PERGAMON

Neuroscience and Biobehavioral Reviews 24 (2000) 763–775

NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS

www.elsevier.com/locate/neubiorev

Behaviors induced or disrupted by complex partial seizures

L.S. Leung*, J. Ma, R.S. McLachlan

Department of Physiology and Clinical Neurological Sciences, University of Western Ontario, London, Ont., Canada N6A 5A5

Abstract

We reviewed the neural mechanisms underlying some postictal behaviors that are induced or disrupted by temporal lobe seizures in humans and animals. It is proposed that the psychomotor behaviors and automatisms induced by temporal lobe seizures are mediated by the nucleus accumbens. A non-convulsive hippocampal afterdischarge in rats induced an increase in locomotor activity, which was suppressed by the injection of dopamine D_2 receptor antagonist in the nucleus accumbens, and blocked by inactivation of the medial septum. In contrast, a convulsive hippocampal or amygdala seizure induced behavioral hypoactivity, perhaps by the spread of the seizure into the frontal cortex and opiate-mediated postictal depression. Mechanisms underlying postictal psychosis, memory disruption and other long-term behavioral alterations after temporal lobe seizures, are discussed. In conclusion, many of the changes of postictal behaviors observed after temporal lobe seizures in humans may be found in animals, and the basis of the behavioral change may be explained as a change in neural processing in the temporal lobe and the connecting subcortical structures.

Keywords: Temporal lobe; Automatism; Psychosis; Postictal behavior; Dopamine; Hippocampus; Amygdala; Nucleus accumbens; Gamma rhythm; Medial septum; Memory; Medial frontal cortex

1. Behavioral alterations following seizures

Behavioral alteration is a symptom of an epileptic seizure. During a convulsive seizure, clonic and tonic contractions of different musculature are observed. In absence seizure, a brief loss of awareness is detected. Auras that precede a focal seizure have been given particular emphasis in the hope of locating the origin of the seizure in the brain. In contrast, there has been little discussion in the literature about the behavioral alterations after a seizure [45]. Thus, it is not surprising that the neural mechanisms underlying the behavioral alterations after seizures are mainly unknown.

In this paper, we will review some of the behaviors that follow seizures (postictal behaviors), focusing on complex partial seizures that induce particularly debilitating behaviors. A complex partial seizure originates focally or locally in the brain ("partial") and results in a decrease or loss of awareness ("complex"). First, we will review briefly the behaviors observed after temporal lobe seizures in humans. Then, we will review the postictal behaviors observed after experimental seizures in animals. We will show that some postictal behaviors in animals, which may be analogous to those in humans, are mediated by the medial septum-hippocampus-nucleus accumbens pathway and others by a amygdala-hypothalamus pathway.

1.1. Postictal behaviors following temporal lobe seizures in humans

Epilepsy affects up to 0.8% of the population [73]. About 25% of epilepsy patients suffer from complex partial seizures of temporal lobe origin. The latter seizures are particularly intractable to anticonvulsant treatment [47].

Various types of alteration of postictal behavior, of different durations, may follow a complex partial seizure of temporal lobe origin (Table 1). A typical behavior is automatism, the performance of non-reflex movements without conscious volition [59,126], which usually lasts for several minutes. Automatisms take various forms such as chewing, swallowing or lip smacking (oral automatisms), rubbing or picking movements of the hands, and walking or running (ambulatory automatisms). They can be quite dramatic and potentially dangerous when patients exhibit an impulsive tendency to wander (poriomania), at times out of the house or into the street [112]. Such patients often actively resist attempts to restrain them by pushing, grimacing with an angry expression or even hitting (reactive automatisms). Some automatisms are lateralized and involve the upper limb of the side of seizure origin. For example, about 50% of patients with temporal lobe epilepsy exhibit

* Corresponding author. Tel.: +1-519-663-3733; fax: +1-519-661-3753.
E-mail address: sleung@julian.uwo.ca (L.S. Leung).

0149-7634/00/$ - see front matter
PII: S0149-7634(00)00035-X

Table 1
Suggested neural mechanisms underlying postictal behaviors induced by temporal lobe seizures

Behavioral symptoms	Duration (postictal)	Suggested mechanisms
Automatisms	Minutes	Increased dopaminergic function in nucleus accumbens
Hypoactivity	Minutes to hours	Opiate-mediated behavioral suppression
Drowsiness	Hours	Cortical mediated suppression of arousal mechanisms
Memory dysfunction	Minutes and hours	Postictal depression of neurons in the temporal lobe
Memory dysfunction	Days and weeks	Long-term changes in temporal lobe circuits
Altered emotional behaviors	Minutes and hours	Postictal depression of temporal cortical neurons
Altered emotional behaviors	Days and weeks	Long-term changes in limbic circuit, e.g. amygdala-hypothalamic pathway
Increased anxiety	Days and weeks	Amygdala/accumbens dysfunction
Altered social interactions	Days and weeks	Limbic system alteration
Postictal psychosis	Days to weeks	Nucleus accumbens/dopaminergic hyperfunction, perhaps with temporal lobe malfunction

postictal nose wiping with one hand, which reliably localizes the seizure to the ipsilateral temporal lobe in 97% of patients [102]. It is unlikely that, automatisms represent a spread of seizure to the frontal lobe, since these complex automatic movements do not resemble the more primitive tonic or clonic movements seen with frontal lobe seizures. We propose that automatisms may represent a subcortical spread of neural activity, e.g. to the nucleus accumbens (below).

Automatisms also occur during the ictal state and thus, postictal automatisms are often mistakenly described as part of the seizure when, in fact, they are occurring minutes after the paroxysmal, high-amplitude activity in the EEG has subsided. Only simultaneous recording of behavior and the EEG will distinguish ictal from postictal automatisms.

A less common behavior that can follow complex partial seizures is postictal psychosis [103], particularly when there is evidence of bilateral temporal lobe dysfunction [146]. The psychotic episodes often start several years after the onset of seizures [150,164]. Typically, after a "lucid interval" of 2–72 h following the seizure, the person develops delusions, paranoia and other symptoms of acute psychosis, often in association with agitation and an altered emotional state [111,146,150]. Symptoms resolve in a matter of days to weeks but usually require some type of antipsychotic drug treatment. There is some evidence suggesting that males with right temporal lobe epilepsy may be more prone to this disorder [111]. During the period of psychosis, the interictal scalp EEG may appear normal, thus the term "forced" or "paradoxical normalization" of the EEG [91,171].

Focal ictal activity may result in postictal symptoms by disrupting the brain area where the seizure occurred. Through this mechanism, an impairment in recent memory immediately following a mesial temporal lobe seizure is expected [70,132]. Memory deficit (amnesia) generally lasts a few minutes, and it is characterized by an inability to recall events that occurred minutes to a few hours before the seizure (retrograde amnesia). Acquisition of new information may also be impaired during and after the seizure (anterograde amnesia), particularly if the seizure arises from the language-dominant left side. Left temporal lobe seizures are also associated with postictal dysphasia or difficulty in processing language, most commonly in the form of word-finding difficulty, which can last up to 30 min. Postictal cognitive alterations typically correlate with a period of suppression and slowing of the EEG, which is maximal in the temporal lobe from which the seizure originates.

Postictal confusion is another common behavior following many types of seizures. Following seizures, confusion can be difficult to distinguish from memory impairment, speech dysfunction and emotional lability. Postictal confusion is typically accompanied by a diffuse and widespread change in the EEG. A focal seizure is less likely to induce a confusional state, unless it becomes secondarily generalized as a tonic clonic seizure. On the other hand, lethargy and hypomobility can appear after either focal or generalized seizure. These symptoms may reflect the depressed function of the neocortex after seizures, or they may result from the spread of seizures to the thalamus, basal forebrain and the reticular activating system in the brainstem (below).

Long-term deficits (duration of weeks) in memory after seizures are difficult to document, but they have been reported by Halgren et al. [72]. Many patients with complex partial epilepsy of temporal origin have a chronic impairment of memory mechanisms [161]. The latter is usually labelled as an interictal deficit, but in part, it may be caused by seizures, i.e. a prolonged postictal disruption of memory. This could explain why patients describe an improvement in their memory if their complex partial seizures have been controlled for several months.

Altered emotional behavior is common following temporal lobe seizures. This usually occurs as depression with a flat affect or anxiety and associated agitation lasting minutes to hours. Chronic emotional disturbances will develop in a substantial number of people with temporal lobe epilepsy. Actual postictal aggression or violence can occur but this is rare and appears usually in reaction to a

stimulus, such as a relative trying to calm the individual [56]. Similarly, Gloor [60] concluded that temporal lobe seizure discharge rarely "induced a well-directed and coordinated aggressive act against another human being" but "reactive defensive behavior" may be quite common "during the postictal confusional state—when well-meaning people interfere with the patient's freedom of action".

2. Approaches to the study of behavioral alterations in animals

Study of experimental seizures in animals offers the possibility of revealing the mechanisms underlying the behaviors in humans after temporal lobe seizures. Studies of postictal behavior in epileptic patients are complicated by the presence of pathological and other conditions that are associated with the seizures, such as mesial temporal lobe sclerosis, infectious disease or traumatic brain damage. Also, postictal and interictal consequences may be difficult to distinguish in patients. Most difficult of all are the neurobiological bases of behavioral alteration in humans cannot be fully studied by experimental manipulations for ethical reasons. Thus, studies in animals are essential.

