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Several models of induction seizure and epilepsy in experimental animals

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Abstract

***Background & Aims*:** Animal models provide crucial tools to study epilepsy which is one of the most common neurological disorder. Experimental models are valid and essential to discover new antiepileptic drugs as well as to elucidate circuitry dysfunction of disease. Therefore, in this review, we summarize the prominent used methods for induction experimental seizures and epilepsy induced by electrical, chemoconvulsants, traumatic brain injury, acoustic stimulation as well as hyperthermia and hypoxia condition.

Material and Methods: In this review data were collected through searching electronic databases of PubMed and Google Scholar for several methods of induction seizure and epilepsy in experimental animals.

Results: The maximal electroshock (MES), pentylentetrazole (PTZ), and 6-Hz seizure models are three simple seizure models for inducing acute seizure in intact animal. The pilocarpine, kainic acid, antibiotics**,** metals and organophosphorus compounds have epileptogenic potency for inducing motor seizures.

The most common type of chronic models of epilepsy are electrical kindling, PTZ-induced kindling and transgenic models. Pharmacoresistance models include the phenytoin- or lamotrigine-pretreated kindled rats model, the 6-Hz mouse model, pentylentetrazole induced seizures in rats pre-exposed to pilocarpine and intrauterine exposure of rats to methylazoxymethanol. Lastly, Posttraumatic epilepsy, audiogenic seizures, hyperthermia and neonatal hypoxia model as well as in vitro models are used to induce and study seizures.

Conclusion: Epilepsy and seizure in experimental animals can be modeled by several factors include acute and chronic stimulation, mechanical insults and changing environmental conditions in both forms in vivo and vitro.

Keywords: Epilepsy, Seizure, Electrical stimulatin, Chemoconvulsants, Pharmacoresistant, Traumatic, Audiogenic, Hyperthermia, Hypoxia

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Introduction

Epilepsy as the most prevalent neurological disorder is characterized by recurrent seizures accompanied by involuntary movement and sometimes with loss of consciousness (1, 2). Epilepsy is defined as having two or more unprovoked seizures and only a seizure does not present epilepsy (3). Seizures are due to excessive or synchronous neuronal activity in different parts of the

brain which most of the time last less than 2 minutes and for longer than 5 minutes is considered status epilepticus (4). Seizures by motor manifestations are called convulsive and with motor features are nonconvulsive (5).

Seizure and epilepsy classifications:

Gastaut was first that introduced a system for seizure and epilepsy classifications in the late 1960s (6). The 2017 ILAE classification system groups definitions of seizures and epilepsies by starting point of brain manifestations. Partial seizures which called focal seizures (60% of all epilepsies) begin focally in a cortical origin and generalized seizures (40% of all epilepsies) affect the whole brain from the beginning which may be with motor manifestations or without muscle movements (6,7). Clonic seizures consist rapid involuntary muscle contractions while tonic convulsions are recognized by sustained flexion or extension of axial or appendicular muscle groups or rigid stretching of the body (6,8,9). Major types of partial seizures are simple focal seizures and complex focal seizures (6,9). First affects a small part of the brain and just accompany by twitching or feeling a strange taste or smell but patients during complex focal seizures are confused or dazed (6,9). If the onset point of the seizure is unclear, it belongs to an unknown onset seizure group (6,9).

Seizures will be arising from both hemispheres or brainstem structures which activating bilaterally the upper brain regions from the outset, considered as primarily generalized including absence seizures, generalized clonic seizures, bilateral myoclonic seizures, atonic seizures and generalized tonic-clonic seizures (8,10). In secondarily generalized seizures, a strong unilateral epileptic activity begins in one part of the brain and spreads over broad regions of the brain (8,10). Major types of generalized seizures are absence seizures and tonic-clonic seizures (8,10). Absence seizures are called petit mal seizures as well as refer to nonmotor generalized seizures which are caused blinking and staring into space (8,10). Tonic-clonic seizures (grand mal seizures) are accompany losing consciousness, jerking or spasm in muscles and falling (8,10). Epilepsies on the basis of etiology divides into three groups: idiopathic, symptomatic, and cryptogenic. Idiopathic epilepsy defines an epilepsy which arises from genetic abnormalities. In symptomatic epilepsies, the cause is known and seizures origin from an acquired or genetic cause or abnormalities and cryptogenic epilepsies involve an epilepsy of presumed symptomatic nature in which the cause has not been identified (2,11,12).

