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Experimental Models of Chronic Focal Epilepsy: A Critical Review of Four Models

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A number of experimental (i.e., animal) models have been developed to induce chronic focal epilepsy. Three of the most commonly employed are the alumina cream, kainic acid, and the electrical kindling techniques. A fourth approach involving the application of minute quantities of tetanus toxin to discrete brain sites, although relatively under-utilized, may be favorably compared to the aforementioned models.

INTRODUCTION

It has been estimated that focal epilepsy affects approximately 0.4 percent to 0.5 percent of the population in the United States [1,2] or about one million people [3]. Experimental (i.e., animal) models are essential for a thorough study of the development and expression of focal epilepsy, as well as the preclinical evaluation of new therapeutic approaches. Over the past 45 years, a variety of such models have been developed. These models may be divided into those which produce an acute epileptogenic focus and those which produce a chronic epileptogenic focus. Herein, the terms "acute" and "chronic" will be used to describe epileptiform syndromes which prevail for several hours to several days, and several days to several months, respectively. While the acute models have contributed to our knowledge of the convulsive state and have been instrumental in single-cell studies as well as the investigation of phenomena such as status epilepticus, the chronic models are probably more appropriate tools for the study of naturally occurring epilepsy, which is essentially chronic. Other models with some characteristics of a chronic nature such as the cobalt [4–6], tungstic acid [7,8], zinc sulfate [9,10], freezing [11], and blood-brain barrier [12,13] methods are not discussed here. These models are disadvantageous and not commonly used for the following reasons: their limited ability to induce chronic epileptogenic foci, their production of diffuse and/or crater-like lesions, and the great length of time they require to produce an epileptiform syndrome. The more effective and commonly used chronic models are those involving alumina cream [14], kainic acid [15], and kindling [16]. Since a comparative review has not been written in fourteen years [17], we present here an updated, critical review of the alumina cream, kainic acid, kindling, and tetanus toxin methods, the latter being a potentially superior but relatively under-utilized model.

THE ALUMINA MODEL

In 1942, L.M. Kopeloff was the first investigator to produce chronic, focal epileptogenic lesions in experimental animals [14]. While studying the effects of

various chemical agents on the pre-central cortex of monkeys and rabbits, Kopeloff found that the application of alumina cream resulted in the experimental induction of spontaneous recurrent seizures [14]. In the past 45 years, the alumina cream technique has become a widely used experimental model for focal epilepsy, as it creates foci which remain active for several months [18] to several years [19] and produces seizures which may increase in frequency until treatment with anticonvulsants becomes necessary [20]. Table 1 presents the major alumina cream studies conducted since 1942 [14,21–50]. A number of points deserve further attention. First, while some techniques produce epileptogenic foci in a wide variety of mammalian, reptilian, and amphibian species, the alumina cream technique has had limited success when applied to animals other than the cat and rhesus monkey. Attempts to produce foci in the cebus monkey, rabbit, and rat have had very limited success.

Alumina cream can be criticized as crude [45], since it creates lesions which are quite large and difficult to reproduce precisely [21,35–40], averaging on the order of 9 mm in diameter in some instances [49,50]. It is also a matter of dispute as to whether the alumina may diffuse away from its site of application. While some investigators have maintained that the lesion stabilizes quickly and that diffusion is limited [40], others have noted the "frequent diffusion of the active substance" [48], its spread to adjacent regions of cortex [32,35], or a progressive increase in the size of the lesion over time [37].

Another drawback of the alumina technique is the long and somewhat unpredictable latency period prior to the clinical and electrographic onset of spontaneous seizures. Table 1 shows that delays of four to eight weeks are not uncommon in cats, while delays of six to twelve weeks are fairly common in rhesus monkeys. Furthermore, a number of authors have noted that results are frequently inconsistent [45]. For example, Stercova was unable to produce an epileptogenic focus in the rat cortex [37] despite the success of others [34]. In addition, individual animals may react to alumina quite differently [14,32,30].

Table 1 also shows that the majority of studies using alumina cream have been restricted to the sensorimotor cortex. It has been observed that other regions of the telencephalon are less susceptible to alumina cream [14,19,20]. For example, Soper et al. [44] found that large amounts of bilaterally administered alumina cream are needed to produce temporal lobe seizures in monkeys. Other investigators have also noted the need for bilateral administration of alumina when dealing with areas outside of the sensorimotor cortex [22,30,33]. It is questionable whether a model which requires large bilateral lesions is a good representation of the human disease process.