Most of the animal literature reviewed is derived from the kindling model of seizures. Kindling is defined to be the process whereby repeated (electrical or chemical) elicitation of afterdischarges (ADs) in the brain, results in a progression of clinical signs of epilepsy including generalized seizures [62,117,139]. This definition of kindling emphasizes the development of generalized seizures. It has been argued that human complex partial seizures do not result in kindling, or the development of a secondary epileptic focus [48,63,124]. In another view, kindling is regarded as a model of seizures that progressively induces long-lasting changes in the brain. Some of these changes may relate to the generation of seizures, while others may relate to changes in neural circuits that mediate behavior.

There appears to be good correspondence between animals and humans on the manifestation of seizures and behavior, using kindling of the amygdala and hippocampus as a model of seizures of temporal lobe origin. In terms of electrophysiology, the phenomena of ictus, postictal neural depression and interictal spikes are common between kindled animals and epileptic patients [117]. It is inferred that both animal and human seizures may involve local and distant, transynaptic changes [49]. At a finer level, similar changes in paired-pulse responses have been found in the rat hippocampus after kindling [101] and in the presumed epileptogenic human hippocampus [169]. The basic mechanisms underlying cortical circuitry and synaptic plasticity are common across laboratory animals and humans. In terms of behavioral changes induced by kindled seizures in animals, some have emphasized the long-term changes that may be induced by both animal and human seizures [2,5,138,155]. Part of the similarities between animals and humans, lie in the common neuro-anatomical connections of the so-called limbic structures, which are present in all mammals [110].

We may use a quasi-theoretical approach to study the behavioral consequences of experimental seizures. This approach is based on the knowledge of neuro-anatomy, seizure spread and localization of functions in the brain. We expect that, the seizure will spread from one area to other areas in the brain by means of known neuro-anatomical pathways. Then, if we know the behavioral functions of the brain areas involved, specific disturbance in behavioral functions may be hypothesized.

In the following, we will review briefly the fundamentals of temporal lobe seizure and behavior, which includes neuro-anatomy, seizure physiology and behavioral functions. Only two structures in the temporal lobe, the hippocampus and the amygdala will be emphasized, since these are the most epileptogenic areas in the temporal lobe in humans [47,59].

2.1. Neuro-anatomical connections of the hippocampus and amygdala

The hippocampus receives highly processed sensory signals from the association neocortices (Fig. 1; see Refs. [8,104,160] for a detailed review). These signals funnel through the perirhinal and postrhinal cortices into the entorhinal cortex. The entorhinal cortex excites a multisynaptic pathway in the hippocampus through the perforant path, involving the dentate gyrus, CA3, CA1 and subiculum [9,104]. CA1 and subiculum in turn, project back to the entorhinal cortex, completing a closed loop. The strong excitatory characteristics of this hippocampus–entorhinal cortex circuit, is in all likelihood a critical factor in its seizure susceptibility. A large projection from the perirhinal cortex to the frontal cortex [27,116], may play a role in secondary generalization (convulsion) induced by temporal lobe seizure. The perirhinal area has also been focused as critical for object recognition memory in monkeys [119,153]. The hippocampus projects to the subcortical areas through the fimbria-fornix [104]. Among the targets are the lateral septal nucleus, the nucleus accumbens and parts of the hypothalamus [8,104,160].

In addition to the neocortical association cortices, the amygdala also receives inputs from the olfactory cortex [10]. The amygdala is directly connected to the temporal hippocampus and indirectly connected to all septotemporal levels of the hippocampus via the entorhinal cortex and subiculum [90,136]. The outputs of the amygdala are directed towards many areas of the brain. The basolateral nucleus of the amygdala projects to the medial and orbital surfaces of the frontal cortex [89]. The lateral nuclei have more prominent reciprocal connections to the perirhinal and insular cortices. Subcortically, the amygdala complex projects

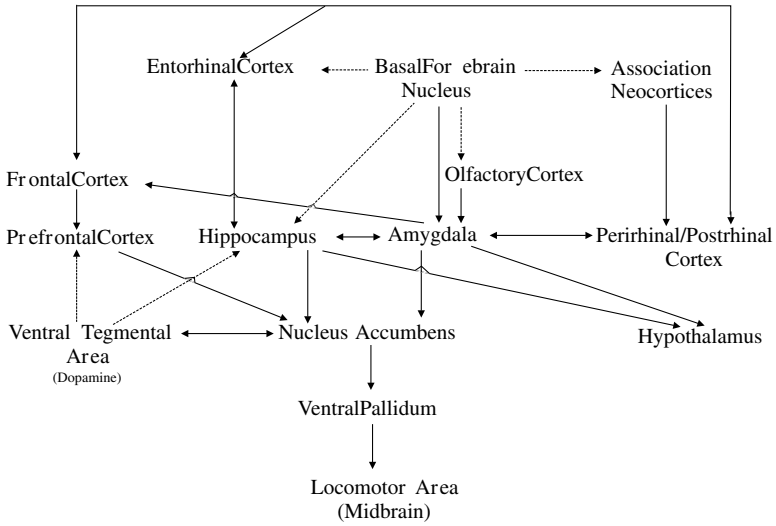

Fig. 1. Schematic diagram of the main connections of the limbic structures, which may be important to mediate behaviors. Solid lines mainly indicate excitatory projections. Dotted lines indicate modulation by basal forebrain nucleus (medial septum, basal nucleus of Meynert) and ventral tegmental area. A reciprocal connection is indicated by arrowheads at both ends of a connection, e.g., between frontal cortex and perirhinal/postrhinal cortex.

to the mediodorsal thalamus, nucleus accumbens, substantia innominata, many parts of the hypothalamus and a few nuclei in the brainstem [10]. The amygdala projection to the hypothalamus and brainstem may serve to mediate endocrine and autonomic functions.

Cholinergic and GABAergic afferents from the basal forebrain, which are known to mediate an arousal pattern in the EEG [54,166], project to both the hippocampus and the amygdala. The hippocampal and entorhinal afferents are derived from the medial septum and the diagonal band of Broca [104], while the amygdala and temporal neocortex afferents are derived from substantia innominata and the basal nucleus of Meynert [10].

2.2. Seizure generation and spread

The balance between excitation and inhibition has long been proposed as a central concept in the generation of seizures. We may emphasize that this interaction between excitation and inhibition is dynamic, and in a dynamical system, instability (or seizure) may result from transient changes of either excitation or inhibition. In partial seizures, paroxysmal activity is presumed to arise locally and then spread to other parts of the brain.

Different types of inhibitory interneurons, using gamma-amino-butyric acid (GABA) as the neurotransmitter, control the excitability of the soma and the dendrites of hippocampal pyramidal cells [54]. These inhibitory interneurons are, in all likelihood, tonically active in the brain and a loss of inhibition will increase seizure susceptibility.

Recurrent excitation among principal neurons may play a role in generating paroxysmal discharges, which may initiate a seizure [163]. Neurons or circuits that generate rhythmic activity may act to synchronize normal and paroxysmal activity [36,47,149]. In addition, transient changes in the brain may determine whether seizures are generated. These transient changes include short-term neuronal plasticity [179] such as presynaptic facilitation, frequency potentiation/depression [41], local accumulation of ions and neurotransmitters, and activity-dependent loss of inhibition [16,43,121].

Seizures spread through the brain by means of existing neuro-anatomical connections. A seizure in the temporal lobe may spread to other brain structures through the excitatory projections of the pyramidal cells. It is, however, possible that seizures may spread by means of devious routes, using mechanisms different from those during normal transmission. The universality or importance of these abnormal routes of neural transmission in the spread of seizures, in vivo, is not known. In some models of seizures, axon terminals are depolarized by the high K^+ concentration in the extracellular medium (resulting from K^+ efflux during a seizure), such that an action potential starts at the axon terminal and propagates back to the soma [69]. Back propagating action potentials, will spread the seizure in the opposite direction of the normal signal flow. In in vitro models of seizures, it has been shown that seizure may spread through the hippocampus by non-synaptic means, probably through electrical and/or gap junctions [134], or by changes in the chemical medium [81] surrounding the neurons and glial cells.

2.3. Cell loss after seizures

Temporal lobe sclerosis is a feature of human temporal lobe epilepsy [8,26]. In particular, principal cells in CA3, CA1 and the dentate gyrus are lost. Loss of entorhinal neurons, in particular those in layer III, and of amygdala

neurons have also been documented. Similar findings have been found after repeated seizures in animals, like extended kindling to more than 30 generalized seizures [34] or seizures induced by kainic acid or pilocarpine. Axonal sprouting may accompany neuronal cell death. More notably, mossy fiber sprouting has been found after both human and animal seizures [35]. Seizures in human apparently do not kill many GABAergic interneurons [12] although animal literature indicate that the GABAergic interneurons may be functionally dormant [15,151].

It seems apparent that, neuronal cell death would contribute to the behavioral disruptions after seizures. However, the brain may undergo functional reorganization after neuronal cell loss, which may compensate for possible behavioral disruptions. Cell loss or other neuropathology is only one manifestation of neural plasticity. Physiological, biochemical and molecular biological studies indicate that many functions of the brain may change after seizures, which are not detected by morphological studies at the light microscopic level.

