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Enhancement of Central Dopaminergic Activity in the Kainate Model of Temporal Lobe Epilepsy: Implication for the Mechanism of Epileptic Psychosis

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There is an increased incidence of schizophrenia-like psychosis in temporal lobe epilepsy (TLE), and several risk factors have been implicated, including the duration of epilepsy and temporal lobe neuropathology. To investigate the biological mechanism of epileptic psychosis, we examined alterations of central dopaminergic systems in the kainate model of TLE. In adult rats, kainate was microinjected into the left amygdala to induce status epilepticus. An indirect dopamine agonist methamphetamine (MAP, 2 mg/kg, i.p.) was administered before and 1 month after the kainate treatment. MAP-induced locomotor activity was significantly enhanced in the kainate group compared with the baseline (pre-kainate) level, which was antagonized by pretreatment with haloperidol. The enhancement of locomotor activity in the kainate group was significantly correlated with the density of hippocampal CA1 neurons. Although the basal extracellular dopamine concentration was significantly lower in the striatum in the kainate group than in the control group (5.5 *vs* 39.2 fmol/20-min sample), the maximal concentration following MAP administration did not differ between the two groups. These results clearly demonstrate that hypersensitivity of the dopamine systems develops in the chronic phase of the kainate-induced TLE model, which may be responsible for the mechanism of epileptic psychosis.

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INTRODUCTION

In the long-term clinical course of epilepsy, there is an increased incidence of schizophrenia-like paranoid symptoms, such as delusion and hallucination. The prevalence of this epileptic psychosis appears to be about 7–11%, which is much higher than in the general population (McKenna *et al*, 1985; Trimble, 1991; Torta and Keller, 1999). Since in some patients with epileptic psychosis there is an inverse correlation between the presence of epilepsy and the psychosis, this phenomenon has been labeled 'forced normalization' or 'alternative psychosis' (see review of Krishnamoorthy and Trimble, 1999). Slater *et al* (1963), on the other hand, reported that the emergence of epileptic psychosis was related to the duration of epilepsy and to brain damage, and was linked to temporal lobe epilepsy (TLE).

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Thus far, the exact etiology of epileptic psychosis remains uncertain, but several risk factors have been implicated, including onset of epilepsy before the age 20 years, a history of epilepsy greater than 10 years, a history of complex partial seizures, and TLE that is focused on the left side (Torta and Keller, 1999). In particular, neurodevelopmental abnormalities in the mesial temporal lobe (eg hamartomatous lesions or gangliogliomas) have been indicated (Taylor, 1975; Roberts *et al*, 1990). More recent studies suggest that therapy with powerful antiepileptic drugs such as vigabatrin (Sander *et al*, 1991; Ferrie *et al*, 1996), and a family history of psychosis (Adachi *et al*, 2000) are also factors involved in the development of epileptic psychosis.

Another hypothesis is that enhanced activity of the mesolimbic dopamine (DA) system is responsible for the development of epileptic psychosis (Trimble, 1977; Krishnamoorthy and Trimble, 1999). In experimental studies, kindling-induced chronic epileptogenesis produced long-lasting hypersensitivity to direct or indirect DA agonists (enhancers of DA release), such as apomorphine (Post *et al*, 1981; Csernansky *et al*, 1988a), methamphetamine (MAP, Sato, 1983), and amphetamine (Leung *et al*, 2000). However, a decreased sensitivity to cocaine (Post *et al*, 1981) and amphetamine (Ehlers and Koob, 1985) has also been reported. Kindling also caused a lasting increase in DA D2 receptor binding in the striatum and nucleus accumbens

(Csernansky *et al*, 1988a, b), an increase in the expression of DA D2 receptor mRNA in the striatum (Gelbard and Applegate, 1994), and a decrease in DA transporter binding in the striatum (Gordon *et al*, 1995). However, *in vitro* DA release was unchanged in these brain sites (Mintz *et al*, 1992; Ohmori *et al*, 1992; Gordon *et al*, 1995).

By contrast, in clinical studies, Ring *et al* (1994) reported reduced binding of [^{123}I]iodobenzamide to striatal DA D2 receptors in TLE patients with psychosis, compared with nonpsychotic patients, using single photon emission computed tomography (SPECT). With the aid of positron emission tomography (PET), Reith *et al* (1994) discovered an increase in the rate of metabolism of an exogenous dopa tracer (6-[^{18}F]fluoro-L-dopa) in the neostriatum of a subgroup of TLE patients who had a history of psychosis. Thus, if the excessive DA hypothesis is true, the exact neuronal mechanism, in particular whether it is a pre- or postsynaptic abnormality and is involved in epileptic psychosis, is unclear.

