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Research report

Schizophrenia-like behavioral changes after partial hippocampal kindling

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Abstract

The effect of hippocampal kindling on behavioral changes following 10 and 21 hippocampal afterdischarges (ADs) or electrographic seizures was examined in behaving rats. As compared to control, non-stimulated rats, 21 but not 10 hippocampal ADs resulted in a decrease in social contact, an increase in social isolation, and an increase in climbing and chasing behavior tested in an open field 3 days after cessation of kindling. Porsolt forced swimming test was not different among the control, 10- or 21-AD groups of rats. A deficit in sensorimotor gating, measured by prepulse inhibition of an acoustic startle, was observed in kindled as compared to control rats at 2 weeks after 21 ADs, but not after 10 ADs. Similarly, methamphetamine (1 mg/kg i.p.) induced higher locomotor activity in kindled rats, as compared to controls, after 21 ADs but not after 10 ADs. Spontaneous locomotor activity in a novel cage, without drug administration, was not different between kindled and control rats. These findings suggest that behavioral alterations after repeated hippocampal electrographic seizures may be mediated by increased dopaminergic functions, which may also mediate the psychiatric symptoms in human epileptic patients.

Keywords: Hippocampus; Behavioral sensitization; Schizophrenia; Temporal lobe epilepsy; Aggression; Social behavior

1. Introduction

It is well documented that a wide range of behavioral and cognitive changes may occur in patients with temporal lobe epilepsy (TLE) [25,40,41,44]. A cluster of temporal lobe seizures may induce postictal psychosis [25,44], and long-term epilepsy has been shown to result in schizophrenic-like symptoms in humans [40].

Kindling of the hippocampus and amygdala, two of the most epileptogenic areas in the temporal lobe [17,37], has been used as a model of human TLE. Hippocampal and amygadala kindling resulted in disturbed social behavior and emotions in rats [20,23,24] and cats [1–3,39]. However, except for the study in cats [2,3], most previous studies used full kindling and some used extended kindling to 99 after-discharges (ADs) [23,24].

It has been suggested that some of the behavioral changes after kindling may result from hyperdopaminergic functions [2,13,15,16]. Glenthøj et al. [16] showed that animals kindled by the ventral tegmental area, which sends dopaminergic fibers to the nucleus accumbens, were more sensitive to a naïve dose of amphetamine, much like rats after repeated injections of amphetamine [36,38]. Similarly, amygdala kindled rats showed a deficit of prepulse inhibition [26] much like rats given a psychotomimetic drug that induced dopamine release in the nucleus accumbens [43].

In a previous study, we showed that a single hippocampal AD resulted in postictal behavioral hyperactivity that could be blocked by injection of a dopamine D_2 antagonist into the nucleus accumbens [30]. If dopamine is released by a single hippocampal AD [42], we hypothesize that repeated hippocampal ADs, perhaps 10 or 21 ADs, will result in schizophrenia-like behavioral alterations. Several types of behaviors associated with schizophrenia—social behavior, prepulse inhibition and methamphetamine-induced locomotion were studied.

2. Materials and methods

The surgical and recording procedures have been described elsewhere [30]. Briefly, under sodium pentobarbital anesthesia, male Long-Evans rats were implanted

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Table 1
Duration (in s) of hippocampal AD for rats given partial hippocampal kindling of 10 or 21 ADs

Group of rats	1st AD	5th AD	10th AD	15th AD	21st AD	P
10-time kindling (9)	22 ± 2	40 ± 2	67 ± 6			< 0.0001
21-time kindling (7)	20 ± 3	44 ± 5	68 ± 7	93 ± 4	105 ± 7	< 0.001

Numbers in parentheses are rats in each group. $P < 0.001$ indicates a significant change in AD duration in the group (one-way ANOVA).

with recording electrodes (100 μm Teflon-insulated wires) in stratum radiatum and stratum oriens of the hippocampal CA1 region on both sides (A −3.5, L ± 2.7, and ventral (V) from skull surface −2.3–3.3; units in mm), according to the stereotaxic atlas of Paxinos and Watson [33]. Two screws were implanted in the frontal skull and cerebellum to serve as the stimulus anode and recording reference, respectively. Rats were allowed to recover at least for 7 days after surgery.

A hippocampal AD was induced by a 1 s, 200 Hz train of stimulus pulses (0.1 ms duration) delivered cathodally to stratum radiatum of one CA1, at an intensity of 3 × the commissural evoked potential threshold. For rats given 21 ADs (21-AD group), a single hippocampal AD was given on first day, and on each of the following 4 days, 5 ADs were given per day, at hourly intervals. For rats given 10 ADs (10-AD group), 5 ADs were given per day for 2 consecutive days. A group of control rats, of similar age as the kindled ones, was implanted with electrodes and handled, but no kindling stimuli were given. Duration of ADs was recorded in the contralateral CA1.