2.4. Synaptic transmission changes after seizure

Long-term potentiation (LTP) is a persistent enhancement of synaptic transmission, after repeated activity of a synaptic pathway [22]. The flip side of LTP is long-term depression [11,14,30], a persistent decrease in synaptic transmission. LTP or LTD is mediated by a Ca^{2+} influx into neurons [11,14,22]. Ca^{2+} may flow through N-methyl-D-aspartate (NMDA) receptors, non-NMDA glutamate receptors and voltage-dependent Ca^{2+} channels. Ca^{2+} may also be released from internal stores of the neurons.

Seizure activity is a type of repeated neural activity, and it has been suggested to induce LTP [28,117,140]. Typically, the same stimulating electrode was used to deliver tetanic stimulation, which induced seizures, and then to test for LTP. Thus, the LTP observed may have resulted from the initial tetanic stimulation and not from the seizure (AD) subsequently evoked. In stimulation of afferents to CA1, we observed that tetanus of a low intensity evoked LTP of 60% (increase from baseline) at 2 h after tetanus [97]. A higher tetanic intensity evoked an AD averaging 28 s, followed by about 5 min depression of synaptic transmission, and then 20% LTP at 2 h after tetanus. We inferred that, a long (>15 s) AD suppressed LTP [97]. However, it is possible that the amount and the channel of Ca^{2+} influx may determine the degree of LTP and LTD [97]. Postictal depression of synaptic responses may depend additionally on the extracellular K^+ concentration [24,152], or activation of a type of K^+ channel [6].

2.5. Behavioral functions mediated by the hippocampus

One function commonly ascribed to the hippocampus in humans is memory [120,153]. The hippocampus is also shown to be important in memory functions in animals, although different researchers emphasize different aspects of the memory, such as context-dependent, configural, spatial or working memory [128,131]. In one view, the hippocampus is responsible for the acquisition of new memory but not for storing old memory [153]. The properties of LTP, such as input-specificity, associativity and persistence, are consistent with a role of LTP as a cellular correlate of memory [22]. However, whether a disruption of hippocampal LTP affects memory is being disputed [13,125,144].

Another function that has been ascribed to the hippocampus is sensorimotor integration [19]. Since memory of sensory events and their contexts is necessary for adaptive motor behaviors, it may be argued that sensorimotor integration is a part of "memory". In most animals, motor or locomotor activity serves to procure food and water, to avoid predation and to reproduce successfully.

In part, the participation of the hippocampus in voluntary movements stems from the initial observation that the hippocampal theta rhythm of 4–12 Hz was correlated with voluntary movements of the rat [166]. The medial septal area drives the hippocampal theta rhythm [19,20,135] through cholinergic and GABAergic afferents [54]. In addition, voluntary movements are associated with desynchronization (reduction of amplitude of irregular slow EEG of <20 Hz) and enhanced gamma (fast) activity of 30–100 Hz [94]. The behavioral-dependent desynchronization, theta and gamma waves all require the integrity of the medial septum [94]. Gamma waves are, in all likelihood, mediated by intrinsic circuits within the hippocampus [23,82,94].

The importance of the septohippocampal system in locomotor activity has been confirmed by the recent work of Oddie et al. [129]. Stimulation of the posterior hypothalamus, evoked locomotor activity in rats, which could be blocked by inactivation of the medial septum with procaine [129]. In our laboratory, we observed that the inactivation of the medial septum blocked spontaneous, self-initiated locomotor behaviors, but the rat could walk, jump and attack if provoked [107].

2.6. The nucleus accumbens and mesolimbic dopaminergic system mediates behaviors

The nucleus accumbens is a major focus of this review. Also known as the ventral striatum, the nucleus accumbens has a major role in movement, similar to that of the dorsal striatum (caudate-putamen). In contrast to the dorsal striatum, which receives inputs from the motor and other neocortex, the ventral striatum receives inputs from the limbic cortex, including the hippocampus, entorhinal cortex, amygdala and medial prefrontal cortex (Fig. 1; [7,68,75,83]). In addition, the nucleus accumbens receives dopaminergic afferents from the ventral tegmental area (VTA). The nucleus accumbens projects massively to the ventral pallidum through a GABAergic pathway, the pallidum to the mesencephalic locomotor region and subpallidum through another mainly GABAergic pathway [67,123]. Mogenson et al. [122,123]

proposed that the nucleus accumbens serves as an interface, to convert motivational signals from the limbic cortex to action/ movement.

The physiological mechanisms, whereby behavior is mediated by the nucleus accumbens are not known for certain [123,133]. Presumably, both glutamatergic excitation of accumbens neurons and a release of dopamine in the nucleus accumbens [18,52] are necessary for an increase in locomotor behavior [25,123,174]. The main action of dopamine may be to mediate the presynaptic inhibition of glutamatergic terminals [173,175,176], in part by acting on D_2 receptors in behaving rats [108,123]. Presynaptic inhibition of GABAergic or dopamine (autoreceptor) terminals has also been documented, while a postsynaptic action of dopamine has rarely been reported [133]. However, it is difficult to account for the behavioral hyper or hypoactivity by massive excitation or inhibition of accumbens neurons; Pennartz et al. [133] speculated that different spatiotemporal firing patterns of the accumbens neurons may cause different behavioral activity.

The mesolimbic dopaminergic system consists of the structures connected with the dopaminergic neurons in the VTA, including the nucleus accumbens and other parts of the limbic system. The mesolimbic dopaminergic system has long been known to be associated with motivation and reward [51,65,83,88,123,170]. Recent literature suggests that, the mesolimbic dopaminergic system is active during a particular environmental stimulus or situation. The system is activated by an object or situation of "motivational" quality, independent of the reward [77,147,168]. Robinson and Berridge [143] proposed that, the nucleus accumbens actively assigns salience and attractiveness to a stimulus. Altered dopaminergic functions in the nucleus accumbens were found in animals that have been behaviorally sensitized with addictive drugs, such as amphetamine and cocaine [83,88,143].

Excessive mesolimbic dopamine activity, especially in the nucleus accumbens, has been proposed as the major derangement in schizophrenia [33]. Schizophrenia is a mental illness characterized by impoverished affect, nonsensical association, autistic behavior and ambivalence, delusions and hallucinations [21]. The psychotic symptoms are ameliorated by dopamine receptor antagonists. Some drugs that enhance dopamine activity, e.g. amphetamine and phencyclidine, induce clinical symptoms in normal humans similar to those in schizophrenia [79]. In addition to the dopaminergic neurons, recent studies emphasize the dysfunction of an integrated neural system in schizophrenia, and this neural system includes the hippocampus and the prefrontal cortex [64,66,74,106,127]. Functional studies suggest that the hippocampus is hyperactive and the frontal cortex hypoactive, in the resting state in schizophrenics [74].

2.6.1. Seizures and dopaminergic functions

Various studies indicate that a change in dopamine function contributes little to seizure susceptibility [38,154]. We propose that, the change in dopamine function contributes to psychomotor behaviors and postictal psychosis.

In experimental models of seizures, metabolic measures indicated that the nucleus accumbens and substantia nigra were activated following hippocampal seizures that induced behavioral convulsions [37,105]. When dentate gyrus stimulation induced a stage 3 seizure and hippocampal AD of 10–30 s duration [157], an increase in dopamine release in the nucleus accumbens was found for 20 min after the AD. We suggest that a non-convulsive hippocampal AD evoked by CA1 stimulation, of 15–30 s duration, would also induce dopamine release in the nucleus accumbens and activate locomotor behavior (below). An increase in the density and expression of D_2 receptors in the nucleus accumbens was found after hippocampal kindling [42,55]. These results indicate that a temporal lobe seizure propagates to the nucleus accumbens and enhances dopaminergic functions.

We showed recently that a single electrographic seizure or AD evoked from the hippocampus resulted in postictal hyperactivity [108]. The increase in postictal behaviors lasted more than 20 min [93] and was characterized by an increase in walking, rearing, face wash and wet-dog shakes. Local injection of a D_2, but not D_1, receptor antagonist in the nucleus accumbens suppressed the postictal increase in locomotion and rearing, without changing the duration of the hippocampal AD [108]. Infusion of a $GABA_A$ receptor agonist, muscimol, in the ventral pallidum also suppressed the postictal hyperactivity [108]. We [109] confirmed the earlier studies by Mogenson et al. [123], which showed that infusion of NMDA in the ventral hippocampus (subiculum) resulted in locomotor activity via the nucleus accumbens. In addition, we showed that hippocampal or subicular ADs were necessary for the induction of locomotor behavior by NMDA, and little hyperactivity was induced by electrical or chemical stimulations that did not evoke an AD [108,109].

Gamma waves in the hippocampus were enhanced tenfold during the postictal behavioral hyperactivity induced by a hippocampal AD [93]. Recently, we showed that inactivation of the medial septum with muscimol, suppressed both the AD-induced increase in hippocampal gamma waves and the locomotor behaviors [107]. Muscarinic cholinergic antagonists also blocked the AD-induced increase in gamma waves and the locomotor behavior increase [93], suggesting that inactivation of cholinergic afferents from the medial septum is sufficient to block the postictal gamma waves and behavioral hyperactivity.

