Review Article

A Review on Chemical Induced Kindling Models of Epilepsy

Anil Kumar[1]*, Nidhi Sharma[2], Manveen Bhardwaj[1], and Sumitra Singh[2]

[1]*Pharmacology Division, University Institute of Pharmaceutical Sciences, UGC Centre of Advanced Study, Panjab University, India*
[2]*Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science & Technology, India*

*Corresponding author
Anil Kumar, Pharmacology Division, University Institute of Pharmaceutical Sciences, UGC-CAS, Panjab University, Chandigarh-160014, India, Email: kumaruips@yahoo.com

Abstract

A variety of animal models have been developed to study the effect of antiepileptic drugs. These models provide the means of inducing changes and causing alterations in neural function which may lead to epileptogenesis. Kindling is a lasting change in brain function caused by repeated stimulation resulting an increased seizure duration and progressive intensification of seizure activity. The kindling model is widely used by investigators to provide insights into epileptogenesis. Kindled seizures can be induced in a number of animal species by electrical stimulation of brain as well as by chemical convulsants. The repeated administration of convulsant agents at sub-threshold concentrations is known as chemical kindling. This phenomenon can be achieved using convulsants like GABAergic antagonists, neurotoxicants, local anaesthetics etc. Chemical kindling has attracted the interest of many investigators as a model to study the effects of multiple seizures on the brain. The present review is an attempt to compare the various chemical models of kindling.

INTRODUCTION

Epilepsy is one of the major neurological disorders which are characterized by recurrent and unpredictable interruptions of normal brain function, called epileptic seizure. Epileptogenesis is the gradual process by which a normal brain develops epilepsy. Epilepsy is a chronic condition in which seizures occur. These changes to the brain occasionally cause neurons to fire in a hyper-synchronous manner. This hyper-synchronous firing of neurons is called seizures. . The discovery and development of new antiepileptic drugs relies heavily on the preclinical use of animal models to establish efficacy and safety prior to first trials in humans [1]. A diversity of animal models is available for the study of epilepsy and these models have a proven history in enhancing our understanding of basic mechanisms underlying epileptogenesis [2]. The kindling model is widely used to study the epileptogenesis and discovery of antiepileptic drugs. Kindling is a lasting change in brain function that results from repeated focal stimulation and leads to the development of a predisposition to epileptiform convulsions [3]. It is associated with Tran's synaptic changes, synaptic re-organization, long term potentiation, changes in synaptic morphology, protein synthesis and axonal transport [4]. It was invented by Goddard in 1967 and now this model has widely been accepted as a functional epilepsy model in which the altered neuronal response develops in the absence of gross morphological damage that is seen in many other epilepsy models [5]. It has become major focus of

the neuroscientific research [6]. The achievement of the kindling criterion takes a long time, usually between 15 and 38 days, depending on the kindling procedure and animal strain [7]. The advantages of the kindling model for epilepsy research are clear: precise focal activation of the target brain sites is possible, development of chronic epileptogenesis is reliably observed, the pattern of seizure propagation and generalization is readily monitored, and interictal, ictal and postictal periods are easily monitored [5].

PHENOMENON OF KINDLING

Kindled seizures can be induced in a number of species, including rats and mice. It can be induced by electrical stimulation of different areas of brain such as the amygdala, hippocampus and frontal cortex [8,9]. It has been shown that an effect similar to electric kindling can be induced by the repeated administration of subconvulsant doses of central nervous system stimulants [10]. Different stages of seizures are observed during kindling. Racine's grading of convulsive stages of kindling was based on electrical stimulation of amygdale which includes five stages. The stages 1 and 2 are primarily associated with facial and oral activities which include ipsilateral eye closure and blinking followed by head bobbing and drooling. Forelimb clonus eventually appears in the stage-3. Soon thereafter, in stage-4, the seizures generalize with stronger clonus and rearing. Then dramatic rearing and falling behaviour is observed in stage-5 [9].

Researchers continue to stimulate the animal in most kindling studies till the development of stage-5 seizures [11]. When more carefully examined, it should be observed that the amygdala kindled stage-5 seizures are not merely clonic but rather tonic-clonic seizures and involves all four limbs. Animal is considered as fully kindled if there is development of stage 5. This effect of kindling is long lasting and may endure for the life of animal [12]. Kindling starts with the limited neural circuits and with increased duration of seizures, changes in brain ability occur [13].