In summary, while the alumina cream model may have been the first experimental model developed to produce chronic epileptogenic foci, a number of factors limit its applicability. For this reason, the alumina model has become less favored relative to other, more recently developed techniques such as kindling and kainic acid.

THE KAINIC ACID MODEL

In 1970, Shinozaki and Konishi showed that kainic acid (KA), an analog of the neuro-excitatory amino acid glutamate, had a potent excitatory effect upon rat cortical neurons [15]. In the late 1970s and early 1980s, investigators became aware of the potential use of kainic acid in experimental models of focal epilepsy. Hence, kainic acid was applied to a variety of cortical and subcortical regions in various mammals.

TABLE 1
Major Alumina Model Studies, 1942–1985

Study	Brain Site	Species	No. of Animals	Latency to First Seizure	Size of Lesion
Kopeloff et al., 1942 [14]	Precentral cerebral cortex	Monkey	26	4.5–6 weeks in 18 animals	
Kopeloff et al., 1942 [14]	Motor cortex	Rabbit	8	Three and seven weeks in two animals. No seizures in six animals.	
Barrera et al., 1944 [21]	Precentral cerebral cortex	Rhesus monkey		Post-operatively to eight weeks. No seizures in some.	
Sloan et al., 1953 [22]	Amygdala—unilateral and bilateral	Monkey		Eight weeks (EEG abnormalities)	
Chusid et al., 1953 [23]	Eight sites in the sensorimotor cortex	Rhesus monkey	7	Three to four weeks	
Kopeloff et al., 1954 [24]	Sensorimotor cortex	Rhesus monkey	4	4.5, 7, 9 weeks	
Faeth et al., 1955 [25]	Motor cortex	Rhesus monkey	24	6–12 weeks	
Kopeloff et al., 1955 [26]	Sensorimotor cortex, primarily. Some parietal cortex as well.	Rhesus monkey	196	>2.5 weeks in 182 animals	
Youmans, 1956 [27]	Temporal lobe	Rhesus monkey	5	One day, one week, seven weeks +. No seizures	
Morrell et al., 1956 [28]	Primary sensory cortex and amygdaloid-hippocampal region	Rhesus monkey	9	16–24 weeks	
Faeth and Walker, 1957 [29]	Thalamus, amygdala, putamen, globus pallidus, pons, nucleus basalis—bilateral	Rhesus monkey, cebus monkey	16	No seizures	
Gastaut et al., 1958 [30]	Amygdala, hippocampus, pyriform cortex—unilateral and bilateral	Cat	14	Three to five weeks in 12 animals. 24 weeks in one animal. One day in one animal.	
Servit and Sterc, 1958 [31]	Motor and acoustic area—unilateral and bilateral	Rat	75	2 days–11 weeks in 25 animals	

TABLE 1—*continued*

Study	Brain Site	Species	No. of Animals	Latency to First Seizure	Size of Lesion
Gastaut et al., 1959 [32]	Amygdala, hippocampus, pyriform cortex, adjacent to the thalamostriatal region	Cat	14	Four, five, one, one, six, six, five weeks in seven animals. One day in one animal. No seizures in six.	
Stamm and Pribram, 1961 [33]	Inferotemporal cortex—bilateral	Rhesus monkey	12	8–14 weeks (EEG abnormalities)	
Sterc, 1962 [34]	Acoustic and motor cortex	Rat		4.5 weeks—audiogenic seizures	
Westrum et al., 1964 [35]	Sensorimotor cortex	Rhesus monkey	8	Four to six weeks	2–3 mm in diameter
Mayman et al., 1965 [36]	Sensorimotor cortex	Cat	16	Three weeks in one animal. Six to eight weeks in 15 animals.	Large (see Fig. 1)
Stercova, 1966 [37]	Motor and acoustic cortex	Rat		No seizures observed	Large (see Fig. 1)
Velasco et al., 1973 [38]	Sensorimotor cortex	Cat	18	5.5 weeks	~1.0–2.5 mm in diameter
Velasco et al., 1973 [39]	Sensorimotor cortex	Cat	16	4.5–6 weeks	3.2–4.3 mm in diameter
Harris, 1973 [40]	Cortex	Rhesus monkey	32	Eight to ten weeks	
Mayanagi and Walker, 1974 [41]	Temporal neocortex	Rhesus monkey	12	$\bar{x}$ = 8 weeks	
Mayanagi, 1976 [42]	Temporal cortex, amygdala, hippocampus	Rhesus monkey	12	6–12 weeks	Large (see Figs. 1, 2)
Lockard et al., 1976 [43]	Sensorimotor cortex	Rhesus monkey	13	6–11 weeks	
Soper et al., 1978 [44]	Hippocampus—unilateral and bilateral	Monkey	16	Three to ten weeks	
Mayanagi, 1979 [45]	Lateral neocortex or deep structures of the temporal lobe	Rhesus monkey	12	~8 weeks	
Feria-Velasco et al., 1980 [46]	Motor cortex	Cat	24	Five to six weeks	
Harris and Lockard, 1981 [47]	Sensorimotor cortex	Rhesus monkey	15	8–12 weeks	
Beaumanoir et al., 1982 [48]	Peri-amygdaloid region	Cat		Three to six weeks	