The involvement of the medial septum in the mediation of locomotor behavior is a significant finding. It may appear surprising that a cholinergic (or GABAergic) input from the basal forebrain may mediate behavior. However, as reviewed above, the hippocampus serves an important role in sensorimotor functions, and the medial septum is the major determinant of hippocampal electrical activity. These two facts together suggest that medial

septum mediates adaptive locomotor behavior through the hippocampus.

2.7. Postictal behavioral depression after convulsive limbic seizures is mediated by opiates and frontal cortical activity

During the early stage of hippocampal kindling, a non-convulsive hippocampal AD induced postictal behavioral hyperactivity (above). However, as kindling progressed, a hippocampal AD would be accompanied by motor convulsions, followed by behavioral hypoactivity. This behavioral depression that followed a convulsive seizure has been well documented, following amygdala or hippocampal stimulation [46,53]. The behavioral depression was pronounced for minutes after the seizure [32], but it was observed up to 2 days [40]. Opiate antagonists were effective in alleviating postictal behavioral depression [32,40,46].

The transition of the postictal behavior from hyper to hypoactivity is, in all likelihood, triggered by generalized convulsions, typically stage 4 or 5 seizures of Racine [139]. The mechanisms underlying the change in postictal behavior are not clear. A possible explanation is that generalized seizures that involved the frontal/motor cortex may activate opiate receptors in the striatum (nucleus accumbens included) or VTA, which then mediate behavioral suppression. It is not clear whether dopamine is still released in the nucleus accumbens, following a limbic seizure followed by generalized convulsions.

In addition to opiates, adenosine released during an AD may also contribute to postictal depression of both the EEG and behavior [17]. Repeated seizures may also alter the function of neuropeptide Y [167], presynaptic $GABA_B$ autoreceptors [172] or metabotropic glutamate receptors [148]. Behavioral consequences of the latter changes in receptor function have not been studied.

2.7.1. Frontal cortex ADs induce behavioral immobility in rats

We have performed some recent experiments to clarify the role of the frontal cortex in postictal behavior. The preliminary results are consistent with the suggestion that limbic seizures invading into the frontal cortex would cause postictal behavioral depression. In these experiments, the medial frontal cortex was implanted with stimulating electrodes, and the behavior and EEG of the rat were observed, following a one-second stimulus train of 3–200 Hz of various intensities. Frontal cortex stimulations that were just below the AD threshold induced behavioral immobility for about 3 min. The immobility was accompanied by slow waves in the cortical and hippocampal EEG, and suppression of hippocampal gamma waves. The mechanism of suppression of EEG and behavior is not known yet. It is possible that the mesolimbic dopaminergic system is suppressed. In addition, activity of the basal forebrain neurons that desynchronizes the cortex [166] may be suppressed.

Frontal cortical AD was evoked at a relatively high threshold of 340 ^ 92 μA ($N = 6$) compared to a hippocampal AD threshold of 103 ^ 31 μA [109], using a one-second train of 200 Hz and 0.1 ms pulses. Short frontal cortical AD was followed by postictal slow EEG of <4 Hz and behavioral immobility. However, if the AD spread to the hippocampus [95], typically after 5–6 frontal cortical ADs, increased locomotor activity and increased hippocampal gamma waves were observed in all the rats. In summary, medial frontal ADs in rats induced brief bouts of immobility accompanied by slow EEG.

2.8. Dopaminergic functions affected by repeated seizures/VTA stimulations

Full kindling of the amygdala induced a long-lasting increase in stereotypic behaviors, induced by apomorphine or methamphetamine [2,138,145]. A single or repeated dose of amphetamine results in a persistent increase in dopaminergic function [143]. There seems to be cross-sensitization between amygdala kindling and amphetamine, in mediating behavior through the nucleus accumbens.

Repeated stimulations of the VTA, induced psychotic-like behaviors in cats [156] and rats [58]. The change in behavior may occur suddenly after repeated stimulation, and a “gentle, friendly” animal became “fearful and withdrawn and exhibited waxy flexibility, fixed posture, crouching, and hiding” for months after cessation of stimulation [156]. Glenthøj et al. [58] reported a decrease in male/male social interactions in the VTA-stimulated animals.

The significance of the VTA stimulation studies lies in the persistent change in psychotic behaviors, which may not relate to the rare seizure or AD induced by VTA stimulation [58,156]. However, VTA may be activated transynaptically by each temporal lobe seizure via the nucleus accumbens and the ventral pallidum [83]. Based on the results in animals, it may be speculated that the development of postictal psychosis in patients (reviewed above) may require VTA sensitization and perhaps the expression of increased dopaminergic receptors in the nucleus accumbens [42]. However, imaging studies in humans revealed a decrease in D_2 receptor binding in the striatum of epileptic patients with peri-ictal psychosis, as compared to those without psychosis [141]. Thus, whether and how dopaminergic hyperfunction underlies postictal psychosis in patients remains to be studied.

2.9. Long-lasting changes in emotional behaviors after seizures

Changes in heart rate, blood pressure, fear and aggression can be elicited by amygdala stimulations in animals [86]. Fear is the most common effect produced during a temporal lobe seizure, and it can also be induced by stimulation of the human amygdala without inducing ADs [60,61]. Thus, postictal changes in emotional behaviors after temporal lobe seizures may be expected.

McInytre and Molino [113] reported a persistent change in conditioned emotional response after amygdala kindling. Conditioned emotional response depends on the integrity of the amygdala, in particular the central nucleus of the amygdala in rats [92]. Pinel and associates [84,137] documented a persistent increase in emotional behaviors in rats after amygdala kindling. The kindled rats resisted capture by an experimenter in the open field, and this behavioral effect persisted at least for one month after 99 amygdala-kindled seizures [137]. Pinel et al. [137] concluded that the kindling-induced emotional behaviors were mostly defensive rather than aggressive in nature. A similar conclusion was made of human behavior after partial complex seizures (above). Adamec [1,3] documented an increase in defensiveness in cats after partial kindling of the amygdala or ventral hippocampus. These behavioral changes lasted from several weeks to several months, and were correlated with the LTP of the amygdala-ventral medial hypothalamic pathway [3]. An increase in anxiety after stimulation of selected nuclei of the amygdala is reported in rats [4,76]. In part, a change in dopaminergic function in the nucleus accumbens has been suggested as contributing to the anxiogenic symptoms [4].

Physiological studies revealed several long-lasting changes within the amygdala in vitro after amygdala kindling, such as a loss in inhibition and changes in metabotropic glutamate receptor functions [148]. How these physiological changes may affect behavioral functions of the amygdala are not known.

2.10. Memory changes after repeated seizures in animals

Immediately after a seizure, the memory function of an animal is clearly compromised. Olton and Wolf [130] demonstrated that rats were deficient in completing a task on a radial arm maze (RAM) when the rat was given a hippocampal AD in the middle of the task. It was suggested that hippocampal seizure would erase a memory trace, established several hours before the seizure [87]. Acquisition of a spatial task on the RAM or Morris water maze was disrupted within 1 h after an AD evoked by stimulation of the hippocampus [29,118,142], septum or amygdala [39,118]. The strong gradient of retrograde amnesia (for several hours) and anterograde amnesia/confusion (within an hour) associated with a seizure are also found in humans (above).

The long-term effects of hippocampal seizures on spatial memory are relatively mild, if the neuronal damage is minimal [101]. It appears that seizures affect the retention of information learned before the seizures more than the acquisition of new information. Retention deficits on the RAM, in both reference and working memory [131], were found after full kindling (5 stage five seizures) [98] or partial kindling of the hippocampus [96,98–100], if the RAM task was learned before kindling. The retention deficits persisted for 3–4 weeks, but not 6 weeks after hippocampal kindling [50,100]. No retention deficit was found for a RAM that emphasized non-spatial cues, such as local cues on the arms [99]. This is in accordance with the notion that the hippocampus is more important in processing spatial (place) than non-spatial (local cue) information [80]. Since the spatial and non-spatial RAMs are similar except for the cues, non-specific factors such as motivational, affective and motor disruptions do not readily account for the differences between kindled and control rats.

Acquisition of spatial information may be affected for days and weeks after hippocampal kindled seizures. However, the deficits were subtle, and they were not revealed in the acquisition of a spatial RAM after full kindling of the perforant path [142], or partial kindling of hippocampal CA1 [99], or in the standard Morris water maze [57,78,118,158]. The only exception is that Corcoran and associates [39,57] reported acquisition deficits after full kindling of CA1. However, if the hidden platform was moved daily to a new location in the Morris water maze, partially kindled rats acquired the task more slowly than control rats at 1 week, but not 1 month after kindling [158]. It was suggested that spatial information processing in kindled rats may be more labile and subjected to interference by past experience and ambiguous cues [158].

Even after extended seizures, which induced hippocampal cell loss and mossy fiber sprouting [34,35,159], acquisition of a spatial task was only mildly disrupted. Cammisuli et al. [31] found that rats given extended kindling of the amygdala or perforant path (300 ADs in each group) showed only transient acquisition deficits on the Morris water maze. In another study [159], a difficulty in maintaining criterion performance on a spatial RAM task was reported. The latter rats were given >30 stage 5 (generalized) seizures by stimulation of the olfactory bulb [159]. The kindled rats did not differ from control rats in the number of trials to reach the first criterion on the RAM (four correct arms in five choices), but they required more trials than control rats to reach 4 consecutive days of criterion performance [159]. Although it was claimed that mossy fiber sprouting may be related to the difficulty in maintaining criterion [159], the behavioral significance of reliable day-to-day performance is unclear. Whether it is an acquisition, retention or non-specific deficit, such as motivation ability and hyperactivity, is not clear.