In the study presented here, to clarify further the DA mechanism in epileptic psychosis, we adopted a focal kainate-induced status epilepticus model (Tanaka *et al*, 1992; Mathern *et al*, 1993). This model is another chronic model for TLE, but unlike the kindling model, it is characterized by the recurrent appearance of spontaneous seizures and mesial temporal lobe neuropathology (eg pyramidal neuron loss and gliosis), which resembles hippocampal sclerosis as most commonly seen in human TLE. Using this model, we measured MAP-induced locomotor activity and striatal extracellular DA concentrations by *in vivo* microdialysis in freely moving rats. MAP or amphetamine has been utilized extensively as an experimental model of psychosis associated with an excessive DA state (see review of Lipska and Weinberger, 2000), since repeated administration of these agents produces schizophrenia-like paranoid symptoms in humans (Ellinwood *et al*, 1973; Sato *et al*, 1983, 1992), and amphetamine aggravates psychotic symptoms with an abnormal increase of striatal DA release in patients with schizophrenia (Laruelle *et al*, 1996; Breier *et al*, 1997; Abi-Dargham *et al*, 1998).

MATERIALS AND METHODS

General Procedure

Adequate measures were taken to minimize pain and discomfort to the animals used in this study, according to the Animal Experiment Guideline of Kagawa University. Male Sprague–Dawley rats weighing 230–320 g were housed individually in cages with free access to food and water. Under anesthesia with sodium pentobarbital (50 mg/kg, intraperitoneal (i.p.) injection), a guide cannula was implanted stereotaxically into the left basolateral amygdala (2.6 mm posterior to bregma, 4.9 mm lateral to the midline, and 6.8 mm below the dura), according to the atlas of Paxinos and Watson (1986), in all rats. The guide cannula was secured with dental cement and anchored using stainless steel screws fixed to the skull. In some rats, screw electrodes were placed on the frontal skull for electroencephalogram (EEG) recordings.

Kainate Model

After a recovery period of 1 week after the surgery, kainate (2 μg/0.5 μl) or the same volume of vehicle was microinjected into the left amygdala at a rate of 0.5 μl/1 min, using a Hamilton microsyringe. The kainate was dissolved in 0.9% phosphate-buffered saline. The injection cannula was inserted into the amygdala in awake rats so that it extended 1 mm below the tip of guide cannula. Behavioral and EEG seizures were monitored for several hours after injection to observe status epilepticus.

Measurement of MAP-Induced Locomotor Activity

Before kainate injection, MAP at 2 mg/kg was administered i.p., and locomotor activity was measured by an infrared detector (ABsystem 3.0; Neuroscience, Inc., Tokyo, Japan) for 240 min afterwards ('baseline' measurement). The rats were then matched for the baseline measurement of MAP-induced locomotor activity and divided into two groups: a kainate group ($n = 12$) and a control group ($n = 11$). To reduce the baseline variation of MAP-induced locomotor activity, only the rats that presented a total number of activity counts between 2000 and 10 000 were used. At 1 month after kainate or vehicle injection, locomotor activity was measured again using the same procedure. We compared the time course and the total number of MAP-induced locomotor activity counts between the kainate and control groups.

Another nine kainate-treated rats were prepared to investigate the effect of haloperidol (HPD: primarily a DA D2 receptor antagonist) on MAP-induced locomotor activity. At 1 month after kainate injection, locomotor activity was measured without and with HPD pretreatment (0.5 mg/kg, i.p., given 1 h before administration of MAP).

Measurement of MAP-Induced Striatal DA Release

In the kainate ($n = 5$) and control groups ($n = 5$), the guide cannula for brain microdialysis was implanted into the left striatum (0.2 mm anterior to bregma, 3 mm lateral to the midline, and 3.5 mm below the dura) under pentobarbital anesthesia, 1 month after kainate or vehicle injection into the left amygdala. After a recovery period of 4–7 days, brain microdialysis probes were inserted into the striatum so that they extended 3 mm below the guide cannula. A Ringer solution (147 mM Na^+, 4 mM K^+, 2.3 mM Ca^{2+}, 155.6 mM Cl^-) was perfused through the probe (2 μl/min) for at least 1 h before sample collection. Dialysis samples were collected every 20 min, and extracellular concentrations of DA were determined using high-performance liquid chromatography (HPLC) with electrochemical detection. After obtaining stable extracellular DA concentrations ('basal value'), MAP was administered i.p., and MAP-induced DA release was compared between the kainate and control groups.