CHEMICAL KINDLING

Kindling induced by repeated administration of convulsant agents at subthreshold concentrations is known as chemical kindling. These agents can induce kindled seizures by direct intracerebral administration or systemic administration. There are many chemicals which possess primary actions on central nervous system function. Some of these chemicals lead to appearance of convulsions with acute high dose exposure [14,15]. Administration of these chemicals in subthreshold doses prior to the electrical stimulation may also demonstrate their subconvulsive properties in a standard kindling paradigm [16]. However, these chemicals also produce kindling effect if delivered repeatedly at low concentrations in the absence of electrical stimulation [17-19]. Different chemoconvulsants used for kindling are shown.

Kindling induced by GABAergic antagonists

γ-Aminobutyric acid (GABA) is the principal inhibitory neurotransmitter which maintains the inhibitory tone to counterbalance the neuronal excitability. Seizures may be caused when this balance is disturbed. Therefore, GABAergic antagonism is a mechanism of action of some chemical agents that induce seizures [20]. Pentylenetetrazole, bicuculline, picrotoxin and β-carbolines are potent GABA antagonists which are preferred to develop kindling models of epilepsy.

Pentylenetetrazole-induced kindling: Pentylenetetrazole (PTZ) has been widely used in experimental models of epilepsy. Absence, myoclonic and generalized tonic-clonic seizures are induced by PTZ administration. It is a commonly preferred behavioural approach used for chemical kindling to study brain excitability. PTZ has a proconflict effect on acute administration and induces convulsions in rats and mice [21]. After repeated injections the susceptibility of seizures was increased [22]. After every PTZ injections seizure score is calculated [23]. Rapid and strong seizures are initiated 5 min after a single high dose of PTZ (50 mg/kg) in animals which lasts for approximately 30 minutes. After repeated daily administration of a subconvulsive dose of PTZ (30 mg/kg) the animals show very weak behavioural overactivity during the first 1-2 weeks. However, stronger epileptic activity is developed in the following 3-4 weeks, and finally leads to full kindling in 4-6 weeks [4].

Various behavioral, neurophysiological and neurochemical changes occur during PTZ-induced kindling. PTZ causes atrophy, selective neuronal loss and astrocytosis in hippocampus, Alterations in GABAergic systems, glutamergic systems and antioxidant defence systems have been observed in PTZ-induced animal models [24].

Kindling produced by PTZ may be related with permanent attenuation of inhibitory function of GABAergic system [21]. This activity is especially due to blockade of $GABA_A$ gated chloride receptors [4,25] $GABA_A$ receptor number or function may be modified by either single or repeated PTZ administration. Injection of a moderate dose of PTZ which produces kindling, has several neurochemical effects including a decrease in GABA binding, [^{35}S] *t*-butylbicyclophosphorothionate (TBPS) binding and in GABA stimulated Cl^- uptake [26].

An alteration in density and sensitivity of different glutamate receptor sub types also occurs due to PTZ. An increase in the density of glutamate receptor, glutamate binding and hence increased glutamate concentrations in the hippocampus after PTZ kindling has been observed [27]. Pentylenetetrazole in toxic doses induces massive release of endogenous glutamate in various structures of the brain. Pentylenetetrazole-induced seizures in rats are associated with glutamate activation of AMPA and NMDA receptors in the brain [28]. It was reported that PTZ kindling phenomenon was sustained by AMPA receptors in cortex and basal ganglia. AMPA has also an important role in appearance of epileptiform burst discharges in hippocampal slices.

Bicuculline induced kindling: Bicuculline is an alkaloid which produces generalized seizures after systemic administration. Unilateral application of bicuculline in deep prepirlform cortex is sufficient to induce generalized seizures [29]. The bicuculline kindling is identical to electrical kindling in many respects. A similar pattern of seizure development has been observed which eventually results in general convulsive seizure. However, the rate of chemical kindling caused by bicuculline is much faster than the electrical kindling. Multiple seizures are caused by a bicuculline injection in the kindled state [30]. The changes in arterial blood gas concentrations, cerebral blood flow and extracellular ionic concentrations have been extensively studied [31]. The kindling effect of bicuculline persists semi-permanently and the phenomenon is not correlated with visible tissue damage at the stimulating site. Bicuculline is a $GABA_A$ antagonist, and thus amygdala neurons bearing $GABA_A$ receptors may play a very important role in the initiation and development of amygdaloid seizures. Bicuculline is supplied as either the free base or a methyl derivative [32]. Bicuculline methiodide is the methylated form of bicuculline which is more active than the parent drug molecule [33,34]. Repeated injection of bicuculline methiodide into the rat amygdala induces chemical kindling [35]. Bicuculline methiodide completely suppresses the fast inhibitory postsynaptic potential without affecting the slow hyperpolarization. At the same time, augmentation of both the fast and slow excitatory postsynaptic potential is caused by bicuculline leading to burst discharges [36].

