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Experimental Epilepsy Models and Morphologic Alterations of Experimental Epilepsy Models in Brain and Hippocampus

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1. Introduction

Epilepsy is a neurological disease arising from abnormal and uncontrollable electrical firings of a group of neurons appearing in the central nervous system. Experimental epilepsy models have been developed to assess the pathophysiology of epileptic seizures and to search for new effective anti-epileptic drugs.

This chapter is designed to describe characteristics of experimental epilepsy models and morphological and anatomical changes of brain, particularly hippocampus (Figure 1), in these models. Because of the hippocampal neuronal hyperexcitability during epileptic seizures, hippocampus has been one of the best choices in terms of target area that reveals most efficiently the effects of seizures in experimental epilepsy models.

The purpose of the study determines which model should be chosen for epilepsies. This type of studies may have three purposes: 1. Developing new drugs, 2. Exploring the mechanisms, 3. Determining the relationships between basic events and the development of events for epilepsy.

An ideal model of epilepsy should have the following characteristics: 1. Seizures should be as the spontaneous recurrent seizures, 2. Seizures should be similar to seizures in humans, 3. The EEG pattern should be similar to related type of epilepsy, and 4. The frequency of seizures should be sufficient to test acute and chronic effects of drugs. However, there is no single model that meets all these criteria.

Some researchers classify seizures according to generation of the epilepsy model, not according to seizures in humans. Experimental models are divided into three groups according to this classification: 1. experimental seizures induced by chemical convulsants or by electrical stimulation, 2. reflex epilepsies, and 3. idiopathic epilepsies.

Epileptic seizures are classified in three groups:

1. Partial seizures, which can be further subdivided into simple partial seizures and complex partial seizures.
2. Generalized seizures which can be further subdivided into tonic, clonic, tonic-clonic (grand mal), absence (petit-mal) seizures, and status epilepticus.
3. Unclassified seizures.

In experimental epilepsy studies, animal models have been developed according to this classification (Table-1).

- 1- Simple partial, acute
- 2- Simple partial, chronic
- 3- Complex partial
- 4- Generalized tonic-clonic
- 5- Generalized absence
- 6- Status epilepticus.

<i>Animal (the experimental) models of the epilepsies:</i>		
<i>1- Simple partial, acute</i>	<i>4- Generalized tonic-clonic</i>	<i>5- Generalized absence</i>
Penicillin	Genetic	Thalamic stimulation
Bicuculline	Photosensitive boboons	Bilateral cortical foci
Picrotoxin	Audiogenic seizures in mice	Systemic penicillin
Strychnine	Mongolian gerbil	Intraventricular opiates
	Epilepsy mice	
	Genetically epilepsy-prone rats	
<i>2- Simple partial, chronic</i>		
Cortically implanted metals	Maximal electroshock	
Aluminum hydroxide	Chemical convulsants	
Cobalt	Pentylenetetrazol	
Zinc	Systemic penicillin (as a tonic-clonic model)	
Manganese	Picrotoxin	<i>6- Status epilepticus</i>
Iron	Bicuculline	Lithium-pilocarpine
Cryogenic injury	Methionine sulfoximide	Cobalt-homocystine
	Bemegride	Recurrent stimulation
	Others	
<i>3- Complex partial</i>	Metabolic derangements	
Kainic acid	Hypoxia	
Tetanus toxin	Hypoglycemia	
Kindling	Hyperbaric oxygen	
	Hypercarbia	
	Drug withdrawal	
	High temperature	

Table 1. Animal (the experimental) models of the epilepsies.

2. Simple partial, acute

Penicillin

The most popular method to study simple partial (focal) seizures has been by application of a topical chemical convulsant. Chemical convulsants are widely used for inducing seizures easily and rapidly. The common antibiotic, penicillin (a chemical convulsant), was

discovered during neurosurgical procedures, in which it was applied to brain to prevent infection. When a cottoned pledget soaked in penicillin is placed on exposed rat or cat cortex, regionally placed electrodes record recurring interictal spikes within a few minutes. These discharges resemble human interictal spikes recorded from cortex. During the interictal spike neurons in the region of the focus tend to fire synchronously. If penicillin is injected into the neocortex, the injected cortical area becomes a source of epileptic seizures. The penicillin epilepsy (PE) model has been one of the most important model for answering questions about the neuronal basis of epilepsy. This model is also suitable for analysis of spread of seizure activity.