TABLE 1—*continued*

Study	Brain Site	Species	No. of Animals	Latency to First Seizure	Size of Lesion
Velasco et al., 1984 [49]	Motor cortex	Cat	63	4.5–5 weeks	5.3 ± 1.0 mm–9.3 ± 1.1 mm in diameter
Velasco et al., 1985 [50]	Motor cortex	Cat	8	4.5–5 weeks	5.3 ± 1.0 mm–9.3 ± 1.1 mm in diameter

Table 2 provides a representative list of studies in which kainic acid has been applied to a variety of structures including the amygdala [51–57], hippocampus [58–67], striatum [68–72], and substantia nigra [69]. In addition, KA has been administered subcutaneously [73–75], intravenously [76–80], and intraventricularly [56,70,81]. Its primary site of action seems to be the CA3 cells of the hippocampus [53,59,61,64,65,70,71,73,77,79,81–85]. While few primary epileptogenic foci have been successfully created outside of the temporal lobe and/or limbic regions, the KA model has emerged as a model for temporal lobe epilepsy [59,61,65,77–79,82], since the resulting clinical signs [69] and pathology [64,72,82] are similar to those seen in patients with temporal lobe disease.

An important drawback of this model is the common but somewhat disputed observation that the effects of KA are not restricted to the site or anatomical structure into which the KA is injected [50–53,55–57,62,64,68,70,72–75,81]. For instance, Zaczek showed that intrastriatal applications of 3H-labeled KA resulted in the spread of KA to the following distant sites: ipsilateral frontal cortex, ipsilateral olfactory cortex, ipsilateral lateral cortex, ipsilateral hippocampus, ipsilateral diencephalon, ipsilateral medulla, ipsilateral pons, contralateral striatum, and contralateral olfactory cortex [71]. Even iontophoretic application has had variable success in eliminating distant damage [63,68]. On the other hand, Scherer-Singler and McGeer reported little diffusion of 3H-labeled KA away from injection sites in the substantial nigra, cerebellum, and neostriatum [86]. While some authors have implicated the direct diffusion of KA [65], it appears that diffusion alone cannot explain the inhomogeneous distribution of distant/secondary lesions [55,82], so that some form of neuronal transport is likely to be involved. It has also been suggested that the lesion at the site of injection may be the result of KA's toxicity, whereas distant lesions may be related to the epileptogenic effects of the drug [50,51,55,62,80,83,86], since pretreatment with anticonvulsants appears to limit distant damage [83].

While KA has been applied to the brains of a number of different species including the baboon [55,57], rabbit [60], cat [58,62], and mouse [75], the large majority of studies have been conducted in the rat (i.e., 29 of 35 studies listed in Table 2). The majority of studies have considered the acute epileptogenic effects of KA administration [52,53,61,66,67,72,74,75,80,82,87]. It appears, however, that KA administration may also result (after a variable silent period following the acute stage) in spontaneous recurrent seizures of a chronic nature [62,65].