β-Carboline induced kindling: β-Carboline alkaloids are a large group of natural and synthetic indole alkaloids [37]. β-Carbolines are identified as potential endogenous ligands for the benzodiazepine binding site, and found to have competitive affinity for benzodiazepine binding sites [38]. The β-carboline family of compounds have since been found to span the complete range from full agonists to full inverse agonists at the benzodiazepine allosteric site for the $GABA_A$ receptor [39]. FG-7142 (N-methyl-p-carboline-3-carboxamide) is an amide

derivative of *β*-carboline-3-carboxylate ethyl ester [39,40]. It is used as proconvulsant and found to potentiate the kindling effect of a subconvulsive dose of PTZ as a negative ligand of benzodiazepine receptor [41,42]. Repeated administration of FG 7142 produces sensitization to its effects so that full seizures develop [43]. DMCM (6,7-dimethoxy-4-ethyl-beta-carboline-3-carboxylate methyl ester and ß-CCM (methyl β- carboline -3-carboxylate) are full inverse agonists of GABA$_A$ benzodiazepine receptor complex and thus are characteristic β-carbolines with convulsant activity in vivo [44,45].

Picrotoxin induced kindling: Picrotoxin is a poisonous crystalline compound, found in the fruit of the plant *Anamirta cocculus* (Moonseed family)*.* Picrotoxin exerts its epileptogenic effect by blocking GABA mediated chloride conductance. Various investigations suggest that picrotoxin kindles seizures by reducing the GABA inhibitory effect. Thus, repetitive excitatory events occur leading to paroxysmal depolarizing shifts [46]. Mechanism of picrotoxin inhibition of this receptor is a complex phenomenon. The inhibitor has been considered to be a simple open-channel blocker [47,48]. A mixed/noncompetitive inhibitor, or a noncompetitive inhibitor that binds to an allosteric site to stabilize a closed or desensitized state of ligand-gated ion channels [49,50]. Detailed analysis of single-channel current recordings suggested a more complex scheme [49]. Neither picrotoxin nor its more active component picrotoxinin had any effect on the conductance of single-channel events mediated by GABA$_A$ receptors [49,51,52]. Single-channel current recordings showed that picrotoxin decreased the channel-opening frequency in a manner compatible with the stabilization of an agonist-bound closed state that perhaps corresponds to a desensitized conformation of the receptor [49,53-55].

Kindling induced by neurotoxicants: Neurotoxicants are the substances which attack nervous system and alter nerve cells functions by altering the neurotransmitters levels. These agents affect neurotransmitter release and binding thus, affecting ion channel receptors. Exposure to these toxic chemicals may induce seizures [56]. Therefore, some of these agents have been used in kindling models.

Endosulfan induced kindling: Endosulfan is a pesticide, belonging to the chemical family of organochlorines, in the subclass of chlorinated cyclodienes containing one double bond [57]. Organochlorine pesticides have been proven to have several deleterious effects on the central nervous system [58], and also a potent proconvulsant compound. Repeated administration of subconvulsive doses of endosulfan induces chemical kindling. This proconvulsant kindling paradigm also contributes to the induction of the spontaneous electrographic and behavioral seizures [59]. The proconvulsant activity of endosulfan has also been investigated using electrical stimulation of amygdala. Endosulfan significantly reduced the number of stimulations required to produce stage 5 generalized seizures. Endosulfan facilitated the development of amygdala kindling [60]. The mechanism of action of endosulfan is binding to γ -amino-butyric acid (GABA) receptor ionophore complex and inhibition of GABA-gated chloride channel, thus inhibiting GABA-induced chloride flux across membranes [57,61,62]. Repeated administration of endosulfan tends to induce seizure by lowering seizure threshold [58,63,64]. Some investigations have suggested that endosulfansulfate, the main metabolite also contributes to the acute endosulfan neurotoxicity. Endosulfan has been reported to compete for binding of GABA at the t-butyl bicycle phosphothionate site (TBPS) [17,62,65,66].

Lindane induced kindling: Lindane (gamma-hexachlorocyclohexane) is a chlorinated hydrocarbon pesticide [67]. Joy and colleagues reported the proconvulsant properties of lindane using an electrical kindling paradigm. In this kindling paradigm, repeated low doses of lindane was delivered prior to each daily electrical kindling stimulation resulting in accelerated rate, generalized seizures development and prolongation of the electrographic seizures accompanying each kindling stimulus [68]. The mechanism of action of lindane includes its binding to the GABA receptor ionophore complex which results in the disturbed effect of GABA and GABAergic neurotransmission [69,70]. Lindane stereospecifically binds to the t-[^{35}S] butyl bicyclophosphorothionate (TBPS) site on the GABA receptor/ionophore complex [71] and inhibits GABA induced Cl influx [66].