PE model is one of the most useful acute models in the field of experimental epilepsy studies. This model is also essential for analysis in synchronous and spread of epileptogenic seizure activity. It allows obtaining EEG records as in acute partial epilepsy by application penicillin to cortical surface. Penicillin-induced epileptic activity begins focally, but then spread and cause generalized epilepsy. In this regard, it resembles the grand-mal epilepsy.

PE model leads to neuronal loss in CA1-CA2-CA3 subfields of hippocampus and hippocampal volume decrease in rats, in proportion to the given dose.

However, there are no neuronal loss and volume decrease in dentate gyrus of penicillin epileptic rats.

Bicuculline, Picrotoxin, Strychnine

Bicuculline is an alkaloid that is used only in experimental studies. There are structural similarities between bicuculline and penicillin. Picrotoxin is a poisonous crystalline plant compound, found primarily in the fruit of the climbing plant *Anamirta cocculus*. Strychnine is a poisonous alkaloid that is obtained from seeds of the nux vomica tree (*S. nux-vomica*) and related plants of the genus *Strychnos*. Strychnine acts as a non-competitive blocker of inhibitory glycine. It was shown that topical application of 5% bicuculline to temporal cortex generates paroxysmal depolarization in cats, after a few seconds.

Bicuculline, picrotoxin and strychnine are antagonists to the action of the inhibitory neurotransmitter GABA, and generate epileptiform activity, in particular by blocking GABA_A receptors. The GABA_A antagonists, bicuculline or picrotoxin, greatly increase burst firing in dopaminergic neurons whereas GABA_B antagonists cause a modest shift away from burst firing towards pacemaker-like firing. The three principal GABAergic inputs to nigral dopaminergic neurons arise from striatum, globus pallidus and from the axon collaterals of nigral pars reticulata projection neurons, each of which appear to act in vivo primarily on GABA_A receptors.

Bicuculline induced status epilepticus with duration of 1 or 2 h leads to morphological changes in fronto-parietal cortex and hippocampus of rats. Astrocytic edema and wide-spread neuronal changes of two different kinds occur in the fronto-parietal cortex of the animals. Type 1 injured neurons are characterized by condensation of karyoplasms and cytoplasm (type 1a), which in some neurons become so intense that the nucleus can no longer be clearly discerned (type 1b). The type 2 injured neurons have slit-formed cytoplasmic vacuoles chiefly caused by dilatation of the rough endoplasmic reticulum. In the hippocampus the most conspicuous alteration is astrocytic edema which is most marked around the perikarya of pyramidal neurons in CA1-CA4 and subiculum. In the dentate gyrus the edema is less pronounced and, when present, affects particularly the hilar zone of

the stratum granulosum. The nerve cell changes are less pronounced than in the cerebral cortex. The vast majority of the hippocampal pyramidal neurons in CA1-CA4 show minor configurationally and tinctorial abnormalities (incipient type 1a change). Severe nerve cell alterations (type 1b) are present but very rarely affect the pyramidal neurons of CA1-CA4 and subiculum, whereas in the dentate gyrus pyramidal basket neurons of stratum granulosum and pyramidal nerve cells in stratum polymorphic show the severe type 1b changes.

3. Simple partial, chronic

Cortically implanted metals

Alumina hydroxide

The best validated and most realistic models for the epilepsies are those employing implantation of metals in brain to generate a state of 'spontaneously' recurrent simple partial seizures. The prototype of this group of models is the alumina hydroxide gel model. In a typical preparation 4% alumina hydroxide will be injected into surgically exposed monkey neocortex at a few adjacent sites. A similar model can be produced in the cat. Spontaneous and recurrent seizures generally begin one to two months after the injection, and persist for as long as several years. The seizures themselves are similar to simple partial seizures in humans, with rhythmic jerking of an extremity or face contra lateral to the aluminum lesion, and occasional progression to secondarily generalized tonic-clonic seizures. Interictal and ictal EEGs appear similar to clinical studies. Neuropathological specimens obtained from biopsies in the region of an established alumina focus in monkeys show gliosis and distortion of dendritic neuronal trees, similar to the picture seen in human neocortical foci.