McIntyre and Reichert [114] introduced the concept of state-dependent learning in seized animals, based on the normal and the postictal states of a rat. The postictal state was that which immediately (presumably within minutes) follows bilateral ADs in the amygdala [114] or AD in the hippocampus [115]. State-dependent learning accounts for the fact that performance of a trained response, or memory retrieval, only occurs in the state that the response was learned. McInytre and associates confirmed the latter prediction for the postictal and the normal states [114,115].

State-dependent performance may also be relevant at long times after seizures. As described above, the long-lasting

seizure-induced deficit is mainly one of retrieval and not acquisition, which is consistent with state-dependent learning if we assume that the brain is different for days or weeks after repeated seizures. There is ample evidence of alterations in the brain after seizures. In the partial hippocampal kindling model, the alterations include an increase in synaptic transmission (LTP) of the medial perforant path to dentate gyrus synapses and of the CA3 to CA1 synapses [96,101]; increased paired-pulse inhibition in the dentate gyrus [44,85,165,178] but decreased paired-pulse inhibition in CA1 [85,172,177]; and a different pattern of $GABA_A$ receptor binding [162]. The change in strength of individual synapses (LTP) was relatively weak (<10% at weeks after kindling) and may represent only a small component of the system change after kindling. It has been suggested that the duration of change in physiology may parallel the change in spatial RAM performance [100,101]. The recovery of RAM performance in 6 weeks after kindling may be temporally related to the normalization of physiological alterations [100,101].

3. Conclusions

We have reviewed some of the literature on postictal behaviors in animals, and suggested possible neurobiological bases for these behaviors (Table 1). The same neural mechanisms may underlie the postictal behaviors after human complex partial seizures, but these need to be further investigated. While specific structures are proposed as the cause of some postictal behaviors (Table 1), absolute localization of function in the temporal lobe or limbic system is not possible for technical and conceptual reasons (see e.g. Ref. [71]).

There may be differences between the neurobiological mechanisms underlying the postictal behaviors in animals and humans. For seizures that involve the hippocampus, the lack of a ventral hippocampal commissure in humans [6] as compared to non-primates, in all likelihood, accounts for the frequent occurrence of unilateral hippocampal AD in humans, in contrast to the bilateral hippocampal AD in rats [93]. Species-specific behaviors have to be considered. A type of defensive behavior in cats may not have the same manifestation in humans, although it may be argued that the neurobiological basis of the defensiveness (e.g. mediation by the hypothalamus) may be the same. Locomotion is probably more important in rats than in humans, as an adaptive behavior. These differences may explain why rats may show more postictal locomotor hyperactivity than humans.

The involvement of dopaminergic functions in the nucleus accumbens in postictal psychomotor behaviors has been emphasized in this review. A dopamine antagonist is expected to suppress the automatisms of patients with complex partial seizures. Dopamine antagonists are also known to be effective in treating postictal psychosis. There is no known remedy for the memory disruption, short and long term, after a seizure. However, proposing that the memory disruption is mediated by specific changes in neuronal synapses and circuits in the temporal lobe offers the possibility that these changes may be prevented or reversed. The same ray of hope may extend to possible amelioration of the behavioral and emotional disruptions after seizures.

Acknowledgements

Experimental work in our laboratories was supported by a grant from the Natural Sciences and Engineering Research Council of Canada and, in part, by NS-25383 from the National Institutes of Health (USA). Dr J. Ma was supported by a postdoctoral fellowship from the Ontario Mental Health Foundation.

References

[1] Adamec RE. Behavioral and epileptic determinants of predatory attack behaviour in the cat. In: Wada JA, editor. Kindling. New York: Raven Press, 1976. p. 135–54.
[2] Adamec RE. Does kindling model anything clinically relevant? Biol Psychiatry 1990;27:249–79.
[3] Adamec RE. Partial kindling of the ventral hippocampus: identification of changes in limbic physiology which accompany changes in feline aggression and defense. Physiol Behav 1991;49:443–53.
[4] Adamec RE. Amygdala kindling and rodent anxiety. In: Corcoran ME, Moshe S, editors. Kindling 5. New York: Plenum Press, 1998. p. 327–48.
[5] Adamec RE, Stark-Adamec C. Limbic kindling and animal behavior-implications for human psychopathology associated with complex partial seizures. Biol Psychiatry 1983;18:269–93.
[6] Alger BE, Pitler TA, Williamson A. A prolonged post-tetanic hyperpolarization in rat hippocampal pyramidal cells in vitro. Brain Res 1990;521:118–24.
[7] Alheid GF, Heimer L, Switzer RC. Basal ganglia. In: Paxinos G, editor. The human nervous system. San Diego: Academic Press, 1990. p. 483–582.
[8] Amaral DG, Insausti R. Hippocampal formation. In: Paxinos G, editor. The human nervous system. San Diego, CA: Academic Press, 1990. p. 711–56.
[9] Amaral DG, Witter MP. The three-dimensional organization of the hippocampal formation: a review of anatomical data. Neurosciences 1989;31:571–91.
[10] Amaral DG, Price JL, Pitkanen A, Carmichael ST. Neurobiological aspects of emotion, memory and mental dysfunction. In: Aggleton JP, editor. The Amygdala. New York: Wiley-Liss, 1992. p. 1–66.
[11] Artola A, Singer W. Long-term depression of excitatory synaptic transmission and its relationship to long-term potentiation. Trends Neurosci 1993;16:480–3.
[12] Babb TL, Pretorius JK, Kupfer WR, Crandall PH. Glutamate decarboxylase-immunoreactive neurons are preserved in human epileptic hippocampus. J Neurosci 1989;9:2562–74.
[13] Barnes CA, Jung MW, McNaughton BL, Korol DL, Andreasson K, Worley PF. LTP saturation and spatial learning disruption: effects of task variables and saturation levels. J Neurosci 1994;14:5793–806.
[14] Bear MF, Abraham WC. Long-term depression in the hippocampus. Ann Rev Neurosci 1994;19:437–62.
[15] Bekenstein JW, Lothman EW. Dormancy of inhibitory interneurons in a model of temporal lobe epilepsy. Science 1993;259:97–100.