Effect of various chemoconvulsants on GABAergic system

Trimethylolpropane phosphate induced kindling: Trimethylolpropane phosphate (TMPP) is an ethyl bicyclophosphate convulsant. It is produced during the partial pyrolysis of certain synthetic, ester-based turbine lubricants supplemented with phosphate-based lubricity additives. Repeated exposure to subconvulsive doses of TMPP results in facilitation of the electrical kindling of amygdale [72]. It mimics the responses shown by the GABA$_A$ antagonist bicuculline. The studies suggest that TMPP acts by a competitive antagonism of GABA inhibitory function. Binding assays have revealed that bindingof TMPP to the GABA$_A$-benzodiazepine receptor complex occurs with more affinity than picrotoxin, but less affinity than *tert*-butyl-bicyclo-[2.2.2]-phosphorothionate (TBPS). The epileptogenic effects caused by TMPP are consistent with this binding [61,73-75]. Furthermore, the benzodiazepines have been found effective against TMPP by increasing the time of seizures occurrence and reducing the severity of generalized convulsions [61,74-76]. These effects of benzodiazepines have also been observed against trimethylolpropanephosphite, a structurally related compound. Some investigations have shown that TMPP blocks the Cl current in hippocampal neurons [74,75,77].

Kindling induced by local anaesthetics

The use of local anaesthetics in excessive doses caused occurrence of convulsions in humans. Previous exposure to these agents or other kindling substances has been a predisposing factor. Thus, the local anaesthetics have been attributable to the kindling process Kindling seizures produced by these agents seems to be affected by the dose and frequency with which these agents are administered for kindling to occur [78].

Cocaineinducedkindling: Cocaine (benzoylmethylecgonine) is a CNS stimulant and found in the leaves of *Erythroxylon coca Erythroxylaceae.*, trees that are indigenous to Bolivia and Peru (WHO, 2004). Multiple forms of toxicity are associated with cocaine abuse and seizures represent one of the major fatalities

induced by cocaine. In chronic cocaine abusers, kindling has been suggested as a possible mechanism for seizures [79]. Cocaine induce upregulation of cortical NMDA receptors. The findings suggest that cocaine induced kindling is associated with upregulation of striatal, amygdala and hippocampal NMDA receptors. However, the maintenance of kindling depends upon the increase in NMDA receptor binding in amygdala and hippocampus [79]. NMDA receptors are involved in the process of sensitization to behavioral and convulsive effects of cocaine. Activation of the NMDA receptors also leads to the brain nitric oxide synthase (NOS) stimulation which is entailed in the induction and expression of cocaine kindled seizures [80]. Furthermore, expression and development of cocaine induced kindled seizures are inhibited by NMDA receptor antagonists [81]. Cocaine kindling also results in enhancement of the depolarization-dependent release of glutamate and enhanced glutamate neurotransmission which may play an important role in kindling process [82]. Long-lasting increase insensitivity to convulsive effect is developed as a result of repeated administration of cocaine at high doses. Thus, cocaine induced kindling is a useful model to study sensitizing and epileptogenic effects of repeated cocaine administration and their neurochemical mechanisms [83,84].

Lidocaine induced kindling: Lidocaine induced seizures are qualitatively similar to the electrical kindling of amygdale [85]. It is suggested that the lidocaine induces kindled seizures inthe limbic system. High doses of lidocaine cause alteration of limbic system excitability and ultimately seizure discharges are induced. Limbic structures activation caused by lidocaine is selective and marked activation is produced particularly in hippocampus and amygdale [86]. In high doses, lidocaine is excitatory and induces generalized convulsions [87]. Some studies suggest that lidocaine induced seizures by binding to the GABA-ionophore receptor complex [88].

LIMITATIONS OF THE CHEMICAL KINDLING

Although it is very beneficial to used the chemical kindling but there are some limitations of this model. Like as compared to electrical kindling chemical kindling model has the less experimental control on the timings of evocation of seizures. Delay in time occurs from the time of drug delivery to the onset of clinical signs of seizures. A care should be done there in between the interval of the stimulations so that there should be less accumulation of drugs.

REFERENCES

1. Löscher W. Critical review of current animal models of seizures and epilepsy used in the discovery and development of new antiepileptic drugs. Seizure. 2011; 20: 359-368.