Cobalt

Cortical implantation of cobalt can produce chronic or subacute models of recurrent seizures in animals. GABA receptors have been found to be decreased in the region of cobalt foci of rat motor cortex, 2-3 weeks after establishment of the focus. Furthermore in the unilateral cobalt model, the lack of anatomic differences in the white or gray matter outside the areas of MR signal loss caused by cobalt suggests no widespread cerebral injury.

Zinc, Copper, Manganese, Iron

Intraventricular application of the metals, such as zinc, copper, manganese, iron leads seizures. These effects of these metals are thought to be occur by blocking Na,K-ATPase membrane pump.

A chronic model for experimental epilepsy can be generated by injecting 10 µl zinc sulfate into rabbit hippocampus. In this model, epileptic seizure continues for weeks and clinical or electrophysiological aspects are similar to complex partial and secondary generalized seizures in addition to simple partial seizures. Neuronal loss in both hippocampus and cerebellum has been found after intracortical zinc injection. Also, zinc model generates spontaneous epileptic seizures and generalized convulsions in rabbits but not in rats. It should be remembered that aluminum model generates spontaneous seizures in rats.

In oxygen and glucose deprivation model of trans-synaptic Zn^{2+} movement, Ca-A/K channels have been expected to play a late role in neuronal injury. It is suggested with

strong presynaptic activation, basal numbers of Ca-A/K channels permit sufficient Zn^{2+} entry to mediate rapid neuronal damage in a study of oxygen and glucose deprivation model. These observations may provide new rationale for neuroprotective strategies targeting Ca-K channels and Zn^{2+} passage through them in conditions of ischemia or epilepsy, which are associated with rapid synaptic Zn^{2+} release.

Cryogenic injury

One model that doesn't require injection of exogenous drugs into brain is cryogenic or freeze exogenous drugs into brain is cryogenic or freeze lesion model for partial simple seizures. Ethylchloride lesions or cold trauma from a liquid nitrogen probe produces a highly epileptogenic lesion, giving rise to seizures within a few hours of the lesion and persisting for a few days. Substantial cerebral edema generally accompanies the lesion.

4. Complex partial

Complex partial seizures are usually arise from the limbic lobe, including amygdala, hippocampus, and less often, temporal neocortex or extratemporal structures.

Kainic acid

Kainic acid (KA) is a rigid analog of the putative excitatory neurotransmitter, glutamate and potent agonist of the AMPA/kainate class of glutamate receptors. KA has been used to induce limbic seizures. Systemic and intracerebral administration of KA initially induces a characterized pattern of seizure activity that lasts for hours, followed by a latent seizure-free period of weeks, preceding the development of spontaneous recurrent focal seizures that begin between 3 and 4 weeks. Injection of KA is followed by cytotoxic brain edema, characterized by massive swelling of perineuronal and perivascular astroglia, resulting in parenchymal necrosis of the affected region.

Primary interest in KA has derived from its ability to produce relatively selective lesions of cell bodies in brain, while sparing axons of passage. For reasons that are still incompletely understood, KA has an especially prominent toxic effect on hippocampus, even when injected systemically, or at brain sites remote from hippocampus. In doses less than those required to produce cell injury, KA can induce seizures in hippocampus. Animals given KA 4 mg/kg i.v., or 0.8-2.0 μ g intra-hippocampally, will show periodic arrest of activity, masticatory movements, complex motor activity, and some times extension to generalized tonic-clonic activity. Stereo-encephalography shows major spike activity originating in the limbic system. KA is a prototype of an excitotoxic compound. KA produces an acute or substance model of seizures, lasting hours to days. The accompanying hippocampal lesions may be considered to confound the model, or alternatively, to portray the pattern of limbic cell damage which can occur with clinical status epilepticus.

KA treated rats have been found to have significantly smaller hippocampus and a significant increase in ventricular size. The histological findings were neuronal loss and neuronal degeneration in CA1 and CA3 of the hippocampus, which was accompanied by strong microglia activation. The MRI of KA treated rats showed enlarged ventricles. Volumetric analysis of MRI images demonstrated a significant reduction in hippocampal volume of experimental rats 10 days following KA injection, whereas the cingulate cortex, retrosplenial cortex, and total brain volumes of these animals were not changed. Even 10 days after the KA injection neuronal loss was still ongoing.

The dentate gyrus of epileptic KA treated rats are strikingly similar to those of reported for human temporal lobe epilepsy, so the findings of neuron loss and axon reorganization in the hippocampus of KA treated rats may be important in epileptogenesis.