To summarize, when KA is applied to the brains of various animals, it produces predominantly limbic seizures which appear within a matter of minutes [52,53,55] and remit after hours or days, but which may reappear spontaneously after a silent period

TABLE 2
Major Kainate Model Studies, 1979–1984

Study	Region or Method of KA Administration	Species	Latency to First Seizure	Last Observed Seizure	Comments	Locations of Distant Lesions
Ben-Ari et al., 1979 [53]	Amygdala	Rat	12 minutes	Several hours	Focal seizures followed by generalized seizures	Ipsilateral hippocampus
Menini et al., 1979 [55]	Amygdala	Baboon	Four to eight minutes	15–150 hours		Ipsilateral hippocampus and neocortical regions
Ben-Ari et al., 1980 [56]	Amygdala	Rat				Lateral septum, claustrum, contralateral cortical regions, ipsilateral hippocampus
Ben-Ari et al., 1980 [52]	Amygdala	Rat	5–60 minutes	Two to six hours		Hippocampus, contralateral amygdala, bilaterally in midline thalamic nuclei, contralateral claustrum, cortical regions, lateral septum
Olney et al., 1981 [54]	Amygdala	Rat			Limbic seizures	Piriform and entorhinal and temporoparietal cortices, hippocampus, thalamus, lateral septum
Cepeda et al., 1982 [57]	Amygdala	Baboon		48–72 hours	Status epilepticus	Bilateral hippocampus, cortical regions, thalamus
Tremblay et al., 1983 [51]	Amygdala	Rat				
Zaczek et al., 1978 [67]	Hippocampus	Rat		Two to six hours	Tonic-clonic seizures	

TABLE 2—*continued*

Study	Region or Method of KA Administration	Species	Latency to First Seizure	Last Observed Seizure	Comments	Locations of Distant Lesions
Schwarcz et al., 1978 [61]	Hippocampus	Rat		12 hours		
Kohler et al., 1978 [64]	Hippocampus	Rat				Overlying cortex, thalamus, amygdala, piriform cortex
Nelson et al., 1980 [66]	Hippocampus	Rat	30–50 minutes			
Munoz and Grossman, 1980 [63]	Hippocampus	Rat			Iontophoretic application	No damage at distant sites
Tanaka et al., 1981 [58]	Hippocampus	Cat			Status epilepticus. Secondary amygdaloid focus	Both amygdalas
Smialowski and Smialowska, 1981 [60]	Hippocampus	Rabbit			Prolonged convulsions	
French et al., 1982 [59]	Hippocampus	Rat			Frozen appearance during seizures	
Cavalheiro et al., 1982 [65]	Hippocampus	Rat	Three to five hours	48–72 hours; 22–46 days	Silent period from day 2 or 3 until day 21	
Tanaka et al., 1982 [62]	Hippocampus	Cat	17–45 minutes	Two to four days	Small doses	
Tanaka et al., 1982 [62]	Hippocampus	Cat	Approximately 10.8 days	Approximately 21.6 days	Large doses	Both amygdalas and piriform cortex
Schwarcz and Coyle, 1977 [69]	Striatum	Rat	Six to eight hours	Three to five days	Silent period on days 1 and 2	
Schwob et al., 1980 [70]	Striatum	Rat				Cortex overlying striatum
Zaczek et al., 1980 [71]	Striatum	Rat				
Pisa et al., 1980 [72]	Striatum	Rat	Immediate	Four to five days	Clonic jerking	Piriform cortex, hippocampus, frontal cortex

TABLE 2—*continued*

Study	Region or Method of KA Administration	Species	Latency to First Seizure	Last Observed Seizure	Comments	Locations of Distant Lesions
Pisa et al., 1980 [72]	Striatum	Rat		35–77 days	Generalized seizures	Piriform cortex, hippocampus, frontal cortex
Ruth, 1982 [68]	Striatum	Rat			Iontophoretically applied	Hippocampi are not damaged. Damage found in substantia nigra, ventral thalamus, pars reticulata.
Schwob et al., 1980 [70]	Intracerebral	Rat				Widespread distant damage
Schwarcz and Coyle, 1977 [69]	Substantia nigra	Rat	Immediate	Five days		
Schwob et al., 1980 [70]	Intravenously	Rat	30–90 minutes			Olfactory cortex, amygdala, thalamus, hippocampus, neocortical regions
Lothman and Collins, 1981 [80]	Intravenously	Rat		One to two hours	Limbic seizures	
Lothman et al., 1981 [77]	Intravenously	Rat			Limbic seizures	
Tremblay et al., 1984 [78]	Intravenously	Rat			Limbic seizures	
Nitecka et al., 1984 [79]	Intravenously	Rat				
Olney et al., 1974 [75]	Subcutaneously	Mice	15 minutes	Two to three hours		Arcuate nucleus and hypothalamus
Olney et al., 1979 [73]	Subcutaneously	Rat				Hippocampus
Sperk et al., 1983 [74]	Subcutaneously	Rat	Five minutes, 15–30 minutes, two hours	Five hours	Staring. Myoclonic twitching. Tonic-clonic seizures	Amygdala, piriform and entorhinal cortices, olfactory areas