2. Sarkisian MR. Overview of the Current Animal Models for Human Seizure and Epileptic Disorders. Epilepsy Behav. 2001; 2: 201-216.

3. Goddard GV, McIntyre DC, Leech CK. A permanent change in brain function resulting from daily electrical stimulation. Exp Neurol. 1969; 25: 295-330.

4. Luthman J, Humpel C. Pentylenetetrazol kindling decreases N-methyl-D-aspartate and kainate but increases gamma-aminobutyric acid-A receptor binding in discrete rat brain areas. Neurosci Lett. 1997; 239: 9-12.

5. Morimoto K, Fahnestock M, Racine RJ. Kindling and status epilepticus models of epilepsy: rewiring the brain. Prog Neurobiol. 2004; 73: 1-60.

6. Barnes SJ, Pinel JP. Conditioned effects of kindling. Neurosci Biobehav Rev. 2001; 25: 745-751.

7. Schmoll H, Badan I, Grecksch G, Walker L, Kessler C, Popa-Wagner A. Kindling status in sprague-dawley rats induced by pentylenetetrazole: involvement of a critical development period. Am J Pathol. 2003; 162: 1027-1034.

8. Goddard GV. The kindling model of epilepsy. Elsevier Science Publishers BV. Amsterdam. 1983.

9. McIntyre DC, Kelly ME, Dufresne C. Fast and slow amygdala kindling rat strains: comparison of amygdala, hippocampal, piriform and perirhinal cortex kindling. Epilepsy Res. 1999; 35: 197-209.

10. Racine RJ. Modification of seizure activity by electrical stimulation. I. After-discharge threshold. Electroencephalogr Clin Neurophysiol. 1972; 32: 269-279.

11. Racine RJ. Modification of seizure activity by electrical stimulation. II. Motor seizures, Electroencephalogr Clin Neurophysiol. 1972; 32: 281-294.

12. McNamara JO, Russell RD, Rigsbee L, Bonhaus DW. Anticonvulsant and antiepileptogenic actions of MK-801 in the kindling and electroshock models. Neuropharmacology. 1988; 27: 563-568.

13. Bertram E. The relevance of kindling for human epilepsy. Epilepsia. 2007; 48: 65-74.

14. Gilbert ME. Does the kindling model of epilepsy contribute to our understanding of multiple chemical sensitivity? Ann N Y Acad Sci. 2001; 933: 68-91.

15. Magos L. WJ Hayes, ER Laws Handbook of Pesticide Toxicology: General Principles. Academic Press. New York. 1991.

16. Gilbert ME. The phenomenology of limbic kindling. Toxicol Ind Health. 1994; 10: 343-358.

17. Gilbert ME. A characterization of chemical kindling with the pesticide endosulfan. Neurotoxicol Teratol. 1992; 14: 151-158.

18. Gilbert ME. Repeated low level exposure to lindane leads to behavioral sensitization and facilitates electrical kindling. Neurotoxicol Teratol. 1995; 17: 131-142.

19. Joy RM, Stark LG, Peterson SL, Bowyer JF, Albertson TE. The kindled seizure: production of and modification by dieldrin in rats. Neurobehav Toxicol. 1980; 2: 117-124.

20. Treiman DM. GABAergic mechanisms in epilepsy. Epilepsia. 2001; 42: 8-12.

21. Corda MG, Orlandi M, Lecca D, Carboni G, Frau V, Giorgi O. Pentylenetetrazol-induced kindling in rats: effect of GABA function inhibitors. Pharmacol Biochem Behav. 1991; 40: 329-333.

22. Rajabzadeh A, Bideskan AE, Fazel A, Sankian M, Rafatpanah H, Haghir H. The effect of PTZ-induced epileptic seizures on hippocampal expression of PSA-NCAM in offspring born to kindled rats. J Biomed Sci. 2012; 19: 56.

23. Dhir A. Pentylenetetrazol (PTZ) kindling model of epilepsy. Curr Protoc Neurosci. 2012; Chapter 9: Unit9.

24. Erkec OE, Arihan O. Pentylenetetrazole Kindling Epilepsy Model. Epilepsi. 2015; 21: 6-12.

25. Bahçekapılı N, Akgün-Dar K, Albeniz I, Kapucu A, Kandil A, Yağız O, et al. Erythropoietin pretreatment suppresses seizures and prevents the increase in inflammatory mediators during pentylenetetrazole-induced generalized seizures. Int J Neurosci. 2014; 124: 762-770.