The similarities in patterns of neuron loss and granule cell axon reorganization between the epileptic human dentate gyrus and that of KA treated rats and other experimental models of epilepsy suggest the existence of population of highly vulnerable neurons that can be killed by naturally occurring traumatic events (e.g., status epilepticus, head injury, cerebral infections) and experimental treatments (e.g., kainate or pilocarpine toxicity and repetitive stimulation of the perforant pathway).

There are also functional similarities in the dentate gyrus of KA treated rats and in human temporal lobe epilepsy. So, homologous regions of the dentate gyrus suffer the most severe cell loss and axon reorganization in epileptic KA treated rats and in human temporal lobe epilepsy.

In addition, administration of KA activates ionotropic glutamate receptors, and selectively induces excitotoxic cell death in the CA3 and CA1 hippocampal subfields and within the dentate gyrus, while sparing neurons in the CA2 subfield and the dentate granule cell layer. Furthermore, there is a direct relationship between the generation epileptiform activity and the extent of damage in hippocampal subfields. Many features of this rodent model, such as hippocampal sclerosis and mossy fiber sprouting, resemble human temporal lobe epilepsy. As a result the KA model replicates several phenomenological features of human temporal lobe epilepsy and can be used as an animal preparation to understand the basic mechanisms of epileptogenesis.

Following a single 9mg/kg KA injection to rats, the most important histopathological changes are occur time dependent and include neuronal degeneration, microgliosis, astrogliosis. Focus of the neuronal damage in CA1 prior to CA3 damage resembling human lesions as opposed to CA3 dominance observed in some rodent models; hilar neuronal loss; activated microgliosis; astrogliosis; and aberrant mossy fiber sprouting in the inner molecular layer of dentate gyrus. Intracerebroventricular administration of KA induces selective neuronal loss in the CA3 subfield and activates glial cells in the rat hippocampus.

Similar to rats, administration of kainic acid (KA) to mice elicits epileptic behavior in a dose-dependent manner and causes distinct neuronal degeneration in limbic structures such as the hippocampus. KA treated mice show acute neuronal loss in the CA1 and CA3 regions of hippocampus, which is followed by the activation of glial cells and delayed neural cell death. KA treated mice also observe volume decrease in dorsal and ventral hippocampus.

Also, systemic administration of KA to rodents is a widely used experimental model of epilepsy and neurodegeneration. This treatment results in the appearance of chronic, spontaneous, recurrent seizures and neurodegenerative changes in the dentate gyrus.

Tetanus toxin

A model of recurrent, chronic partial seizures can be produced by injection of tetanus toxin into rat or cat hippocampus. Categorization of the model with complex partial seizure models results from the location of the usual injection site in limbic structures, rather than the properties of the toxin itself. The tetanus toxin model resembles those produced by injection of other convulsant substances into hippocampus, but it has some intriguing idiosyncrasies.

Tetanus is a disease produced from the gram-positive bacteria, *Clostridium tetani*. In the disease state toxin is transported from the periphery to the spinal cord, where it is believed to interfere with presynaptic release of inhibitory neurotransmitter. In contrast, injection into hippocampus of a dose of toxin 3-6 times the mouse probably produces effects only locally. Seizures may occur within a day after injection and then on a chronically recurrent basis over weeks. A seizure in a rat typically begins with arrest of activity. Followed by myoclonic jerks of the front limbs, and in some animals generalized tonic-clonic seizures. Whether or not the seizure generalizes depends upon several factors, including spread to the cingulate area.

A single dose of tetanus toxin, injected unilaterally into the hippocampus, produced a time-dependent neuronal loss in the CA1 pyramidal cell layer accompanied by a reduction in the binding of gamma-[3H]aminobutyric acid ([3H]GABA) to GABA_A but not GABA_B sites in the pyramidal cell layer.

Kindling

Kindling is a phenomenon by which repeated shocks to various parts of brain result in enhanced electrical excitability of brain. Kindling has become one of the most popular ways to model long-term plastic changes in brain excitability. Such plastic changes are believed to participate not only in epileptogenesis, but also in memory and learning. The kindling model is conceptually related to models for long term potentiation, although kindling paradigms tend to be more chronic than those for long-term potentiation (LTP), and focus more on epileptic changes than on enhanced evoked electrical responses.