[16] Ben-Ari Y, Krnjevic K, Reinhardt W. Hippocampal seizures and failure of inhibition. Can J Physiol Pharmacol 1979;57:1462–6.
[17] Berman RK, Jarvis MF, Lupica CR. Adenosine involvement in kindled seizures. In: Wada JA, editor. Kindling 4. New York: Plenum Press, 1990. p. 423–40.
[18] Blaha CD, Yang CR, Floresco SB, Barr AM, Phillips AG. Stimulation of the ventral subiculum of the hippocampus evokes glutamate receptor-mediated changes in dopamine efflux in the rat nucleus accumbens. Eur J Neurosci 1997;9:902–11.
[19] Bland BH. The physiology and pharmacology of hippocampal formation theta rhythms. Prog Neurobiol 1986;26:1–54.
[20] Bland BH, Colom LV. The physiology and pharmacology of hippocampal formation theta rhythms. Prog Neurobiol 1993;41:157–208.
[21] Bleuler E. Dementia praecox. New York: International University Press, 1911 (translated in 1950 by H. Zinkin).
[22] Bliss TVP, Collingridge GC. Synaptic model of memory: LTP in the hippocampus. Nature 1993;361:31–9.
[23] Bragin A, Jando G, Nadasdy Z, Hetke J, Wise K, Buzsaki G. Gamma (40–100 Hz) oscillation in the hippocampus of the behaving rat. J Neurosci 1995;15:47–60.
[24] Bragin A, Penttonen M, Buzsaki G. Termination of epileptic afterdischarge in the hippocampus. J Neurosci 1997;17:2567–79.
[25] Brudzynski SM, Gibson CJ. Release of dopamine in the nucleus accumbens caused by stimulation of the subiculum in freely moving rats. Brain Res Bull 1997;42:303–8.
[26] Bruton CJ. The neuropathology of temporal lobe epilepsy. New York: Oxford University Press, 1988.
[27] Burwell R, Witter MP, Amaral DG. Perirhinal and postrhinal cortices of the rat: a review of the neuroanatomical literature and comparison with findings from the monkey brain. Hippocampus 1993;5:390–408.
[28] Cain DP. Long-term potentiation and kindling: how similar are the mechanisms? Trends Neurosci 1989;12:6–10.
[29] Cain DP, Hargreaves EL, Boon F, Dennison Z. An examination of the relations between hippocampal long-term potentiation, kindling, afterdischarge, and place learning in the water maze. Hippocampus 1993;3:153–64.
[30] Calabaresi P, Pisani A, Mercuri NB, Bernardi G. The corticostriatal projection: from synaptic plasticity to dysfuncitons of the basal ganglia. Trends Neurosci 1996;19:19–24.
[31] Cammisuli S, Murphy MP, Ikeda-Douglas CJ, Balkissoon V, Holsinger RM, Head E, Michael M, Racine RJ, Milgram NW. Effects of extended electrical kindling on exploratory behavior and spatial learning. Behav Brain Res 1997;89:179–90.
[32] Caldecott-Hazard S, Yamagata N, Hedlund J, Camacho H, Liebeskind JC. Changes in simple and complex behaviors following kindled seizures in rats: opioid and nonopioid mediation. Epilepsia 1983;24:539–47.
[33] Carlsson A. The current status of the dopamine hypothesis of schizophrenia. Neuropsychopharmacology 1988;1:179–203.
[34] Cavazos JE, Das I, Sutula TP. Neuronal loss induced in limbic pathways by kindling: evidence for induction of hippocampal sclerosis by repeated brief seizures. J Neurosci 1994;14:3106–21.
[35] Cavazos JE, Golarai G, Sutula TP. Mossy fiber synaptic reorganization induced by kindling: time course of development, progression and permanence. J Neurosci 1991;11:2795–803.
[36] Cobb SR, Buhl EH, Halasy K, Paulsen O, Somogyi P. Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. Nature 1995;378:75–8.
[37] Collins RC, Tearse RG, Lothman EW. Functional anatomy of limbic seizures: focal discharges from medial entorhinal cortex in rat. Brain Res 1983;280:25–40.
[38] Corcoran ME, Mason ST. Role of forebrain catecholamines in amygdaloid kindling. Brain Res 1980;190:473–84.
[39] Corcoran ME, Armitage LL, Gilbert TH, Hannesson DK, Mohapel P. Kindling and spatial cognition. In: Corcoran ME, Moshe S, editors. Kindling 5. New York: Plenum Press, 1998. p. 377–93.
[40] Cottrell GA, Nyakas C, Bohus B. Hippocampal kindling-induced after-discharge and behavioural depression: immediate and long-term attenuation by opiate antagonists. Eur J Pharmacol 1988;20:1–8.
[41] Creager R, Dunwiddie T, Lynch G. Pair-pulse and frequency facilitation in the CA1 region of the in vitro rat hippocampus. J Physiol (Lond) 1980;299:409–24.
[42] Csernansky GJ, Kerr S, Pruthi R, Prosser ES. Mesolimbic dopamine receptor increases two weeks following hipocampal kindling. Brain Res 1988;449:357–60.
[43] Davies CH, Davies SN, Collingridge GL. Paired-pulse depression of monosynaptic GABA-mediated inhibitory postsynaptic responses in rat hippocampus. J Physiol (Lond) 1990;424:513–31.
[44] deJonge M, Racine RJ. The development and decay of kindling-induced increases in pair-pulse depression in the dentate gyrus. Brain Res 1987;412:318–28.
[45] Devinsky O, Kelly K, Yacubian EMT, Sato S. Postictal behavior. A clinical and subdural electroencephalographic study. Arch Neurol 1994;51:254–9.
[46] Ehlers CL, Koob GF. Locomotor behavior following kindling in three different brain sites. Brain Res 1985;326:71–9.
[47] Engel Jr J. Seizures and epilepsy. Philadelphia, PA: Davis, 1989.
[48] Engel Jr J, Cahan L. Potential relevance of kindling to human partial epilepsy. In: Wada J, editor. Kindling 3. New York: Raven Press, 1986.
[49] Engel Jr J, Rocha L. Interictal behavioral disturbances: a search for molecular substrates. Epilepsy Res Suppl 1992;9:341–50.
[50] Feasey-Truger KJ, Kargl L, ten Bruggencate G. Differential effects of dentate kindling on working and reference spatial memory in the rat. Neurosci Lett 1993;151:25–8.
[51] Fibiger HC. Mesolimbic dopamine: an analysis of its role in motivated behavior. Semin Neurosci 1993;5:321–7.
[52] Floresco SB, Yang CR, Phillips AG, Blaha CD. Basolateral amygdala stimulation evokes glutamate receptor-dependent dopamine efflux in the nucleus accumbens of the anaesthetized rat. Eur J Neurosci 1998;10:1241–51.
[53] Frenk H, Engel Jr J, Ackermann RF, Shavit Y, Liebeskind JC. Endogenous opioids may mediate post-ictal behavioral depression in amygdaloid-kindled rats. Brain Res 1979;167:435–40.
[54] Freund TF, Buzsaki G. Interneurons of the hippocampus. Hippocampus 1996;6:345–470.
[55] Gelbard HA, Applegate CD. Persistent increases in dopamine D_2 receptor mRNA expression in basal ganglia following kindling. Epilepsy Res 1994;17:23–9.
[56] Gerard ME, Spitz MC, Towbin JA, Shantz D. Subacute postictal aggression. Neurology 1998;50:384–8.
[57] Gilbert TH, McNamara RK, Corcoran ME. Kindling of hippocampal field CA1 impairs spatial learning and retention in the Morris water maze. Behav Brain Res 1996;82:57–66.
[58] Glenthøj JB, Mogensen J, Laursen H, Holm S, Hemmingsen R. Electrical sensitization of the meso-limbic dopaminergic system in rats: a pathogenetic model for schizophrenia. Brain Res 1993;619:39–54.
[59] Gloor P. Neurobiological substrates of ictal behavioral changes. Adv Neurol 1991;55:1–34.
[60] Gloor P. The temporal lobe and limbic system. Oxford: Oxford University Press, 1997.
[61] Gloor P, Olivier A, Quesney LF, Andermann F, Horowitz S. The role of the limbic system in experiential phenomena of temporal lobe epilepsy. Ann Neurol 1982;12:129–44.
[62] Goddard GV, McIntyre DC, Leech CK. A permanent change in brain function resulting from daily electrical stimulation. Exp Neurol 1969;25:295–330.
[63] Goldensohn ES. The relevance of secondary epileptogenesis to the treatment of epilepsy: kindling and the mirror focus. Epilepsia 1984;25(Suppl. 2):S156–73.
[64] Goldman-Rakic PS, Selemon LD. Functional and anatomical aspects