26. Corda MG, Giorgi O, Longoni B, Orlandi M, Biggio G. Decrease in the

function of the gamma-aminobutyric acid-coupled chloride channel produced by the repeated administration of pentylenetetrazol to rats. J Neurochem. 1990; 55: 1216-1221.

27. Rössler AS, Schröder H, Dodd RH, Chapouthier G, Grecksch G. Benzodiazepine receptor inverse agonist-induced kindling of rats alters learning and glutamate binding. Pharmacol Biochem Behav. 2000; 67: 169-175.

28. Gmiro VE, Serdyuk SE. Bulletin of Experimental Biology and Medicine. 2008; 145.

29. Piredda S, Lim CR, Gale K. Intracerebral site of convulsant action of bicuculline. Life Sci. 1985; 36: 1295-1298.

30. Uemura S. Epileptiform response induced by acute or chronic intraamygdaloid injection of bicuculline. J Jpn Epi Soc. 1988; 6: 232-239.

31. Campbell AM, Holmes O. Bicuculline Epileptogenesis in the Rat. Brain Res. 1984; 323: 239-246.

32. Khawaled R, Bruening-Wright A, Adelman JP, Maylie J. Bicuculline block of small-conductance calcium-activated potassium channels. Pflugers Arch. 1999; 438: 314-321.

33. Pong SF, Graham LT. N-methyl bicuculline, a convulsant more potent than bicuculline. Brain Res. 1972; 42: 486-490.

34. Mares P, Chino M, Kubová H, Mathern P, Veliký M. Convulsant action of systemically administered glutamate and bicuculline methiodide in immature rats. Epilepsy Res. 2000; 42: 183-189.

35. Uemura S, Kimura H. Amygdaloid kindling with bicuculline methiodide in rats. Exp Neurol. 1988; 102: 346-353.

36. Nakanishi H, Ukai K, Nakagawa T, Watanabe S, Kamata O, Yamamoto K. Enhancement of NMDA receptor-mediated synaptic potential evoked in rat medial-amygdala neuron following olfactory bulbectomy. Brain Res. 1990; 532: 69-75.

37. Cao R, Peng W, Wang Z, Xu A. Beta-Carboline alkaloids: biochemical and pharmacological functions. Curr Med Chem. 2007; 14: 479-500.

38. Braestrup C, Nielsen M, Olsen CE. Urinary and brain beta-carboline-3-carboxylates as potent inhibitors of brain benzodiazepine receptors. Proc Natl Acad Sci U S A. 1980; 77: 2288-2292.

39. Evans AK, Lowry CA. Pharmacology of the beta-carboline FG-7,142, a partial inverse agonist at the benzodiazepine allosteric site of the GABA$_A$ receptor: neurochemical, neurophysiological, and behavioral effects. CNS Drug Rev. 2007; 13: 475-501.

40. Little HJ, Nutt DJ, Taylor SC. Bidirectional effects of chronic treatment with agonists and inverse agonists at the benzodiazepine receptor. Brain Res Bull. 1987; 19: 371-378.

41. Stephens DN, Turski LA, Turner JD, Schneider HH. Are changes in glutamatergic mechanisms responsible for kindling to the benzodiazepine receptor inverse agonist, FG 7142? Br J Pharmacol. 1989; 98 Suppl: 837P.

42. Kulkarni SK, George B. Anticonvulsant Action of *Withania somnifera* (Aswaganda) Root Extract against Pentylenetetrazol-induced Kindling in Mice. Phytotherapy Res. 1996; 10: 447-449.

43. Little HJ, Nutt DJ, Taylor SC. The effects of drugs acting at the GABAA-receptor/ionophore after chemical kindling with the benzodiazepine receptor ligand FG 7142. Br J Pharmacol. 1986; 88: 507-514.

44. Prado de Carvalho L, Grecksch G, Cavalheiro EA, Dodd RH, Chapouthier G, et al. Characterization of convulsions induced by methyl beta-carboline-3-carboxylate in mice. Eur J Pharmacol. 1984; 103: 287-293.

45. Chaix Y, Ferraro TN, Lapouble E, Martin B. Chemoconvulsant-induced seizure susceptibility: toward a common genetic basis?. Epilepsia.

2007; 48: 48-52.

46. Cain DP. Kindling by repeated intraperitoneal or intracerebral injection of picrotoxin transfers to electrical kindling. Exp Neurol. 1987; 97: 243-254.

47. Etter A, Cully DF, Liu KK, Reiss B, Vassilatis DK, Schaeffer JM, et al. Picrotoxin blockade of invertebrate glutamate-gated chloride channels: subunit dependence and evidence for binding within the pore. J Neurochem. 1999; 72: 318-326.