Kindling is usually initiated by electrical stimulation of the amygdala, but most regions of forebrain can be kindled. To produce the model, bipolar stimulating wires are implanted in amygdala or elsewhere in brain. The animal recovers from the surgery, then daily electrical stimulus trains are applied via the electrodes. A fairly wide range of stimulation parameters may be effective in induction of kindling. After a few days of stimulation a train of shocks begins to induce electrical after discharges, which become progressively more complex and prolonged with each kindling stimulus. At this time, the animal is said to be 'kindled'. If continued for a few weeks, rodents exhibit "spontaneous" epileptic seizures.

Rapid kindling paradigms able to model status epilepticus in rodents, within a few hours or days of kindling have been described. Repeated stimulation by excitatory chemicals can also produce kindling.

The amygdala possesses the lowest threshold for the induction of kindling, an established experimental model of temporal lobe epilepsy in which daily electrical stimulation results in a gradual progression and intensification of limbic motor seizures.

Kindling through daily administration of brief electrical stimulations to the left basolateral nucleus of the amygdala resulted in a significant impairment of LTP in both the lateral amygdala and the CA1 of rat hippocampus. In contrast to KA model, DNA fragmentation and reactive microglia in the CA1, CA3, and hilus of the dentate gyrus region do not detected in the kindling model. Neuronal death occurs as a result of DNA fragmentation in hippocampal pyramidal cells in KA model.

Dentate gyrus of kindled rats is enlarged. The increase in area associated with kindling is the result of an enlargement of the molecular layer and the hilus of the dentate gyrus. Absolute neuronal counts show no change following kindling in the hilus of the dentate gyrus.

After kindling, i.e., specific electrical stimulation of the rat ventral hippocampus, cells numbers are significantly decrease in hippocampus, the hilus, and dentate gyrus.

5. Generalized tonic-clonic seizures

Genetic

There are no good animal models for primary generalized, spontaneously recurrent tonic-clonic (grand mal) seizures. Because idiopathic grand mal epilepsy shows a genetic component, investigators have attempted to develop models from genetically aberrant strains of animals; including baboons, beagles, Mongolian gerbils, mice, and rats. Each of these models has distinctions from clinical grand mal, either in the requirement for certain types of precipitating stimuli, or other associated non-epileptic deficits.

Epilepsy mice

The 'epilepsy' (abbreviated 'El') mice exhibit seizures that are best induced by vestibular stimuli, such as tossing or spinning the mice. Manifestations of seizures in this strain may include limb and face automatisms such as chewing and salivating. Electrical discharges originate in deep limbic structures. These features are analogous to clinical complex partial epilepsy. Like human complex partial epilepsy, seizures may generalize to tonic-clonic activity. Heritability of vestibulogenic seizure tendency in El is dominant, but the gene locus or loci and neurochemical defects are unknown. EEG studies have revealed that interictal discharge originate from parietal cortex and especially from hippocampus. In other words, these rats have temporal lobe epilepsy. Degeneration of neurons in stratum pyramidale (in CA1-CA2 subfields) and increase of GABA and VIP containing neurons in stratum radiatum have been reported in the hippocampus of El mice.

Genetically epilepsy-prone rats

Genetically epilepsy-prone rat model is one of the best known genetic epilepsy model. Previously it has been known that only audiogenic stimuli can induce seizures in this strain but afterwards it has been understood that also many other physical and chemical stimuli such as hyperthermia, electroshock, pentylenetetrazol and bicuculline can easily induce seizures.

Maximal electroshock

Maximal electroshock (MES) is arguably the best studied and most useful animal model of seizures. In particular, this model is often used to study of antiepileptic drug development. A distinction is made between minimal and maximal seizures. Minimal seizures are characterized by a 'stun reaction' and clonic movements of the face and forelimbs. Maximal seizures show tonic hind-limb extension and flexion, followed by clonus. A MES seizure meets criteria if there is tonic hind-limb extension. Studies may choose to evaluate either minimal or maximal electroshock seizures.

Chemical convulsants

Numerous chemical compounds can induce generalized seizures when administered systematically. Pentylenetetrazol, penicillin, bemegride, picrotoxin, bicuculline, strychnine, allylglycine, flurothyl, homocysteine are a few of those of greatest interest for epilepsy research.