Histology

Following the experiments, all rats were perfused transcardially with phosphate-buffered saline and a 4% formalin solution while under deep anesthesia. The brains were removed and postfixed in a solution of 4% formalin and

15% sucrose. In total, 10 μm, frozen coronal sections were cut and subsequently stained with cresyl violet for visualization of dorsal hippocampal neurons (CA1 and CA3 regions). The sections were photographed with the aid of a digital camera attached to a microscope. Measurements were made at a magnitude of ×400 (using a ×20 objective). For quantification of neuronal density, five sections that were cut every 50 μm in a caudal direction from 2.6 mm posterior to the bregma according to the atlas of Paxinos and Watson (1986) were collected from each rat, the number of pyramidal neurons per visual unit (180 × 250 μm) placed randomly in CA1 and CA3 was counted by two persons blindly, and the average density of hippocampus pyramidal neurons in each case was estimated. Neurons that contained clear nucleoli in the nuclei were counted as hippocampal pyramidal neurons. The neurons density is expressed as neurons/mm^2. The correlation between hippocampal neuronal damage and enhancement of MAP-induced locomotor activity was examined.

Statistic Analysis

All data are expressed as the mean ± SEM. The data were evaluated by two-way analysis of variance (ANOVA) with repeated measures over time. The data for total locomotor activity, neuronal density, and extracellular DA concentration were evaluated statistically using Student's *t*-test.

RESULTS

Alterations of MAP-Induced Locomotor Activity

Intra-amygdala kainate injection produced acute limbic status epilepticus for several hours in all rats; this condition was not observed in any of the rats in the control group. During the chronic phase (1 month after status epilepticus), recurrent spontaneous seizures were frequently observed, with EEG epileptiform discharges recorded in some rats (data not shown).

The locomotor activity induced by a novel environment (during the 60 min before MAP administration) remained unchanged at 1 month in both the kainate and control groups. However, MAP-induced locomotor activity was significantly enhanced in the kainate group compared with the baseline (pre-kainate) level ($P<0.001$, two-way ANOVA), while it was not significantly changed in the control group ($P=0.91$, Figure 1). When total counts of locomotor activity were measured during the first 4 h after MAP administration, they were significantly increased in the kainate group compared with the baseline ($P<0.05$) and the control group ($P<0.05$, Figure 2). Pretreatment with HPD significantly reduced the enhanced locomotor activity during the first 4 h after MAP administration in the kainate group ($P<0.05$), and the enhanced locomotor activity recovered nearly to the baseline level (Figure 3).

In most of the kainate-treated animals, histological examination confirmed apparent neuron loss in the left hippocampus ipsilateral to the site of kainate injection, but the degree of hippocampal damage varied greatly between individuals. The neuronal numerical density was significantly decreased in the kainate group (384.4 ± 75.6 neurons/mm^2 in the CA1 region, $P<0.01$; and 348.9 ± 48.9 neurons/mm^2 in

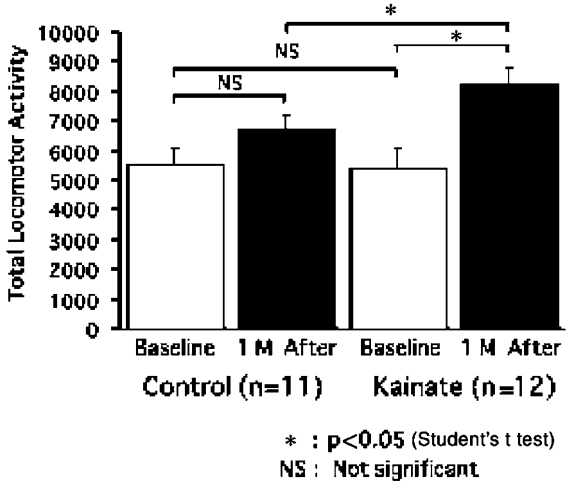

Figure 2 Total counts of locomotor activity following MAP administration in the kainate model of TLE. MAP (2 mg/kg, i.p.) was administered before ('baseline') and 1 month after an intra-amygdala injection of vehicle (the control group; left) or kainate (the kainate group; right). Each value represents total counts of locomotor activity during the 4 h following MAP administration. Note that the total counts of locomotor activity were increased in the kainate group, compared with the baseline and control levels.