TABLE 2—*continued*

Study	Region or Method of KA Administration	Species	Latency to First Seizure	Last Observed Seizure	Comments	Locations of Distant Lesions
Nadler et al., 1978 [81]	Intravenously	Rat				Hippocampus
Ben-Ari et al., 1980 [56]	Intravenously	Rat			Seizures	Pyriform cortex, claustrum, hippocampus, contralateral cortex

[62,65]. The pathological, clinical, and electrographic characteristics of the resulting seizure syndrome strongly resemble those seen in human temporal lobe epilepsy. However, the production of numerous lesions outside of the injection site, as well as the overly high susceptibility of temporal lobe structures, limit the use of the KA model.

THE ELECTRICAL KINDLING MODEL

In 1961, Delgado and Sevillano observed that repeated electrical stimulation of the cat hippocampus resulted in seizure activity [88]. In 1967 [16] and again in 1969 [89], Goddard et al. reported that the repeated administration of low levels of electrical current to subcortical regions in rats, cats, and rhesus monkeys resulted in localized seizure discharges, automatisms, and, eventually, clonic convulsions. He coined the term "kindling" to refer to the aforementioned phenomenon [89]. "Kindling" may be defined as "the phenomenon whereby repeated administration of an initially subconvulsive electrical or chemical stimulus results in progressive intensification of seizure activity, culminating in a generalized seizure" [88]. In the past several decades, a multitude of papers have been published on the kindling technique, as it is probably the most widely employed experimental model of chronic focal epilepsy in use today. Table 3 provides the reader with a representative list of electrical kindling technique studies conducted in the past twenty-five years [16,89–107]. Some of the advantages of this technique are as follows. The kindling technique may be employed on a wide variety of species, including frog [97,98], lizard [102,103], rat [90,91,105], mouse [96], rabbit [92], dog [101,104], cat [93,100], rhesus monkey [89], and baboon [94,99]. In addition, kindling does not produce destructive pathologies such as those associated with most other experimental models [108]. Rather, it has been suggested that kindling may be associated only with the structural modification of pre-existing synapses [109]. Finally, the kindling technique is applicable to numerous cortical regions [109].

Despite the advantages offered by the kindling technique, there are a number of problems associated with it. First, there seems to be a hierarchy of sensitivity in various brain sites to the kindling technique. The amygdala and globus pallidus appear to be the most sensitive structures, while the hippocampus appears to be relatively less sensitive [89,95]. It may require as long as 8.5 weeks of daily electrical stimulation to kindle seizures in the rat hippocampus [95], 13 weeks to kindle seizures in the cat prefrontal cortex [100], 21 weeks to kindle seizures in the baboon mesial frontal cortex

TABLE 3
Representative Electrical Kindling Studies, 1967–1985

Study	Region of Brain	Species of Experimental Animal	Number of Experimental Animals	Time Elapsed Prior to First Tonic-Clonic Seizure	% of Animals Which Progressed Through All Stages of Kindling	Were Seizures Spontaneous?
Goddard, 1967 [16]	Amygdala, septal area caudate, putamen, globus pallidus	Rat	77	4–136 days	58	No
Goddard et al., 1969 [89]	Subcortical structures, dorsal cortex, entorhinal cortex, olfactory bulb	Rat	294	22–77 days		No
		Cat	Several	30–60 days		No
	Amygdala	Rhesus monkey	Six	Six months		No
Racine, 1972 [90]	Amygdala, hippocampus, mesencephalon, reticular formation	Rat	140			
Racine, 1972 [91]	Amygdala, hippocampus	Rat	56	5–65 days		No
Tanaka, 1972 [92]	Amygdala	Rabbit				
Wada et al., 1974 [93]	Amygdala	Cat	21	5–36 days	100	Sometimes
Wada et al., 1975 [94]	Amygdala	Baboon	Four		100	Yes
Burnham, 1976 [95]	Amygdala, septal region, hippocampus	Rat	80	6–60 days		No
Leech and McIntyre, 1976 [96]	Amygdala—piriform area	Mice	37			
Morrell and Tsuru, 1976 [97]	Hippocampus	Frog	60			Sometimes
Morrell et al., 1976 [98]	Hippocampus	Frog	60			Sometimes
Wada et al., 1976 [99]	Pre-frontal cortex	Baboon	Two	318 days in one animal		No
Wake and Wada, 1976 [100]	Amygdala	Cat	14	15–36 days	100	No
	Cortical regions	Cat	Eight	8–91 days	100	No
Wauquier et al., 1976 [101]	Amygdala, hippocampus	Dog				