Pentylenetetrazol model

Pentylenetetrazol (PTZ) is one of the mostly used chemicals to study of antiepileptic drug development. PTZ is tetrazol derivative with consistent convulsive actions in mice, rats, cats and primates, when given by the parenteral route. PTZ initially produces myoclonic jerks, which than become sustained, and may lead to waves or polyspikes.

PTZ-treatment leads to hippocampal atrophy in rats. PTZ-treated rats show selective neuronal loss and astrocytosis in the hippocampus. MRI studies on PTZ-treated rats show decrease in cerebellum volume.

On the other hand, PTZ treatment needs repeated injections to result in cell loss in hippocampus, which might be a result of enhanced activity of glutamergic systems.

Systemic penicillin as a tonic-clonic model

Penicillin was discussed above as an agent able to produce acute seizures, when placed on cortex. Clinical experience has indicated that high systemic doses of penicillin in humans can produce myoclonus, generalized tonic-clonic seizures and encephalopathy. In the hospital setting encephalopathy occurs most commonly with i.v. dosages above 20 million units per day, especially if concurrent renal failure maintains high levels and alters the blood-brain barrier. It was shown that parenteral penicillin could produce generalized seizures in cats.

Other inhibitory antagonists

Other popular systemic convulsants include picrotoxin, bicuculline, methionine sulfoximine, bemegride, allyglycine, strychnine, and certain general anesthetics.

Bemegride (Megimide) is a glutarimide derivative similar in action to PTZ. It has been used to produce clonic or tonic-clonic seizures, or to activate focal epilepsy. Several of drugs used to produce partial seizures when focally applied, for example picrotoxin and bicuculline, will produce generalized clonic and tonic-clonic seizures, when given systemically.

Brain metabolism early in bicuculline-induced generalized tonic-clonic seizures is greatest in neocortex and synaptically linked regions, as opposed to brainstem. A potent generalized seizure model can be produced by i.v. injection of strychnine. Strychnine interacts with GABA-benzodiazepine receptors, but a more important action of strychnine is probably against glycine. Glycine is an important inhibitory neurotransmitter in brainstem and spinal cord with structural homology to the much larger strychnine molecule. Strychnine serves as a non-competitive inhibitor of glycine receptor. Resulting seizures differ in character from those produced by primary GABA antagonists in that they are mainly extensor tonic, with little cortical EEG seizure activity.

Some convulsants apparently act by mimicry of excitatory neurotransmission. It is often difficult to induce seizures by systemic administration of glutamate, although monosodium glutamate can penetrate to brain and produce convulsions in 10-day-old rats.

Metabolic derangements

In clinical practice many metabolic derangements can lead to seizures including, hypoxia, hypoglycemia, uremia, drug withdrawal and high temperature. These conditions have not in general been useful for studying mechanisms of the epilepsies because they usually produce other central nervous system disturbances peculiar to the model employed. Three metabolic disturbances have, however, been employed in a few studies of generalized seizures; hyperbaric oxygen, and hypercarbia.

Hyperthermic seizures-but not hyperthermia alone-results in numerous argyrophilic neurons in discrete regions of the limbic system; within 24 hours of seizures, a significant proportion of neurons in the central nucleus of the amygdala and in the hippocampal CA3 and CA1 pyramidal cell layer are affected.

6. Generalized-absence seizures

Thalamic stimulation

The concept of a thalamic reticular formation is able to influence wide areas of cortex. Stimulation of midline and intralaminar thalamus can produce absence and EEG spike-waves. The role of thalamus versus cortex in the generation of absence epilepsy remains a subject of great interest and controversy. The thalamic stimulation model for petit mal is, however, infrequently used because of the need for chronic electrode implantation, and for ongoing stimulation during testing.

Bilateal cortical foci

Models of petit mal produced by bilateral cortical foci derive from the hypothesis that absence epilepsy is a result of diffuse cortical dysfunction. Application of dilute convulsants such as estrogen, PTZ, and penicillin to widespread regions of cat cortex produces bursts. A similar model can be produced in rhesus monkeys.

Systemic penicillin

Intramuscular injection of 300,000 units/kg of penicillin G into a cat results in recurrent episodes of arrested activity, staring, myoclonus, facial-oral twitching and occasional progression to generalized tonic-clonic seizures. Seizure activity begins about 1 h after injection of drug and continues intermittently for 6-8 h. The EEG shows a variety of spike-wave morphologies, emerging from a relatively normal background. These features are similar to those seen with clinical absence, except of course that clinical absence recurs apparently spontaneously for years.