of prefrontal pathology in schizophrenia. Schizophrenia Bull 1997;23:437–58.
[65] Gratton A, Wise RA. Drug—and behavior—associated changes in dopamine-related electrochemical signals during intravenous cocaine self-administration in rats. J Neurosci 1994;14:4116–30.
[66] Gray JA, Joseph MH, Hemsley DR, Young AMJ, Warburton EC, Boulenguez P, Grigoryan G, Peters SI, Rawlins JNP, Taib CT, Yee BK, Cassady H, Weiner I, Gal G, Gusak O, Joel D, Shadach E, Shalev U, Tarrasch R, Feldon J. The role of mesolimbic dopaminergic and retrohippocampal afferents to the nucleus accumbens in latent inhibition: implications for schizophrenia. Behav Brain Res 1995;71:19–31.
[67] Groenewegen HJ, Berendse HW, Haber SN. Organization of the output of the ventral striatopallidal system in the rat. Ventral pallidal efferents. Neuroscience 1993;57:113–42.
[68] Groenewegen HJ, Vermeulen-Van der Zee E, te Kortschot A, Witter MP. Organization of the projections from the subiculum to the ventral striatum in the rat. A study using anterograde transport of Phaseolus vulgaris leucoaggglutinin. Neuroscience 1987;23:103–20.
[69] Gutnick MJ, Prince DA. Effects of projected cortical epileptiform discharges on neuronal activities in cat VPL. I. Interictal discharge. J Neurophysiol 1972;37:1310–27.
[70] Halgren E, Wilson CL. Recall deficits produced by afterdischarges in the human hippocampal formation and amygdala. Electroencephalogr Clin Neurophysiol 1985;61:375–80.
[71] Halgren E, Walter RD, Cherlow DG, Crandall PH. Mental phenomena evoked by electrical stimulation of the human hippocampal formation and amygdala. Brain 1978;101:83–117.
[72] Halgren E, Stapleton J, Domalski P, Swartz BE, Delgado-Excueta AV, Walsh GO, Mandelkern M, Blahd W, Ropchan J. Memory dysfunction in epilepsy patients as a derangement of normal physiology. Adv Neurol 1991;55:385–410.
[73] Hauser WA, Kurland LT. The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. Epilepsia 1975;16:1–60.
[74] Heckers S, Rauch SL, Goff D, Savage CR, Schacter DI, Fischman AJ, Alpert NM. Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. Nature Neurosci 1998;1:318–23.
[75] Heimer L, Alheid GF, Zahm DS. Basal forebrain organization: an anatomical framework for motor aspects of drive and motivation. In: Kalivas P, Barnes CD, editors. Limbic motor circuits and neuropsychiatry. Boca Raton, FL: CRC Press, 1993. p. 1–44.
[76] Helfer V, Deransart C, Marescaux C, Depaulis A. Amygdala kindling in the rat: anxiogenic-like consequences. Neuroscience 1996;73:971–8.
[77] Hollerman JR, Schultz W. Dopamine neurons report an error in the temporal prediction of reward during learning. Nature Neurosci 1998;1:304–9.
[78] Holmes GL, Chronopoulos A, Stafstrom CE, Mikati MA, Thurber SJ, Hyde PA, Thompson JL. Effects of kindling on subsequent learning, memory, behavior and seizure susceptibility. Dev Brain Res 1993;73:71–7.
[79] Iversen SD. Biochemical and pharmacological studies: the dopamine hypothesis. In: Wing JK, editor. Schizophrenia, London: Academic Press, 1978. p. 89–116.
[80] Jarrard LE. On the role of the hippocampus in learning and memory in the rat. Behav Neural Biol 1993;60:9–26.
[81] Jefferys JGR, Haas HL. Synchronized bursting of CA1 hippocampal pyramidal cells in the absence of synaptic transmission. Nature 1982;300:448–50.
[82] Jefferys JGR, Traub RD, Whittington MA. Neuronal networks for induced 40 Hz rhythms. Trends Neurosci 1996;19:202–8.
[83] Kalivas P, Churchill L, Klitenick MA. The circuitry mediating the translation of motivational stimuli into adaptive motor responses. In: Kalivas P, Barnes CD, editors. Limbic motor circuits and neuropsychiatry, Boca Raton, FL: CRC Press, 1993. p. 237–87.
[84] Kalynchuk LE, Pinel JP, Treit D, Barnes SJ, McEachern JC, Kippin TE. Persistence of the interictal emotionality produced by long-term amygdala kindling in rats. Neurosciences 1998;85:1311–9.
[85] Kamphuis W, Gorter JA, Wadman WJ, Lopes da Silva FH. Hippocampal kindling leads to different changes in paired-pulse depression of local evoked field potentials in CA1 area and in fascia dentata. Neurosci Lett 1992;141:101–5.
[86] Kapp BS, et al. In: Aggleton JP, et al., editors. The amygdala; neurobiological aspects of emotion, memory and mental dysfunction. New York: Wiley-Liss, 1992. p. 229–54.
[87] Knowlton B, McGowan M, Olton DS. Hippocampal stimulation disrupts spatial memory even 8 h after acquisition. Behav Neural Biol 1985;44:325–37.
[88] Koob B. Drugs of abuse: anatomy, pharmacology and function of reward pathways. Trends Neurosci 1992;13:177–84.
[89] Krettek JE, Price JL. Projections from the amygdaloid complex to the cerebral cortex and thalamus in the rat and cat. J Comp Neurol 1977;172:687–722.
[90] Krettek JE, Price JL. Projections from the amygdaloid complex and adjacent olfactory structures to the entorhinal cortex and to the subiculum in the rat and cat. J Comp Neurol 1977;172:723–52.
[91] Landolt H. Serial electroencephalographic investigations during psychotic episodes in epileptic patients and during schizophrenic attacks. In: Lorantz de Haas AM, editor. Lectures on epilepsy. Amsterdam: Elsevier, 1958. p. 91–133.
[92] LeDoux JE. The amygdala: contributions to fear and stress. Semin Neurosci 1994;6:231–7.
[93] Leung LS. Hippocampal electrical activity following local tetanization. I. Afterdischarges. Brain Res 1987;419:173–87.
[94] Leung LS. Generation of theta and gamma rhythms in the hippocampus. Neurosci Biobehav Rev 1998;22:275–90.
[95] Leung LS, Boon KA. Kindling in the posterior cingulate cortex: electrographic and behavioral characteristics. Electroencephalogr Clin Neurophysiol 1990;76:177–86.
[96] Leung LS, Shen B. Hippocampal CA1 evoked response and radial 8-arm maze performance after hippocampal kindling. Brain Res 1991;555:353–7.
[97] Leung LS, Shen B. Long-term potentiation in hippocampal CA1: effects of afterdischarges, NMDA antagonists and anti-convulsants. Exp Neurol 1993;119:205–14.
[98] Leung LS, Boon KA, Kaibara T, Innis NK. Radial maze performance following hippocampal kindling. Behav Brain Res 1990;40:119–29.
[99] Leung LS, Brzozowski D, Shen B. Partial hippocampal kindling affects retention but not acquisition, place but not cue task on the radial arm maze. Behav Neurosci 1996;110:1017–24.
[100] Leung LS, Zhao D, Shen B. Long-lasting effects of partial hippocampal kindling on hippocampal physiology and function. Hippocampus 1994;4:696–704.
[101] Leung LS, Wu C, Wu K, Shen B, Sutherland R, Zhao D. Long-lasting behavioral and electrophysiological effects induced by partial hippocampal kindling. In: Corcoran ME, Moshe S, editors. Kindling 5. New York: Plenum Press, 1998. p. 395–408.
[102] Leutmezer F, Serles W, Lehrner J, Patarala E, Zeiler K, Baumgartner C. Postictal nose wiping: a lateralizing sign in temporal lobe complex partial seizures. Neurology 1998;51:1175–7.
[103] Logsdail SJ, Toone BK. Postictal Psychoses: a clinical and phenomenological description. Br J Psychiatry 1988;152:246–52.
[104] Lopes da Silva FH, Witter MP, Boeijinga PH, Lothman AHM. Anatomic organization and physiology of the limbic cortex. Physiol Rev 1990;70:453–511.
[105] Lothman EW, Hatlelid JM, Zorumski CF. Functional mapping of limbic seizures originating in the hippocampus: a combined 2-deoxyglucose and eletrophysiologic study. Brain Res 1985;360:92–100.
[106] Luchins DJ. A possible role of hippocampal dysfunction in schizophrenic symptomatology. Biol Psychiatry 1990;31:87–91.
[107] Ma J, Leung LS. Medial septum mediates the increase in postictal

behaviors and hippocampal gamma waves after an electrically induced seizure. Brain Res 1999;833:551–7l.
[108] Ma J, Brudzynski SM, Leung LS. Involvement of the nucleus accumbens-ventral pallidal pathway in postictal behavior induced by a hippocampal afterdischarge in rats. Brain Res 1996;739:26–35.
[109] Ma J, Brudzynski SM, Leung LS. A role of subicular and hippocampal afterdischarges in initiation of locomotor activity in rats. Brain Res 1998;793:112–8.
[110] MacLean PD. The triune brain in evolution: role in paleocerebral functions. New York: Plenum Press, 1990.
[111] Manchanda R, Miller H, Mclachlan RS. Post-ictal psychosis after right temporal lobectomy. J Neurol Neurosurg Psychiatry 1993;56:277–9.
[112] Mayeux R, Alexander MP, Benson DF, Brandt J, Rosen J. Poriomania. Neurology 1979;29:1616–9.
[113] McIntyre DC, Molino A. Amygdala lesions and CER learning: long term effect of kindling. Physiol Behav 1972;7:1055–8.
[114] McIntyre DC, Reichert H. State-dependent learning in rats induced by kindled convulsions. Physiol Behav 1971;7:15–20.
[115] McIntyre DC, Stenstrom RJ, Taylor D, Stokes KA, Edson N. State-dependent learning following electrical stimulation of the hippocampus: intact and split-brain rats. Physiol Behav 1985;34:133–9.
[116] McIntyre DC, Kelly ME, Staines WA. Efferent projections of the anterior perirhinal cortex in the rat. J Comp Neurol 1996;369: 302–18.
[117] McNamara JO, Bonhaus DW, Shin C, Crain BJ, Gellman RL, Giacchino JL. The kindling model of epilepsy: a critical review. CRC Crit Rev Neurobiol 1985;1:341–91.
[118] McNamara RK, Kirkby RD, dePape GE, Skelton RW, Corcoran ME. Differential effects of kindling and kindled seizures on place learning in the Morris water maze. Hippocampus 1993;3:149–52.
[119] Meunier M, Bachevalier J, Mishkin M, Murray EA. Effects of visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkeys. J Neurosci 1993;13:5418–32.
[120] Milner B. Memory and the medial temporal regions of the brain. In: Pribram KH, Broadbent DE, editors. Biology of memory. New York: Academic Press, 1970.
[121] Mody I, De Koninck Y, Otis TS, Soltesz I. Bridging the cleft at GABA synapses in the brain. Trends Neurosci 1994;17:517–25.
[122] Mogenson GJ, Jones DL, Yim CY. From motivation to action: functional interface between limbic and motor systems. Prog Neurobiol 1980;14:69–97.
[123] Mogenson GJ, Brudzynski SM, Wu M, Yang CR, Yim CYC. In: Kalivas P, Barnes CD, editors. Limbic motor circuits and neuropsychiatry. Boca Raton, FL: CRC Press, 1993. p. 193–236.
[124] Morrell F, Wada JA, Engel Jr J. Potential relevance of kindling and secondary epileptogenesis to the consideration of surgical treatment for epilepsy. In: Engel Jr J, editor. Surgical treatment of the epilepsies. New York: Raven Press, 1987. p. 699–705.
[125] Morris RGM. Synaptic plasticity and learning: selective impairment of learning in rats and blockade of long term potentiation in vivo by the N-methyl-D-aspartate receptor antagonist AP5. J Neurosci 1989;9:3040–57.
[126] Niedermeyer E. Neurology aspects of epilepsy. In: Blumer D, editor. Psychiatric aspect of epilepsy. Washington, DC: American Psychiatric Press, 1984. p. 99–142.
[127] O'Donnell P, Grace AA. Synaptic interactions among excitatory afferents to nucleus accumbens neurons: hippocampal gating of prefrontal cortical input. J Neurosci 1995;15:3622–39.
[128] O'Keefe J, Nadel L. Hippocampus as a cognitive map. London: Oxford University Press, 1978.
[129] Oddie SD, Stefanek W, Kirk IJ, Bland BH. Intraseptal procaine abolishes hypothalamic stimulation-induced wheel-running and hippocampal theta field activity in rats. J Neurosci 1996;16:1948–56.
[130] Olton DS, Wolf WA. Hippocampal seizures produce retrograde amnesia without a temporal gradient when they reset working memory. Behav Neural Biol 1981;33:437–52.
[131] Olton DS, Becker JT, Handelman GE. Hippocampus, space, and memory. Behav Brain Sci 1979;2:313–22.
[132] Palmini AL, Gloor P, Jones-Gotman M. Pure amnestic seizures in temporal lobe epilepsy. Brain 1992;115:745–69.
[133] Pennartz CMA, Groenewegen HJ, Lopes da Silva FH. The nucleus accumbens as a complex of functionally distinct neuronal ensembles: an integration of behavioural electrophysiological and anatomical data. Prog Neurobiol 1994;42:719–61.
[134] Perez-Velazquez JL, Valiante TA, Carlen PL. Modulation of gap junctional mechanisms during calcium-free induced field burst activity: a possible role for electrotonic coupling in epileptogenesis. J Neurosci 1994;14:4308–17.
[135] Petsche H, Stumpf C, Gogolak G. The significance of the rabbit's septum as a relay station between the midbrain and the hippocampus. I. The control of hippocampal arousal activity by the septum cells. Electroencephalogr Clin Neurophysiol 1962;14:202–11.
[136] Pikkarainen M, Ronkko S, Savander V, Insausti R, Pitkanen A. Projections from the lateral, basal and accessory basal nuclei of the amygdala to the hippocampal formation in rat. J Comp Neurol 1999;403:229–60.
[137] Pinel JP, Kalynchuk LE, Treit D. Long-term amygdala kindling and defensive behavior of rats. In: Corcoran ME, Moshe S, editors. Kindling 5. New York: Plenum Press, 1998. p. 349–60.
[138] Post RM, Ballenger JC, Uhde TW, Putnam FW, Bunney Jr WE. Kindling and drug sensitization: implications for the progressive development of psychopathology and treatment with carbamazepine. The psychopharmacology of anticonvulsants. Oxford: Oxford University Press, 1981.
[139] Racine RJ. Modification of seizure activity by electrical stimulation: II. Motor seizure. Electroencephalogr Clin Neurophysiol 1972;32:281–94.
[140] Racine RJ, Chapman CA, Teskey GC, Milgram NW. Post-activation potentiation in the neocortex. III. Kindling-induced potentiation in the chronic preparation. Brain Res 1995;702:77–86.
[141] Ring HA, Trimble MR, Costa DC, Moriarty J, Verhoeff NPLG, Ell PJ. Striatal dopamine receptor binding in epileptic psychoses. Biol Psychiatry 1994;35:375–80.
[142] Robinson GB, McNeil HA, Reed RD. Comparison of short- and long-lasting effects of perforant path kindling on radial maze learning. Behav Neurosci 1993;6:1–8.
[143] Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Rev 1993;18:247–91.
[144] Saucier D, Cain DP. Spatial learning without NMDA receptor-dependent long-term potentiation. Nature 1995;378:186–9.
[145] Sato M. Long-lasting hypersensitivity to methamphetamine following amygdaloid kindling in cats: the relationship between limbic epilepsy and the psychotic state. Biol Psychiatry 1983;18:525–36.
[146] Savard G, Andermann F, Olivier A, Remillard GM. Postictal psychosis after partial complex seizures: a multiple case study. Epilepsia 1991;32:225–31.
[147] Schultz W, Apicella P, Ljungberg T. Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. J Neurosci 1993;13:900–13.
[148] Shinnick-Gallagher P, Keele NB, Neugebauer V. Long-lasting changes in pharmacology and electrophysiology of amino acid receptors in amygdala-kindled neurons. In: Corcoran ME, Moshe S, editors. Kindling 5. New York: Plenum Press, 1998. p. 75–87.
[149] Singer W. Synchronization of cortical activity and its putative role in information processing and learning. Ann Rev Physiol 1993;55: 349–74.