The search for antiepileptic drugs with better efficacy and tolerability have been relied on validated animal models of seizures and epilepsy for the last 80 years (13). Animal models can obtain an accurate view into pathogenesis of dysfunction(s) and ability to predict clinical activity of compounds. The first antiseizures like bromides, phenobarbital and mephobarbital were the result of clinician's observations on patients who used them (13,14). Searching for drugs in an animal model was begun in 1937 by Merritt and Putnam (13).

The intentions of an experiment such as testing high numbers of compounds in short time, mortality rate of animal, ability to control seizures, similarity to clinical conditions and cost of procedure are essential for selection of a suitable animal model (14). On the other hand, since epilepsy is characterized by recurrent seizures, a pure seizure which is induced in a normal animal cannot be used as a model of epilepsy (14). Therefore, it is important for researchers to understand the difference between animal models of epilepsy and animal models of epileptic seizures. So in this study several models of induction epilepsy and seizure in animals were reviewed.

Results

Animal models of seizures and epilepsy:

In this review, we summarized the most used models of seizures and epilepsies including models of acute seizures such as chemoconvulsants and electrical models, chronic models, pharmacoresistant seizures, posttraumatic epilepsy, audiogenic, hyperthermia and hypoxia seizures as well as in vitro model of epilepsy.

1. Models of acute Seizures:

Simple seizure models allow to screen high numbers of compounds in a short time. Acute seizure models (i.e. single seizure) are models which an epileptic seizure is induced in a normal non-epileptic animal than models with spontaneous recurrent seizures (14). The maximal electroshock seizures (MES), pentylenetetrazol (PTZ) and the 6 Hz "Psychomotor" seizure tests are three simple models for inducing acute seizure in intact animal which have been developed over the 60 years ago (13,14). These seizure tests are easy-to implement, time and cost-efficient to identify activity of novel compounds prior to their administration to humans (14). Maximal electroshock and subcutaneous pentylenetetrazol tests (s.c PTZ) are two basic tests for inducing generalized tonic-clonic seizures that stimulate both brain hemispheres and 6-Hz seizure model is as an appropriate model for pharmacoresistant partial seizures (13).

1.1. Maximal electroshock :

The maximal electroshock test created by Toman et al. which represents an ideal screening tool for assessment drugs that block voltage gated sodium channels and identifies compounds which prevent seizure spread (15,16). In this model which mostly mice or rats are used, seizures are induced by an alternating current of 60 or 50 Hz frequency or low-frequency stimulation (usually 6 Hz). Two types of seizures might be induced in these models: minimal seizures with righting ability and maximal seizures with a loss of righting reflexes (17).

Minimal seizures display a model of myoclonic seizures. They are produced by threshold corneal stimulation (17,18). Minimal threshold electroshock seizures consist of clonic seizures of the head and the forelimb muscles (18). Maximal electroshock seizures are induced by delivering currents (0.250 s in duration with 60-Hz frequency and an intensity of 50 mA for mice and 150 mA for rats via saline-moistened corneal electrodes and less common transcranial electrodes or ear clips (19,20,21). Successful induction of seizure is signified by tonic flexion and tonic extension and clonus (rapid involuntary rhythmic contraction- relaxation of limbs) (20). The duration of hind limb tonic extension is the range of seconds (20). After a compound has been tested in mice, it is also tested in the MES model in rat. It is worth notice that for correct prediction of compound efficacy against seizure, other models are needed too because some drugs that protect against in patients fails in the PTZ or MES tests (14,22). There are additional assay options available to evaluate the activity of compounds include the kindled mouse and an in vitro assay (22).

1.2. Pentylenetetrazol:

Pentylenetetrazol (Cardiazol, Metrazol, Leptazol, pentetrazol, pentazol), a γ-aminobutyric acid ($GABA_A$) receptor antagonist, is used as a convulsing drug by blockade of receptors and involving the reticulate formation, diencephalic region and caudal hypothalamus (23,24). The antiepileptic compounds which effect on GABAergic mechanisms and T-type Ca2+ channels, inhibit seizures induced by PTZ by increasing seizure threshold (25,26). PTZ dissolves in saline or water and doses 100mg/kg IP or sub-Q are used then seizures occur within 20 minutes (23). Then latency/severity/duration of seizure is recorded. The threshold dose (100mg/kg intraperitoneally (IP) or subcutaneously (SC) to induce seizures is calculated by dose-response by using various doses (27).