TABLE 3—*continued*

Study	Region of Brain	Species of Experimental Animal	Number of Experimental Animals	Time Elapsed Prior to First Tonic-Clonic Seizure	% of Animals Which Progressed Through All Stages of Kindling	Were Seizures Spontaneous?
Rial and Gonzalez, 1977 [102]	Telencephalon	Lizard				
Rial and Gonzalez, 1978 [103]	Dorsal telencephalic cortex	Lizard	80	17 days		No
Wauquier et al., 1979 [104]	Amygdala	Dog	Eight	2–14 days	100	Sometimes
Le Gal La Salle, 1981 [105]	Amygdala	Rat	83	15–45 days	97	No
Araki et al., 1983 [106]	Amygdala, frontal cortex, reticular formation, hippocampus	Rat				No
Wada et al., 1985 [107]	Mesial frontal cortex	Monkey	Six	62–147	50	Sometimes
	Orbital cortex	Monkey	Three		0	No

[107], and 45.5 weeks to kindle seizures in the baboon prefrontal cortex [99]. It has also been suggested that kindling becomes increasingly difficult in phylogenetically more advanced experimental animals. It is unclear whether this is a problem inherent in either of the aforementioned models.

Second, while the kindling technique may induce recurrent focal seizures, these seizures are not consistently spontaneous. Often, they must be triggered by electrical stimulation [99,107]. In addition, it is frequently observed that all animals placed under identical experimental conditions do not fully progress through all five stages of kindling. More important, numerous animals fail to develop any seizure activity [16,107].

THE TETANUS TOXIN MODEL

Tetanus toxin is a potent neurotoxin-protein which is produced by the gram-positive bacillus *Clostridium tetani* [110]. After binding to the gangliosides GD1b and GT1b [111], the toxin is transported up axons in a retrograde fashion [112] until it reaches the synapses, where it seems to act by blocking the presynaptic release of inhibitory neurotransmitters, especially GABA and glycine [112,113].

Tetanus toxin was first used to create chronic epileptiform events in 1962 [114], when Carrea and Lanari applied it to the cerebral cortex of 63 dogs. The toxin induced epileptogenic foci which were present for up to two months [114]. Mellanby and George write that "because of its potency, its large molecular size and the fact that it is rapidly bound to receptors, tetanus toxin would appear to be an ideal agent for

TABLE 4
Major Tetanus Toxin Model Studies, 1962–Present

Study	Region of Brain	Species of Experimental Animal	Number of Experimental Animals	Time Elapsed Prior to Onset of First Seizure	Last Observed Seizure	Size of Lesion
Carrea and Lanari, 1962 [114]	Cerebral cortex	Dog	63	Two to seven days, 34 animals	Two months	Small
Brooks and Asanuma, 1962 [115]	Motor cortex	Cat		Two to six hours		
Glaser and Yu, 1977 [116]	Dorsal hippocampus	Cat		Two hours	26 hours	
Mellanby et al., 1977 [117]	Hippocampus	Rat		>7 days	Two months	Small
Mellanby and George, 1979 [110]	Hippocampus	Rat		Approximately three days	Five weeks	
McGeer et al., 1980 [118]	Substantia nigra and thalamus	Rat	>8	Immediately	Three to five days (death)	
McGeer et al., 1980 [118]	Caudate	Rat	>4	Three to five days	Ten days (death)	
McGeer et al., 1980 [118]	Hippocampus	Rat		None observed		
Darcey and Williamson, 1985 [121]	Hippocampus	Cat	Eight	Two to five weeks		