48. Inoue M, Akaike N. Blockade of gamma-aminobutyric acid-gated chloride current in frog sensory neurons by picrotoxin. Neurosci Res. 1988; 5: 380-394.

49. Newland CF, Cull-Candy SG. On the mechanism of action of picrotoxin on GABA receptor channels in dissociated sympathetic neurones of the rat. Physiol. 1992; 447: 191-213.

50. Krishek BJ, Moss SJ, Smart TG. A functional comparison of the antagonists bicuculline and picrotoxin at recombinant GABAA receptors. Neuropharmacology. 1996; 35: 1289-1298.

51. Dillon GH, Im WB, Carter DB, McKinley DD. Enhancement by GABA of the association rate of picrotoxin and tert-butylbicyclophosphorothionate to the rat cloned alpha 1 beta 2 gamma 2 GABAA receptor subtype. Br J Pharmacol. 1995; 115: 539-545.

52. Shan Q, Haddrill JL, Lynch JW. A single beta subunit M2 domain residue controls the picrotoxin sensitivity of alphabeta heteromeric glycine receptor chloride channels. J Neurochem. 2001; 76: 1109-1120.

53. Ikeda T, Nagata K, Shono T, Narahashi T. Dieldrin and picrotoxinin modulation of GABA(A) receptor single channels. Neuroreport. 1998; 9: 3189-3195.

54. Porter NM, Angelotti TP, Twyman RE, MacDonald RL. Kinetic properties of alpha 1 beta 1 gamma-aminobutyric acidA receptor channels expressed in Chinese hamster ovary cells: regulation by pentobarbital and picrotoxin. Mol Pharmacol. 1992; 42: 872-881.

55. Ramakrishnan L, Hess GP. Picrotoxin Inhibition Mechanism of a ç-Aminobutyric Acid A Receptor Investigated by a Laser-Pulse Photolysis Technique. Biochemistry. 2005; 44: 8523-8532.

56. Feldman RG, Ratner MH. Behavioral syndromes in neurotoxicology. In: Schiffer RB, Rao SM, Foge BS, editors. Neuropsychiatry, Lippincott Williams & Wilkins, 2003.

57. Marilyn H. Silva. Endosulfan risk characterization document volume i medical toxicology and worker health and safety branches department of pesticide regulation california environmental protection agency.

58. Arora SK, Batra P, Sharma T, Banerjee BD, Gupta S. Role of organochlorine pesticides in children with idiopathic seizures. ISRN Pediatr. 2013; 2013: 849709.

59. Gilbert ME. Proconvulsant activity of endosulfan in amygdala kindling. Neurotoxicol Teratol. 1992; 14: 143-149.

60. Gilbert ME. Neurotoxicants and limbic kindling. In the Vulnerable Brain and Environmental Risks. Vol. 1: Malnutrition and Hazard Assessment, Plenum. New York. 1992; 173-192.

61. Casida JE, Eto M, Moscioni AD, Engel JL, Milbrath DS, Verkade JG. Structure-toxicity relationships of 2,6,7-trioxabicyclo(2.2.2)octanes and related compounds. Toxicol Appl Pharmacol. 1976; 36: 261-279.

62. Abalis IM, Eldefrawi ME, Eldefrawi AT. High-affinity stereospecific binding of cyclidiene insecticides and gammahexachlorocyclohexane to gamma-aminobutyric acid receptors of rat brain. Pesticide Biochem Physiol. 1985; 24: 95-102.

63. Fishman BE, Gianutsos G. CNS biochemical and pharmacological effects of the isomers of hexachlorocyclohexane (lindane) in the

SciMedCentral

mouse. Toxicol Appl Pharmacol. 1988; 93: 146-153.

64. Gilbert ME, Mack CM. Seizure thresholds in kindled animals are reduced by the pesticides lindane and endosulfan. Neurotoxicol Teratol. 1995; 17: 143-150.

65. Cole LM, Casida JE. Polychlorocycloalkane insecticide-induced convulsions in mice in relation to disruption of the GABA-regulated chloride ionophore. Life Sci. 1986; 39: 1855-1862.

66. Eldefrawi ME, Sherby SM, Abalis IM, Eldefrawi AT. Interactions of pyrethroid and cyclodiene insecticides with nicotinic acetylcholine and GABA receptors. Neurotoxicology. 1985; 6: 47-62.

67. Gilbert ME. Repeated exposure to lindane leads to behavioral sensitization and facilitates electrical kindling. Neurotoxicol Teratol. 1995; 17: 131-141.