Depending on dosage, PTZ represents nonmotor and motor seizure behaviors in a mouse (26). At low doses (20 mg/kg), only nonmotor seizures including psychic or autonomic activity were produced, with a high dose of PTZ (60 mg/kg), also motor seizures (limb, facial, or whisker twitching, falling) are represent (28,29). Almost rat expressions same behaviors like mice except some behaviors like whisker trembling, tonic extension which are not observed in rats (29). In subcutaneous test**,** PTZ (85 mg/kg dose) is administered to skin of neck animals (26,29). In timed intravenous pentylenetetrazol infusion test, PTZ solution infuses by a needle (size 27 G) attached to a 5 ml syringe prefilled with heparinized PTZ solution which is inserted the tail vein of animal has move freely in the box. Next, the latencies time of first clonus and first tonic extension is recorded (26).

1.3. Pilocarpine:

Pilocarpine is an agonist of muscarinic acetylcholine receptors. systemic (IP) injection of pilocarpine by hyperactivation of these receptors induces seizures as well as presents a useful model for complex partial seizures (30).

The pilocarpine model was developed by Turski's group which systemic injection of pilocarpine (400 mg/kg, i.p.) produced seizures in adult rats and scored seizures according by Racine scales (31). According to Turski et al., irrespective of the dose (100 to 400 mg/kg in adult rats), animals were immobile for 5–10 min and subsequently presented gustatory and olfactory automatisms for 45 min (32). Then, animals experienced discontinuous seizures 30 min after injection for 90–150 min. By highest dose of pilocarpine (400 mg/kg) was induced limbic motor seizures such as rearing, clonus as well as falling every 5–15 min till 1–2 h. In 400 mg/kg dose in rats, mortality rate is 100%(31). For limiting peripheral side effects as well as decreasing pilocarpine doses, scopolamine methylbromide (1 mg/kg sub-Q) and lithium chloride (LiCl,3mEq) may be injected before the pilocarpine (23).

1.4. Kainic Acid:

In 1970, Shinozaki and Konishi observed a potent excitatory effect of kainic acid (KA) in rat (33). Kainic acid is an analog of glutamate as well as a neurotoxin (34). It is served to produce complex partial and secondarily generalized seizures (17). Using intracerebral administration of KA in the hippocampus or amygdala could present a model for temporal lobe epilepsy (34). Low doses (0.4 μg) induce focal seizures and high doses (1.6 μg) produce a generalized seizure (34). KA can be dissolved in phosphate buffered saline (pH 7.4) which is recommended the IP route (23). There is somewhat limited penetration of KA to brain in mature animal therefore in adult rats, doses of 10 to 14mg/kg and in young rats, doses of 1 to 4 mg/kg are used (23). It should be noticed that mice need higher doses (20 to 60 mg/kg). Systemically administered KA leads to hypoactivity for about 20 to 30 minutes (23).

1.5. Antibiotics:

The epileptogenicity of antibiotics were reported in many species including monkeys, humans, rats and cats (23). Epileptogenie effects of antibiotic drugs such as sulfonamides was first showed by Jasper, et al. in 1943 (35). It is well known that administered some antibiotics represent a model for focal seizures as well as by spreading from the initial focus, clonic seizures may occur (23,36).

Penicillin is a major antibiotic for studding epilepsy in research animals (23). Penicillin as a convulsant affects through inhibition GABA transmission or benzodiazepine receptor in the cerebral cortex (37). Intracortical penicillin-induced epilepsy may be a good model to screen mechanisms of the anti-epileptic drugs (38). Injection of penicillin intracortically induces epileptiform bilateral spikes and spike–wave complexes (39). In a hippocampal slice technique by recording spikes in rat tissue was shown cephalothin (≥ 1 gm/liter), gentarnicin (≥80 mg/liter), chloramphenicol (≥ 1 gm/liter), erythromycin (≥ 1 gm/liter), cloxacillin (≥ 1 gm/liter), ciprofloxacin (≥ 50 mg/liter) and ampicillin (_> 1 gm/liter) represented moderate to marked epileptogenic effects, but cefotaxime, vancomycin, clindamycin ,cefuroxime and tobramycin, didn't show epileptogenic effects (40).

1.6. Metals:

Metals including nickel, antimony, cobalt, alumina cream and iron have epileptogenic potency which are good for inducing focal motor seizures and screening anticonvulsant drugs effective against onset seizures in animals (23). In the FeCl3–induced epileptic model, through a hole in skull bone over the somatosensory cortex by injecting iron solution ($FeCl_3$,5 μl 100 mM) , an epileptogenic focus is produced and severity of seizures are recorded according Racine scale includes mouth and facial movements; head nodding ;forelimb clonus; rearing and falling for 4 hours on day (41).