Clinical absence (petit mal) epilepsy has been hypothesized to originate subcortically, with participation of brainstem and thalamic reticular formation. Absence seizures in the feline penicillin model have been difficult to reconcile with this hypothesis. Application of penicillin to wide regions of cortex, but no to thalamus, can produce SW EEG discharges. Discharges in this model probably originate cortically, but are maintained and elaborated by recurrent thalamo-cortical circuitry.

Intraventricular opiates

Low dose morphine sulfate is believed to be anticonvulsant, but high dose parenteral morphine can induce clonic convulsions in rodents. The behavioral-EEG pattern after intraventricular opiates can be classified either with the complex partial or the absence models of the epilepsies. Relation to petit mal epilepsy has been supported by ontogenetic studies of opiate-induced seizures and by the relatively specific responsiveness of these seizures to anti-petit mal agents.

7. Status epilepticus

Status epilepticus is a condition characterized by an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals. Certain research questions require

models of recurrent seizures or status epilepticus. Many of the chemical convulsants able to produce seizures—for example, KA, flurothyl, bicuculline, and PTZ can also produce status epilepticus when administered in large quantities to rodents.

Lithium-pilocarpine

One recently popularized model of status epilepticus is the lithium-pilocarpine model. In this model rats are pretreated with lithium chloride. At least 20 h later the cholinergic agent pilocarpine is given. Generalized clonic or tonic-clonic seizure activity begins about 30 min after administration of pilocarpine, and continues for several hours. The EEG pattern displays a progression very similar to the stages seen in human status epilepticus. Chronic pretreatment for one month with daily lithium reduces the convulsant threshold of pilocarpine 26-fold.

In lithium-pilocarpine treated adult rats, neuronal damage and neuronal death develops mainly in the hippocampus, the hilus of the dentate gyrus, the piriform and entorhinal cortices, the amygdala, the neocortex and the thalamus. Also, lithium-pilocarpine treatment leads to hippocampal damage that is typically observed in the CA1 and CA3 pyramidal cell layers and the hilus of the dentate gyrus in mice with status epilepticus.

Cobalt-homocysteine

Another drug combination able to induce status epilepticus in animals is focal cobalt in conjunction with systemic homocysteine. Homocysteine is an agent able on its own to produce powerful tonic-clonic seizures. This model also has the advantage of a “focus” for frequently recurring seizures.