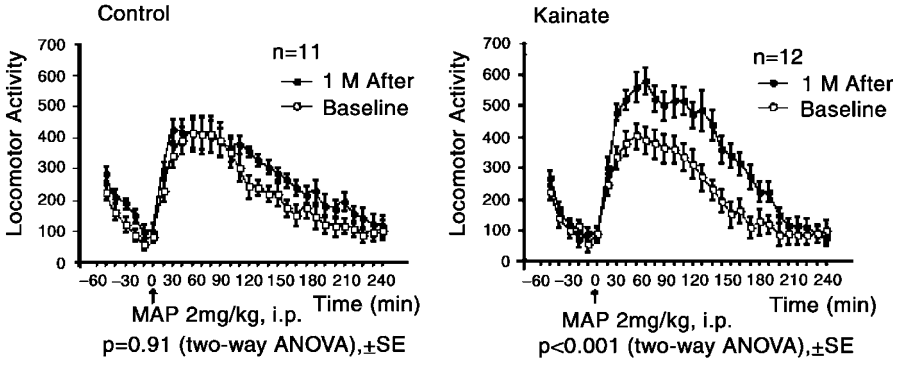

Figure 1 Enhancement of MAP-induced locomotor activity in the kainate model of TLE. MAP (2 mg/kg, i.p.) was administered before and 1 month after an intra-amygdala injection of vehicle (the control group; left) or kainate (the kainate group; right). Locomotor activity was counted every 20 min for 60 min before, and for 240 min following MAP administration. Note the significant enhancement of MAP-induced locomotor activity in the kainate group, but not in the control group.

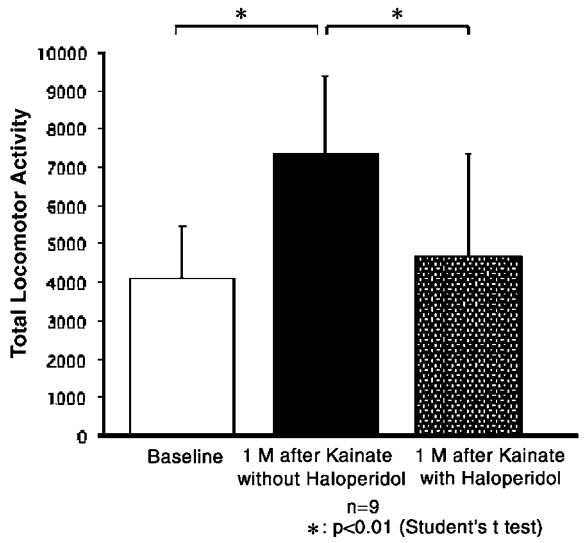

Figure 3 Effects of HPD on the enhanced MAP-induced locomotor activity in the kainate model of TLE. Each value represents the total counts of locomotor activity during the 4 h after MAP administration at 1 month after the intra-amygdala kainate injection. Animals were pretreated with HPD (0.5 mg/kg, i.p.) 1 h prior to MAP (2 mg/kg, i.p.) administration. Note a significant antagonism between HPD and the enhanced MAP-induced locomotor activity.

the CA3 region, $P<0.01$), compared with that in the control group (653.3 ± 26.7 and 591.1 ± 31.1 neurons/mm^2, respectively). The increment of MAP-induced locomotor activity (total count; '1 month after kainate' minus 'baseline') was significantly correlated with the density of hippocampal pyramidal neuron in the CA1 regions in the kainate group ($r=0.67$, $P<0.01$, Figure 4). However, there was no such significant correlation in the hippocampal CA3 region ($r=-0.07$, $P=0.83$).

Alterations in MAP-Induced DA Release

The basal extracellular concentration of DA in the striatum (immediately before MAP administration) was significantly lower in the kainate group than in the controls (5.5 *vs* 39.2 fmol/20-min sample, $P<0.05$, Figure 5). Following MAP administration, extracellular concentrations of DA were significantly elevated in both groups. The maximal DA concentration following MAP administration, however, did not differ between the two groups (828.6 *vs* 395.2 fmol/20-min sample, Figure 5). Histological examination showed that the tip of microdialysis probe was located within the ventral striatum in all cases (Figure 6).