1.7. Organophosphorus Compounds:

Organophosphorus compounds such as tabun, cyclosarin, and sarin, soman which are extremely toxic

and dangerous for humans have ability in producing seizure (42). They are potent and inhibitors of acetylcholine esterase which can activate all subtypes of the acetylcholine receptors (43). These nerve agents can be dissolved in saline and the median lethal dose is from 8mg/kg to 300mg/kg. subcutaneous administration is usually used. Seizures appears by a tremor and twitching as well as continuing to loss of righting (23).

2. Chronic models of epilepsy:

The most common type of animal models has been used to study epilepsy is model of epileptic seizures. Since epilepsy is characterized by repeated seizures, an acute seizure induced in a normal non-epileptic animal cannot display a suitable model for studding epilepsy. There are some chronic models of epilepsy for instance electrical kindling, PTZ-induced kindling and transgenic animals which are more like to human epilepsy (14).

Electrical kindling is a chronic model of epilepsy which can be produced by repeated focal electrical stimulation to a brain structure and is a useful tool to study partial and secondarily generalized seizures (44,45). This model only reflects partial epileptogenesis because kindled rats do not display spontaneous recurrent seizures but for inducing seizures at any time, it largely simplifies drug testing in this model (17,46). Kindling stimulations are applied with an electrode using a 3 s train of 50Hz monophasic square pulses with 1ms duration and the threshold intensity (45). Seizure severity is evaluated according to the Racine scale after every stimulation: stage 1: facial clonus, wet dog shakes and mouth; stage 2: facial movement and head nodding; stage3: forelimb clonus; stage4: rearing and tonic extension of forelimbs; stage 5: falling and loss of balance. The electrical stimulations are continued until emerging stage 5 seizures (45,47).

The PTZ-induced kindling was first described by Mason and Cooper in rats which is induced by repeated injections of PTZ (48). In this model, animals receive 12-15 doses of PTZ, 35 mg/kg for mice or 40 mg/Kg for rat, dissolved in 1 ml of saline, intraperitoneal, every second day (48). Generally, 12-15 doses in a period of 24-30 days are given to each rat (48). The seizure severity is evaluated during 30 min after every injection using to the Racine score: stage 0, no response; stage 1, ear and facial twitching; stage 2, myoclonic jerks without upright position; stage 3, myoclonic jerks, upright position with bilateral forelimb clonus; stage 4, tonic–clonic seizures; stage 5, generalized tonic–clonic seizures, loss of postural control (48). A challenge dose of PTZ (40 mg/kg for rat or 75 mg/Kg for mice) is given to animals 10 days after the last injection to check the kindling state. If animals present generalized tonic–clonic seizure, they are used as kindled (48).

Genetic epileptic models have been reported in mice, gerbils, rats, dogs, baboons and chickens (49). Transgenic animal models are the result of manipulation and disruption genes as well as the loss of the functional gene product can reconstruct and identify human disease mechanisms which is generated by transgenic approaches (49).

3. Pharmacoresistant models of epilepsy:

Pharmacoresistant is a major problem in treatment of epilepsy in which resistance to two or more traditional antiseizure drugs occurs (14,50). Drug resistance models are screening approaches to show mechanisms of resistance and present an opportunity to obtain a novel drug as well as more effective control of seizures (51). Over the last 30 years, several animal models have been discussed features of pharmacoresistance, such as the phenytoin- or lamotrigine-pretreated kindled rats, the 6-Hz mouse model, pentylentetrazole induced seizures in rats pre-exposed to pilocarpine, intrauterine exposure of rats to methylazoxymethanol (51).

Lamotrigine-pretreated kindled rats are useful to search more effective drugs against secondarily generalized partial seizures as well as in therapy-resistant patients. Lamotrigine (5 mg/kg, i.p.) as a voltage gated sodium channel blocker when administered one hour prior to kindling acquisition, leads to resistance to lamotrigine, phenytoin and carbamazepine in fully kindled rats (14,51,52). Likewise, pentylentetrazole induced seizures in rats pre-exposed to pilocarpine has been reported as a model of

kindling resisted to phenytoin and sodium valproate (53). Both pentylenetetrazole and pilocarpine produce seizures in experimental models (54). Therefore, it seems that co-administration of pilocarpine (50 mg/kg) and pentylentetrazole (37.5mg/kg) is appropriate for a faster kindling induction and providing a model resistant to treatment too (53).