[150] Slater E, Beard AW. The schizophrenia-like psychoses of epilepsy I. Psychiatric aspects. Br J Psychiatry 1963;109:95–150.
[151] Sloviter RS. Permanently altered hippocampal structure, excitability, and inhibition after experimental status epilepticus in the rat: the dormant basket cell hypothesis and its possible relevance to temporal lobe epilepsy. Hippocampus 1991;1:41–66.
[152] Somjen GG, Aitken PG, Giacchino JL, McNamara JO. Interstitial ion concentrations and paroxysmal discharges in hippocampal formation and spinal cord. Adv Neurol 1986;44:663–80.
[153] Squire LR. Memory and the hippocampus: a synthesis from findings with rats, monkeys and humans. Psychol Rev 1992;99:195–231.
[154] Starr MS. The role of dopamine in epilepsy. Synapse 1996;33:159–94.
[155] Stevens JR. Psychosis and the temporal lobe. Adv Neurology 1991;55:79–96.
[156] Stevens JR, Livermore AH. Kindling of the mesolimbic dopamine system: animal model of psychosis. Neurology 1978;28:36–46.
[157] Strecker RE, Moneta ME. Electrical stimulation of the kindled hippocampus briefly increases extracellular dopamine in the nucleus accumbens. Neurosci Lett 1994;176:173–7.
[158] Sutherland RJ, Leung LS, Weisend MP, Schlife J, McDonald RJ. An evaluation of the effect of partial hippocampal kindling on place navigation by rats in the Morris water task. Psychobiology 1997;25:126–32.
[159] Sutula T, Lauersdorf S, Lynch M, Jurgella C, Woodard A. Deficits in radial arm maze performance in kindled rats: evidence for long-lasting memory dysfunction induced by repeated brief seizures. J Neurosci 1995;15:8295–301.
[160] Swanson LW, Kohler C, Bjorklund A. The limbic region. I: The septohippocampal system. In: Bjorklund A, Hokfelt T, Swanson LW, editors. Handbook of chemical neuroanatomy Vol. 5: Integrated systems of the CNS. Part I, 1987. p. 125–278.
[161] Thompson PJ. Memory function in patients with epilepsy. Adv Neurol 1991;55:369–84.
[162] Titulaer M, Kamphuis W, Pool CW, van Heerikhuize JJ, Lopes da Silva FH. Kindling induces time-dependent and regional specific changes in the [^{3}H] muscimol binding in the rat hippocampus: a semi-quantitative autoradiographic study. Neuroscience 1994; 59:817–26.
[163] Traub RD, Knowles WD, Miles R, Wong RKS. Synchronized after-discharges in the hippocampus: simulation studies of the cellular mechaism. Neuroscience 1984;12:1191–200.
[164] Trimble MR. Interictal psychoses of epilepsy. Adv Neurol 1991;55:143–52.
[165] Tuff LP, Racine RJ, Adamec R. The effects of kindling on GABA-mediated inhibition in the dentate gyrus of the rat. Brain Res 1983;277:79–90.
[166] Vanderwolf CH. Cerebral activity and behavior: control by cholinergic and serotonergic systems. Int Rev Neurobiol 1988;30:225–340.
[167] Vezzani A, Sperk G, Colmers WF. Neuropeptide Y: emerging evidence for a functional role in seizure modulation. Trends Neurosci 1999;22:25–9.
[168] Wilson C, Nomikos GG, Collu M, Fibiger HC. Dopaminergic correlates of motivated behavior: importance of drive. J Neurosci 1995;15:5169–78.
[169] Wilson CL, Khan SU, Engel Jr J, Isokawa M, Babb TL, Behnke EJ. Paired-pulse suppression and facilitation in human epileptogenic hippocampal formation. Epilepsy Res 1998;31:211–30.
[170] Wise RA. The anhedonia hypothesis: mark III. Behav Brain Sci 1985;8:178–86.
[171] Wolf P. Acute behavioral symptomatology at disappearance of epileptiform EEG abnormality: paradoxical or forced normalization. Adv Neurol 1991;55:127–42.
[172] Wu C, Leung LS. Partial hippocampal kindling decreases efficacy of presynaptic $GABA_B$ autoreceptors in CA1. J Neurosci 1997;17:9261–9.
[173] Wu LG, Saggau P. Presynaptic inhibition of elicited neurotransmitter release. Trends Neurosci 1997;20:204–12.
[174] Wu M, Brudzynski SM. Mesolimbic dopamine terminals and locomotor activity induced from the subiculum. NeuroReport 1995;6:1601–4.
[175] Yang CR, Mogenson GJ. Dopamine enhances terminal excitability of hippocampal-accumbens neurons via D_2 receptor: role of dopamine in presynaptic inhibition. J Neurosci 1986;6:2470–8.
[176] Yim CY, Mogenson GJ. Neuromodulatory action of dopamine in the nucleus accumbens: an in vivo intracellular study. Neurosciences 1988;26:403–15.
[177] Zhao D, Leung LS. Effects of hippocampal kindling on paired-pulse response in CA1 in vitro. Brain Res 1991;564:220–9.
[178] Zhao D, Leung LS. Hippocampal kindling induced paired-pulse depression in the dentate gyrus and paired-pulse facilitation in CA3. Brain Res 1992;582:163–7.
[179] Zucker RS. Short-term synaptic plasticity. Ann Rev Neurosci 1989;12:13–31.