DISCUSSION

In the study presented here, it was demonstrated clearly that the locomotor activity induced by systemic administration of MAP (an indirect DA agonist that facilitates DA release) was significantly enhanced during the chronic phase (1 month after status epilepticus) of the kainate model of TLE, when spontaneous seizures appeared frequently. This enhancement was antagonized by pretreatment with a

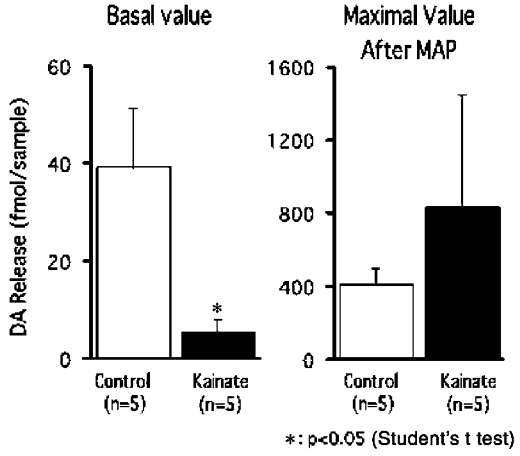

Figure 5 Basal and maximal values of extracellular DA concentration following MAP administration in the striatum of the kainate model of TLE. Extracellular DA concentrations were measured in the striatum by *in vivo* microdialysis at 1 month after the intra-amygdala injection of kainate or vehicle. The basal (left) and maximal values (right) represent DA concentrations measured immediately before and after MAP administration (2 mg/kg, i.p.), respectively. Note that the basal value was significantly lower, but the maximal value was not different in the kainate group.

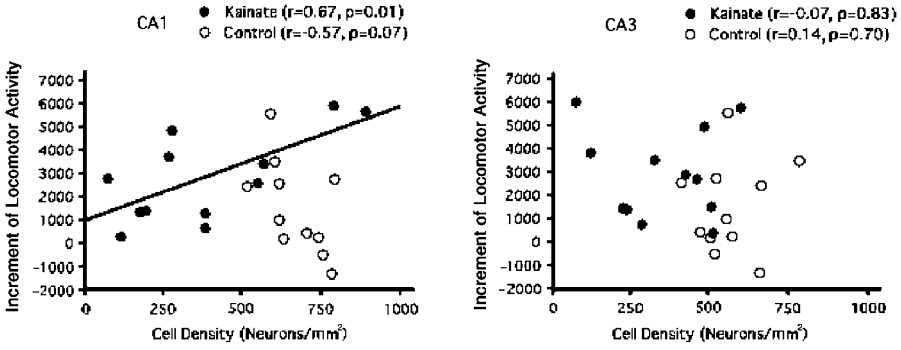

Figure 4 Correlation between the increase in MAP-induced locomotor activity and hippocampal cell counts in the kainate model of TLE. The number of pyramidal neurons/mm^2 was estimated in the hippocampal CA1 (left) and CA3 (right) regions 1 month after the intra-amygdala injection of kainate or vehicle. Note that the neuronal density was decreased in the CA1 and CA3 regions of the kainate group, compared with those of the control group, and that there was a significant positive correlation between the increase in MAP-induced locomotor activity and hippocampal cell density in the CA1 region, but not in the CA3 region, only in the kainate group.