Compounds that are effective in the lamotrigine-resistant kindled rat may be tested in a model like 44mA 6 Hz psychomotor in mice too (13,14). The 6 Hz "psychomotor" seizure test is an electrical model of acute seizures which first described by Toman in 1951 which is differ from maximum electroshock in frequency (6 vs. 50 Hz) and pulse duration (3 vs. 0.2s) (13,55). The 6-Hz model is a model of drug-resistant epilepsy which acute seizures is induced by delivering electrical stimulation with low-frequency pulses (6-Hz) (intensity of 32 mA, pulse width of 0.2 ms) for 3 seconds in naive mice via corneal electrodes (14,55). Stimulations are elicited seizure behaviors which its severity was scored by direct observation according to the bellow ranking: 1, stunned posture and eye blinking; 2, head nodding, straub tail and repetitive rhythmic movements; 3, unilateral or alternating forelimb clonus; 4, generalized tonic-clonic convulsions without loss of posture and 5, generalized tonic-clonic convulsions with loss of posture (56). The rat 6 Hz model similar to the mouse model produces same behaviors (57).

Also, a study in rats exposed to methylazoxymethanol acetate (MAM) in utero exhibited that pre-treatment with valproate (an antiepileptic drug) had no effect in seizure latency induced by kainate administration (15 mg/kg, i.p.) (58). This result suggests MAM-exposed rats as a pharmacoresistant seizures model displays a reduced sensitivity to commonly traditional drugs (51).

Further, strychnine-induced seizures are discussed by some researcher to outline features of difficult-to-treat seizures (20). Strychnine blocks chloride channel associated with glycine receptors which are inhibitory receptors mostly in the spinal cord and brainstem (20,59). Strychnine sulfate dissolves in normal saline (1 mg/ml) (60). Doses between 1 and 4mg/kg IP are used for 3- to 25-day-old rats and for adult rats are around 2 to 3 mg/kg sub-Q (20,60). The animals receive a subcutaneous injection of strychnine for induction of convulsive seizures. Then convulsion onset time and death time and survival rate are recorded (60).

4. Posttraumatic models of Epilepsy:

Traumatic brain injury (TBI), is produced by external mechanical forces to the brain and more than 1 week after injury can lead to neurodegenerative condition like recurrent spontaneous seizures as well as posttraumatic epilepsy (PTE) (61). There are several rodent models of TBI and/or PTE which can help to study the pathophysiological mechanisms of PTE and its treatments including fluid percussion (FPI), controlled cortical impact (CCI), blast-induced TBI (bTBI), penetrating brain injury and Other models (61).

One of the most used methods to cause PTE is the fluid percussion injury (FPI). In this model, a FPI induces a mixed focal-diffuse brain injury pattern that models human head TBI (62). To administer an FPI, after craniotomy, via the a fluid pulse is generated onto the brain. It was reported that in 30–52% of rats after FPI, focal and generalized seizures have been observed (61). Another technique to study TBI is deformation of cortex named controlled cortical impact (CCI) which injury is produced by using a pneumatic or electromagnetic piston onto the dura through a hole. Several studies have reported spontaneous seizures in rodents within 24 h of the impact (61,63).

The other approaches are involved weight-drop models and repetitive mild TBI models as well as blast-induced TBI and penetrating injuries which in first model, after craniotomy over frontal-parietal cortex of rat, a cylinder guiding a weight onto a footplate is situated over the craniotomy (61). The weight is released on the footplate and causes an injury to the dura (61). In second, using a pneumatic barrel, a 100g weight is accelerated toward a small helmet on the rat's head which can produce an impact (64). In TBI caused by exposure to explosive blast, the high energy, supersonic shockwave triggers a pathological response and leads to

onset cerebral edema (65). In penetrating ballistic-like brain injuries are caused by a penetrating bullet (66).

5. Other models:

Audiogenic seizures are generalized seizures induced by acoustic stimulus at 100–120 dB by an electric bell in a sound-isolated chamber for 60 s or until a seizure is evoked (17,67).The animal's behavior and severity of seizure are scored according to the Jobe et al. ranking (e.g., wild running, bouncing clonus, tonic extension of the limbs) (63).The other is hyperthermia seizure which is induced in P10–P12 rodent pups by hot air stream for 30 minutes and their core temperature increases to 40°C–42°C and usually followed by facial automatism and tonic body flexion (17,20). In neonatal hypoxia model, rat pups (P10–P12) are subjected to hypoxy condition (7%–4% O2) for 15 minutes. Rodents exposed to this hypoxia model develop spontaneous seizures later in life (68). Finally, in vitro models by using several brain slices from one animal offer approaches to avoid animal suffering (16). Different factors use to induce seizure in in vitro experiments, such as electrical stimulation extracellular, ion composition and pharmacological intervention (16,69,70,71).

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Conflict of interest

The authors declare that they have no conflict of interest.

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