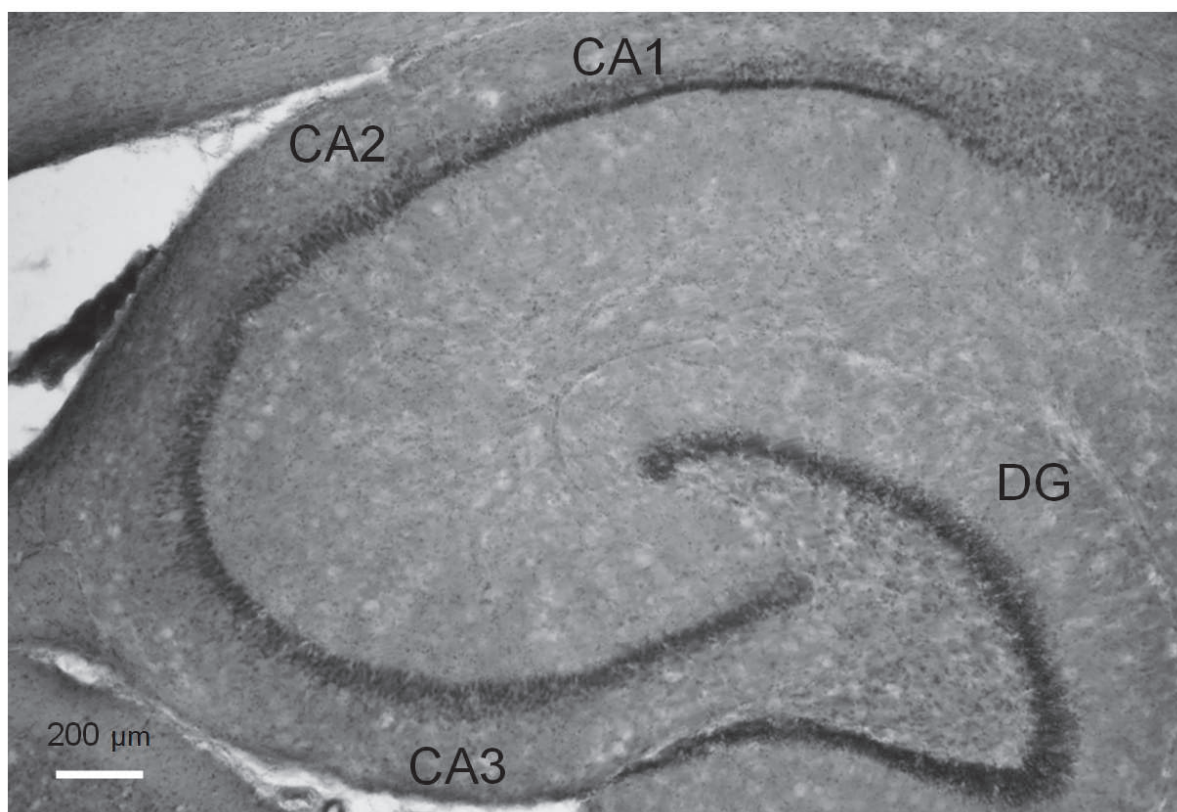


Fig. 1. A representative image for rat hippocampus CA1, CA2 and CA3 subfields. CA1: hippocampus CA field, CA2: hippocampus CA2 field, CA3: hippocampus CA3 field, DG: dentate gyrus, Hematoxyline and eosin stain, 4X magnification, scale bar = 200 μ m.

Recurrent stimulation

Several electrical paradigms have been suggested as a recipe for producing status epilepticus in rats.

8. Conclusion

Epilepsy is a group of neurological disorders characterized by clinical aspects, not an only specific disease. Seizures are outward signs of epilepsy and occur from time to time. A wide variety of models have been developed in order to explore the principal mechanisms of epilepsies, develop more effective anti-epileptic drugs epilepsy and determine the pathological events underlying different types of epileptic seizures. Summary of the results so far obtained from these models:

1. There is not only one model for answering all questions about epilepsy.
2. Studies performed by using experimental models, can only explore the basic mechanisms of the model which is used.
3. Some chemical convulsants can induce more than one epilepsy model. Crystallized penicillin can induce simple partial, generalized myoclonic, generalized tonic-clonic and generalized absence epilepsy when given in different ways. Therefore, EEG and behavior should be analyzed to determine the induced model.
4. Kindling has become one of the most popular models to investigate neurochemical and structural long-term changes in brain.
5. It is not sufficient to use one or a few model in studies of epilepsy. Constantly new and better models should be developed to find the best model that answers the question.
6. Various models should be used constantly to investigate the issues such as the molecular mechanisms, genetic background, ion channels and related molecules in the cell membrane, second messenger systems.

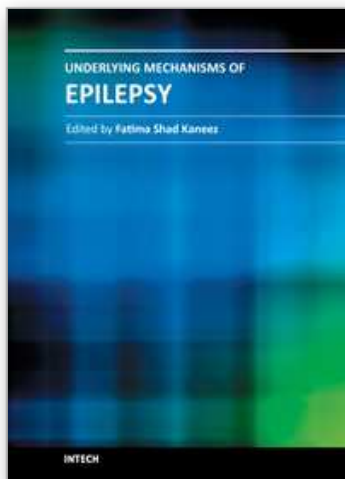
Thus, the basic mechanisms of epilepsy will be better understood, more effective drugs and treatments will be developed for the type of epileptic seizures.

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This book is a very provocative and interesting addition to the literature on Epilepsy. It offers a lot of appealing and stimulating work to offer food of thought to the readers from different disciplines. Around 5% of the total world population have seizures but only 0.9% is diagnosed with epilepsy, so it is very important to understand the differences between seizures and epilepsy, and also to identify the factors responsible for its etiology so as to have more effective therapeutic regime. In this book we have twenty chapters ranging from causes and underlying mechanisms to the treatment and side effects of epilepsy. This book contains a variety of chapters which will stimulate the readers to think about the complex interplay of epigenetics and epilepsy.

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