68. Joy RM, Stark LG, Albertson TE. Proconvulsant actions of lindane: Effects on afterdischarge thresholds and durations during amygdaloid kindling in rats. Neurotoxicol. 1983; 2: 211-219.

69. Matsumura F, Ghiasuddin SM. Evidence for similarities between cyclodiene type insecticides and picrotoxinin in their action mechanisms. J Environ Sci Health B. 1983; 18: 1-14.

70. Lawrence LJ, Casida JE. Interactions of lindane, toxaphene and cyclodienes with brain-specific t-butylbicyclophosphorothionate receptor. Life Sci. 1984; 35: 171-178.

71. Llorens J, Suñol C, Tusell JM, Rodríguez-Farré E. Lindane inhibition of [35S]TBPS binding to the GABAA receptor in rat brain. Neurotoxicol Teratol. 1990; 12: 607-610.

72. Lin J, Cassell J, Ritchie GD, Rossi J 3rd, Nordholm AF. Repeated exposure to trimethylolpropane phosphate induces central nervous system sensitization and facilitates electrical kindling. 1998; 65: 51-58.

73. Bowery NG, Collins JF, Hill RG. Bicyclic phosphorus esters that are potent convulsants and GABA antagonists. Nature. 1976; 261: 601-603.

74. Higgins GM, Gardier RW. Gamma-Aminobutyric acid antagonism produced by an organophosphate-containing combustion product. Toxicol Appl Pharmacol. 1990; 105: 103-112.

75. Lin J, Ritchie GD, Stenger DA, Nordholm AF, Pancrazio JJ, Rossi J 3rd. Trimethylolpropane phosphate induces epileptiform discharges in the CA1 region of the rat hippocampus. Toxicol Appl Pharmacol. 2001; 171: 126-134.

76. Kimmerle G, Eben A, Gröning P, Thyssen J. Acute toxicity of bicyclic phosphorus esters. Arch Toxicol. 1976; 35: 149-152.

77. Kao WY, Liu QY, Ma W, Ritchie GD, Lin J, Nordholm AF, et al. Inhibition of spontaneous GABAergic transmission by trimethylolpropane phosphate. Neurotoxicology. 1999; 20: 843-849.

78. Dorris RL, Lotzof L. Studies on lidocaine-induced kindling. Life Sci. 1992; 51: 25-28.

79. Itzhak Y, Martin JL. Cocaine-induced kindling is associated with elevated NMDA receptor binding in discrete mouse brain regions. Neuropharmacology. 2000; 39: 32-39.

80. Itzhak Y. Attenuation of cocaine kindling by 7-nitroindazole, an inhibitor of brain nitric oxide synthase. Neuropharmacology. 1996; 35: 1065-1073.

81. Itzhak Y, Stein I. Sensitization to the toxic effects of cocaine in mice is associated with the regulation of N-methyl-D-aspartate receptors in the cortex. J Pharmacol Exp Ther. 1992; 262: 464-470.

82. Kaminski RM, Núñez-Taltavull JF, Budziszewska B, Lasoń W, Gasior M, Zapata A, et al. Effects of cocaine-kindling on the expression of NMDA receptors and glutamate levels in mouse brain. Neurochem Res. 2011; 36: 146-152.

83. Post RM, Weiss SR, Pert A. Cocaine-induced behavioral sensitization and kindling: implications for the emergence of psychopathology and seizures. Ann N Y Acad Sci. 1988; 537: 292-308.

84. Leśkiewicz M, Budziszewska B, Jaworska-Feil L, Kubera M, Basta-Kaim A, Lasoń W. Inhibitory effect of some neuroactive steroids on cocaine-induced kindling in mice. Pol J Pharmacol. 2003; 55: 1131-1136.

85. Post RM, Kopanda RT, Lee A. Progressive behavioral changes during chronic lidocaine administration: relationship to kindling. Life Sci. 1975; 17: 943-950.

86. Post RM, Squillace KM, Pert A, Sass W. The effect of amygdala kindling on spontaneous and cocaine-induced motor activity and lidocaine seizures. Psychopharmacology (Berl). 1981; 72: 189-196.

87. Fujita H, Maru E, Shimada M, Suzuki H, Ogiuchi H. A decrease in seizure susceptibility to lidocaine in kindled epileptic rats. Anesth Analg. 2000; 90: 1129-1134.

88. Stone WE, Javid MJ. Anticonvulsive and convulsive effects of lidocaine: comparison with those of phenytoin, and implications for mechanism of action concepts. Neurol Res. 1988; 10: 161-168.