 1990) and Houser (Houser, 1999) stated that the neuronal loss and synaptic reorganization in TLE. It has remained unclear whether the appearance of heterotopic granule cells is related to granule cell loss in the epileptic hippocampus. Granule cell dispersion has not been observed when a cell loss is minimal (Lurton et al., 1997). We also determined decreased number of neurons in the GD region in the acute- and chronic-PTZ groups. There was a significant difference between the number of GD neurons between the groups. Brevard and colleagues (2006) have found that GD was twice as active as other hippocampal areas, but peaked just before seizure onset in the PTZ-induced seizure in rats. Neurons in this area might contribute to the neural network controlling the initiation of generalized tonic-clonic seizures. Some studies have also been shown that MFs were decreased in epilepsy. It is suggested that sprouting of MFs or their axon collaterals occurs in hippocampal epilepsy and the reorganized fibers contain at least one of the neuropeptides that are normally present in this system. Such fibers could form recurrent excitatory circuits and contribute to synchronous firing and epileptiform activity, as suggested in studies of experimental models of epilepsy (Houser et al., 1990). Hippocampal MFs represented a major input from DGCs to the hippocampal CA3 field. They exhibit several forms of presynaptic modulation of transmitter release, including marked short-term (Salin et al., 1996) and long-term (Harris & Cotman, 1986) use-dependent plasticity. They are sensitive to several neurotransmitters that depress transmitter release, including glutamate (Kamiya et al., 1996), GABA (Min et al., 1998; Vogt & Nicoll, 1999), and peptides (Weisskopf et al., 1993) acting on metabotropic receptors. MF transmission might be under such profound modulation because hippocampal principal cells are highly vulnerable to excitotoxicity (Meldrum, 1993). Nevertheless, these modulatory mechanisms

could break down: excessive activity in the DG can spread into the hippocampus and result in neuronal loss that resembles similar to that seen after KA administration (Sloviter,1987; Sloviter,1991). An anatomic and neurobiologic study revealed functional abnormalities in the GD of epileptic KA-treated rats; however, lateral inhibition persists, suggesting that vulnerable hilar neurons were not necessary for generating lateral inhibition in the GD (Buckmaster & Dudek, 1997a; Buckmaster & Dudek, 1997b). Histological and quantitative stereological techniques were used to estimate numbers of neurons per GD of various classes and to estimate the extent of granule cell axon reorganization along the septotemporal axis of the hippocampus in control rats and epileptic KA-treated rats. Findings from the GD of epileptic KA-treated rats were strikingly similar to those reported for human TLE, and it was suggested that neuron loss and axon reorganization in the temporal hippocampus might be important in epileptogenesis (Buckmaster & Jongen-Relo,1999). Failure of modulation of MF transmission might also contribute to the delayed development of spontaneous seizures (Chandler, 2003). In their study, Sloviter and colleagues (2006) in chronically epileptic rats demonstrated that DGCs were maximally hyperexcitable immediately after SE, prior to MF sprouting, and that synaptic reorganization following KA-induced injury was temporally associated with GABA (A) receptor-dependent granule cell hyper-inhibition rather than hypothesized progressive hyperexcitability. Mortazavi and colleagues (2005) have revealed that neuronal loss in the CA1 area and increased MF sprouting in the GD were similar to what was observed in human epilepsy. These results indicated that PTZ kindling provides a useful model of postseizure dysfunction, which can serve as a screen for potential treatments for those cognitive, emotional, and neuropathological deficits that resemble those symptoms observed in human epilepsy. In our study, hippocampal CA1 sections were examined in transmission EM samples of controls and PTZ-induced animals. According to ultrastructural appearance of the neuropil and nucleus, we determined that repeated-PTZ injections caused both necrotic and apoptotic neuronal death in the CA1 region of the hippocampus in the chronic-PTZ group. A few dying neurons were seen in the apoptotic morphology as described by Portera-Cailliau and colleagues (1997a; 1997b), in PTZ-induced groups. This feature could be distinguished from the signs of necrosis in the CA1, including overt swelling, cytolysis, and pyknotic nucleus with irregular contour of the chromatin. In another study (Jerman et al., 2005), it was shown that cell loss was relatively uniform after ibotenic acid injections into areas CA1 and CA3, but variable after colchicine injections into the GD. CA1 and CA3 lesions appeared mostly localized to those relative subregions, and DG lesions appeared highly localized to the GD. Pavlova and colleagues (2006) have suggested that, in a PTZ kindling model, oxidative damage of neurons resulting in neurodegeneration in the hippocampus was not directly related to the convulsive activity. PTZ-kindling in rats has been induced moderate neuronal cell loss in hippocampal fields CA1-4, and DG. They have suggested that PTZ-kindling might be a suitable model to study the mechanisms of seizure-induced neuronal death. Neuron death in the hippocampus is also accompanied by increases in oxidative stress, this is also being independent of the external manifestations of the brain seizure activity.

## 6. Conclusion

In conclusion, NSE immunoreactivity may be a valuable marker for determining the number of metabolically active neurons and the regions where these changes take place after single

and repeated seizures. New studies investigating the neuronal activity changes during the epileptic seizure, including modulation of gene expression, will give a new insight for future research. While necrotic neurons of CA1 and CA3 regions were rarely seen, these cells were observed extensively in the GD region of a group treated with PTZ in our study. There was a significant difference between the number of GD neurons considering controls. CFV showed a decreased Nissl of hippocampal neurons in the chronic-PTZ group compared to controls. In the chronic-PTZ group, both necrotic and apoptotic neurons were observed in the CA1 region. There was significant difference between the numbers of CA1 neurons in the chronic-PTZ group and that of controls. In the chronic-PTZ group, both necrotic and apoptotic neurons were observed in the GD region extensively. There was significant difference between the number of GD neurons in the control and chronic-PTZ group ( $p < 0.001$ ). According to the ultrastructural appearance of the cytoplasmic organelles and nuclear components of CA1 regions a few necrotic neurons was seen in the acute-PTZ group. Both necrotic and apoptotic neurons of the CA1 region were observed in the chronic-PTZ group. EM revealed that dying neurons at the CA1 region showed apoptotic cells. These types of necrotic cells were observed in hippocampus of the chronic-PTZ group. The outcome of continuation of epilepsy seizures in the chronic-PTZ group was loss of hippocampal neurons with the decrease of GD and CA1 neurons. These findings might be result of excitotoxic sensitivity of these neurons especially. A decreasing in the numbers of CA1 neurons was determined only in the chronic-PTZ group. However, PTZ injections cause a decreasing of GD neurons in both acute- and chronic-PTZ groups. Our results showed that chronic-PTZ seizures cause neuronal degeneration and neuronal loss of hippocampus.

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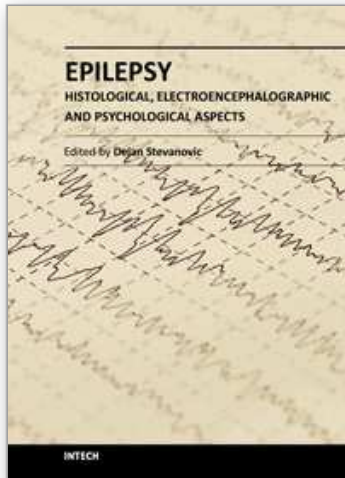
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