producing highly localized 'pharmacological lesions' after local injection into specified brain regions" [110]. Table 4 provides the reader with a list of the major studies involving the direct application of tetanus to the brain. Several points should be emphasized. First, despite the fact that tetanus toxin was first used 25 years ago to create epileptogenic foci in laboratory animals, the tetanus toxin model is still very much in its developmental stages and is utilized in few laboratories. Second, after the local application of tetanus toxin to the brains of experimental animals, there seems to be a relatively short latency period prior to the clinical and electrographic onset of chronic seizures. This latency period varies from several hours to several weeks [110,114–118]. Recently, we have observed the onset of spontaneous and recurrent focal seizures in the cat hippocampus, orbital frontal cortex, and motor cortex within two to three weeks. In addition, tetanus toxin induces seizure foci which may remain chronically active. Mellanby et al. have induced foci in the rat hippocampus which remain active for up to two months [117]. Epileptogenic foci in the cat hippocampus may remain active indefinitely [119].

Tetanus toxin appears to produce a relatively small lesion [117]. Our own observations of the lesions produced in the cat hippocampus confirm that the lesions are relatively small areas of necrosis and reactive gliosis. In addition, the lesions are well confined [117]. A study by Mellanby et al. using small amounts of radioactively labeled tetanus toxin indicated that the toxin remains confined to the site of injection

TABLE 5
A Comparison of Four Experimental Models of Chronic Epilepsy

Characteristic of Particular Model	Alumina Model	Kainate Model	Kindling Model	Tetanus Toxin Model
Short latency period prior to onset of first seizure	No	Yes	No	Yes
Creates a small lesion	*No*	*No*	Yes	Yes
Creates a confined lesion	Yes	*No*	Yes	Yes
Applicable to numerous telencephalic regions	Yes	Yes	Yes	Yes
Equally applicable to different regions	No	No	No	Yes
Produces a chronic focus	Yes	Yes	Yes	Yes
May be employed on a wide variety of species (Number of species which have successfully developed epileptogenic foci)	No (3–4)	No (4)	Yes (9)	Untested (3)
Seizures are always spontaneous	Yes	Yes	No	Yes

Entries in italics imply that the particular characteristic which is not present is important.

(i.e., the hippocampus) [120]. Our own observations of H and E and cresyl violet stained cat hippocampi confirm that the lesion is well confined.

In addition, tetanus toxin is applicable to numerous telencephalic regions, as evidenced by its successful application to the hippocampus [110,116,117,121], substantia nigra [118], thalamus [118], caudate [118], orbital frontal cortex [119], cerebral cortex (region unspecified) [114], and motor cortex [115]. It also seems that many of the aforementioned regions are equally sensitive to the effects of tetanus toxin. For example, we have observed that similar doses of tetanus toxin are required to induce epileptogenic foci in the cat hippocampus, orbital frontal cortex, and motor cortex.

It should be emphasized that the amount of experience with tetanus toxin is relatively limited compared to the other models and that additional work must be conducted in order to better define the model. For example, the toxin has not been applied to very many species. In addition, the optimal schedule of toxin adminsitration has not been established, and the histopathological changes are not well documented. Despite these drawbacks, it is apparent that when tetanus toxin is applied to different regions of the brain in various experimental animals, it induces a chronic epileptogenic focus in a relatively short time. These features make it an attractive and potentially superior experimental model of focal epilepsy.

DISCUSSION

We have reviewed four chronic experimental models of focal epilepsy. Table 5 combines much of the data in a more compact form. We would like to emphasize a number of points. First, it is quite apparent that both the alumina model and the kainate model are associated with drawbacks (see italicized entries in Table 5). With alumina gel, the precise extent of the lesion is difficult to control, which is problematic for studies requiring a very discrete anatomical focus. Kainate may create numerous secondary lesions in spite of great care in its initial application.

The kindling model is associated with fewer flaws than either the alumina or kainate

models. Probably for this reason, the kindling model is more widely used than either of these two models. Kindling does not always result in spontaneous seizures, however, and all regions of the brain are not equally susceptible to this technique.

In so far as it has been studied to date, the tetanus toxin model compares quite favorably with the kindling model and possesses a number of positive features which are not present in the kindling model, such as the short latency prior to onset of seizures, the consistent spontaneity of seizures, and the comparable applicability of the toxin to different telencephalic regions. In short, the tetanus toxin model seems to be an excellent model for the rapid and relatively non-destructive creation of spontaneous recurrent seizures in numerous pre-selected foci of the mammalian brain.

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