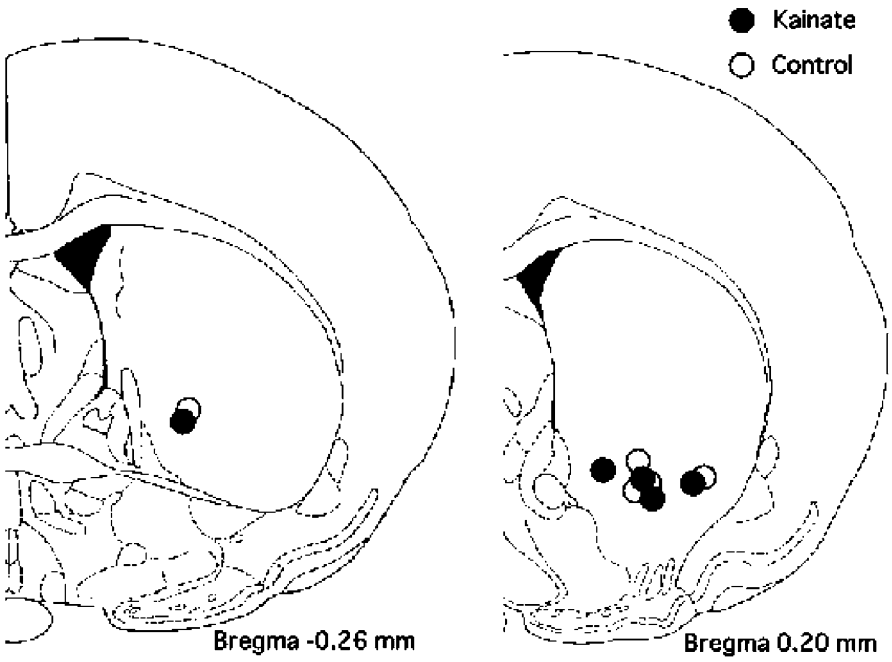

Figure 6 Histological examination for localization of the tip of the microdialysis probe. The data were drawn according to the atlas of Paxinos and Watson (1986). Note that the tip of microdialysis probe was located in the left ventral striatum in all cases.

relatively small dose of HPD (a nonselective DA D2 receptor antagonist). These results indicate that the TLE brain develops a hypersensitivity of the DA system, a state that would contribute to the pathophysiology of epileptic psychosis.

With regard to the biological mechanisms underlying this DA hypersensitivity in TLE, our discussion will focus on the following three possibilities: seizure-induced hippocampal damage, seizure-induced pathological sensitization of the DA system, and synaptic reorganization in the chronic epileptic brain.

Seizure-Induced Hippocampal Damage

A number of studies have revealed that neonatal or adult hippocampal lesions result in DA hypersensitivity, and these animals are regarded as experimental models of schizophrenia (see review of Lipska and Weinberger, 2000). For example, neonatal lesions of the bilateral ventral hippocampus by ibotenate produced augmentation of amphetamine-induced locomotor activity in rats (Lipska *et al*, 1992, 1993; Swerdlow *et al*, 2001). Bilateral hippocampal lesions induced by colchicine and kainate also produced the same effect, which was accompanied by an abnormal increase in amphetamine-induced DA release in the nucleus accumbens in adult rats (Wilkinson *et al*, 1993). In the present study, the intra-amygdala injection of kainate caused a clear loss of pyramidal neurons in hippocampal areas CA1 and CA3 following limbic status epilepticus, while the dentate granule cells were relatively well preserved (data not shown). Therefore, it appears that the DA hypersensitivity seen in TLE brains could indeed be attributable to hippocampal damage.

In our study, however, there was a positive correlation between the density of surviving neurons in hippocampal area CA1 and the degree of enhanced MAP-induced locomotor activity. This result means that more severe damage to hippocampal CA1 neurons by kainate-induced status epilepticus would result in a lesser degree of DA hypersensitivity. Consistent with this, more extensive ibotenate-induced hippocampal lesions, which included the ventral and dorsal hippocampus and the entorhinal cortex, did *not* produce apparent DA hypersensitivity (Swerdlow *et al*, 2001). Rather, selective electrolytic lesions of the fimbria-fornix had much greater effects on the locomotor response to amphetamine compared to complete or partial lesions of the hippocampal formation (Mittleman *et al*, 1998). In addition, it was indicated that patients with mesial temporal lobe sclerosis are less likely to develop epileptic psychosis (Torta and Keller, 1999). Taken together, it is unlikely that hippocampal damage *per se* is directly associated with DA hypersensitivity in the epileptic brain.

Seizure-Induced Pathological Sensitization of the DA System

It is more likely that seizure activity is directly involved in causing DA sensitization. The following evidence support this hypothesis.

First, even in the kindling model of TLE (a 'functional' model without gross brain damage), some of the previous studies, but not all, have shown hypersensitivity of DA systems (see Introduction) similar to our results. Csernansky *et al* (1988b) found that 'superkindled' rats (a standard kindling paradigm with additional electrical stimulation) were supersensitive to apomorphine, while standard kindled rats were subsensitive. From these results, it seems that the development of DA hypersensitivity in the epileptic brain depends on the number or magnitude of previously experienced seizure activity.

Second, seizure activity transiently elevated extracellular DA levels at various brain sites, including the hippocampus, striatum, nucleus accumbens, and prefrontal cortex (Strecker and Moneta, 1994; Dazzi *et al*, 1997; Smolders *et al*, 1997; Khan *et al*, 1999; Becker *et al*, 2000). Furthermore, the seizure-induced elevation of DA release could be enhanced if seizures were induced repeatedly (Strecker and Moneta, 1994; Dazzi *et al*, 1997; Becker *et al*, 2000). This phenomenon is comparable to the process of 'behavioral sensitization', in which repeated administration of DA agonists augment abnormal behaviors with the concominant enhancement of DA release (Kazahaya *et al*, 1989; Hamamura *et al*, 1991; also see review of Kalivas and Stewart, 1991). In our study, the prolonged seizure activity associated with limbic status epilepticus might produce excessive DA release and have such sensitization-like effects on DA systems.

Third, kindling of the ventral tegmental area (VTA), a major source of mesolimbic DA pathways, could produce persistent enhancement of amphetamine- or MAP-induced locomotor activity (Glenthoj *et al*, 1993; Watanabe *et al*, 2004). Repeated administration of MAP, in turn, resulted in a reduction of the electrical threshold of the VTA for eliciting forward locomotion (Watanabe *et al*, 1998), suggesting the existence of bidirectional interactions between VTA kindling and behavioral sensitization. In our study, kainate-induced status epilepticus might have indirectly kindled the mesolimbic DA system, which resulted in the DA hypersensitivity.

Finally, the site of kainate injection we employed was the amygdala, whose connections to the source and targets of DA projections might be at least partly responsible for pathological sensitization of the mesolimbic DA system. It has recently been demonstrated that the amygdala plays an important role in the development of behavioral sensitization induced by systemic or intra-VTA administration of amphetamine (Wolf *et al*, 1995; Bjijou *et al*, 2002).

Seizure-Induced Synaptic Reorganization

In addition to brain damage, it is well known that seizure activity can produce various forms of activity-dependent synaptic plasticity in the hippocampus, for example mossy fiber sprouting (Sutula *et al*, 1988) and dentate granule cell neurogenesis (Parent *et al*, 1997). More recent studies have demonstrated that synaptic reorganization is not limited to the hippocampus, but is extended to widespread brain sites of TLE models. For example, it has been shown that the number of cells that are positive for polysialylated neural cell adhesion molecule (PSA-NCAM) is markedly increased in the bilateral subventricular zone of the striatum after kindling, suggesting the seizure-induced enhancement of migration in the rostral migratory stream to the olfactory bulb (Sato *et al*, 2002). Bromodeoxyuridine-labeled neurogenesis increased in the subventricular zone, and ectopic neuronal expression occurred in the striatum and cerebral cortex following pilocarpine-induced status epilepticus (Parent *et al*, 2002). Synaptophysin immunoreactivity (a molecular marker for synaptogenesis) also increased in the piriform cortex in the kindled brain (Li *et al*, 2002). It is possible that this seizure-induced neurogenesis and synaptogenesis may be associated with the abnormal synaptic plasticity of the DA system that underlies DA hypersensitivity.

Implications for the Mechanism Underlying Epileptic Psychosis

In our microdialysis study, the basal extracellular DA concentrations appeared to be lower (approximately 1/7) in the kainate model of TLE. This result is consistent with the clinical finding that in both patients with epileptic psychosis and schizophrenia, the dopa decarboxylation rate was increased in the striatum, compared with nonpsychotic epileptic patients or normal controls, suggesting suppression of tonic release of striatal DA in these psychotic disorders (Reith *et al*, 1994). The DA hypersensitivity could be attributed, at least in part, to the decreased basal DA levels. On the other hand, there was no significant alteration of DA D1, D2, and D4 receptor binding in the striatum and nucleus accumbens in the chronic phase of the kainate model (Tarazi *et al*, 1998).

In our study, the maximal value of striatal DA release following MAP administration was not significantly changed in kainate-treated rats, despite the enhancement of MAP-induced locomotor activity. A similar discrepancy between amphetamine-induced locomotor activity and DA release was reported in rats with neonatal hippocampal damage, suggesting that DA behavior can occur without biochemical indices of increased DA concentration (Lillrank *et al*, 1999).

In conclusion, DA hypersensitivity develops in the chronic epileptic brain of the kainate model of TLE via pathological sensitization or indirect kindling of the mesolimbic DA systems, which may be responsible for the mechanism of epileptic psychosis.

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