A series of behavioral tests was conducted 3–4 days after the last AD in each kindled group, and equivalent rest time in

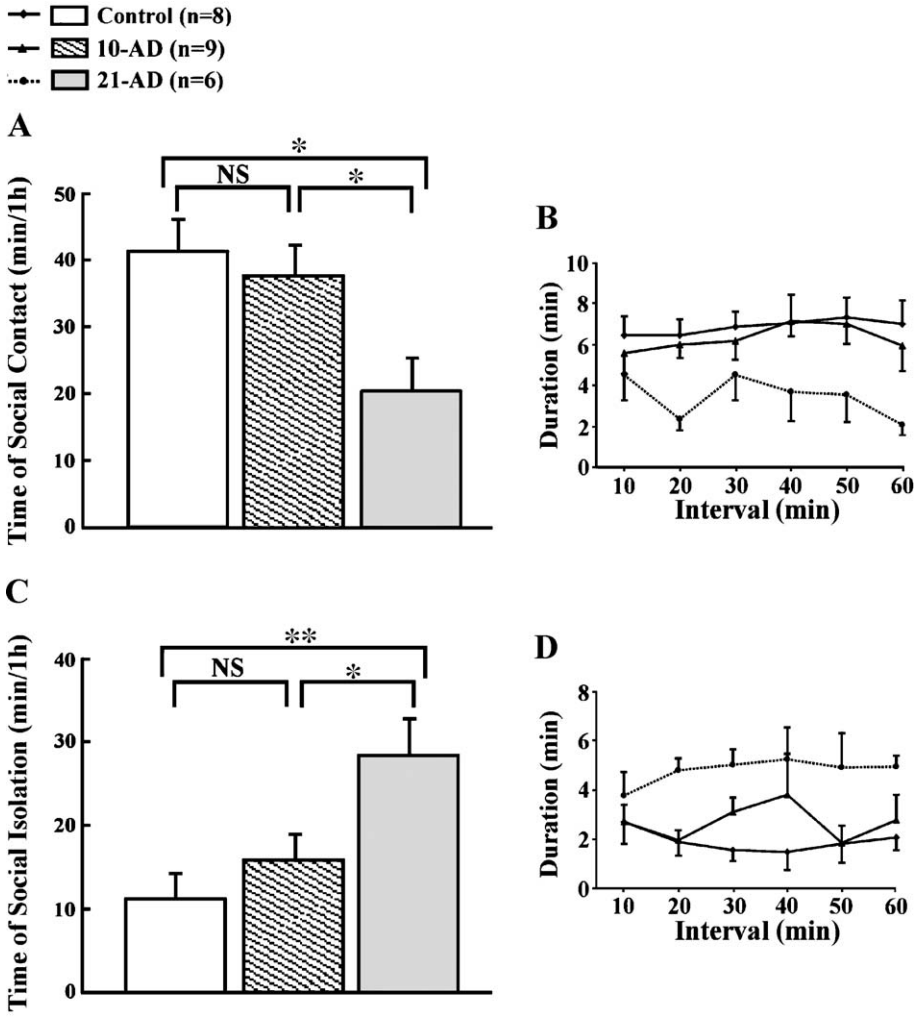

Fig. 1. Effects of 10- and 21-times hippocampal kindling, respectively, 10- and 21-AD groups (AD = afterdischarge), on social contact (A and B) and social isolation in an open field (C and D) measured 3–4 days after last kindling. Total time in min within 1 h of testing was measured in A and C, and duration (min) in every 10 min intervals is shown in B and D. *$P < 0.05$; difference between two groups (Newman–Keuls post hoc test after one-way ANOVA). NS, no significance.

control groups. In order to avoid non-specific stress associated with several sessions of behavioral testing, the prepulse inhibition test and methamphetamine challenge were carried out 2 weeks after the last AD, or equivalent rest in the control group. A 2-week interval was chosen because dopaminergic receptors in the nucleus accumbens were reported to be increased at this time after hippocampal kindling [13]. The prepulse inhibition test was given 1 day earlier than the methamphetamine challenge in order to avoid a possible residual drug effect on prepulse inhibition test.

An open field consisted of an area of 100 cm × 100 cm surrounded by 30 cm high metal walls. Hockey tape on the floor was used to divide the open field into 16 squares. Different rats in the open field were identified by the color of nail varnish painted on the dental cement on top of the rat's head.

2.1. Male/male interaction

Two rats (a test rat that was kindled or control paired with an unfamiliar rat) were placed in the open field for 10 min, and the cumulated duration of chasing was estimated. Chasing was defined when the test rat ran after the unfamiliar one, with or without attacking the chased rat. All rats were used only once for this test.

2.2. Social behaviors

Four rats were put into the open field. Behavioral activities were recorded for 2 h by camera on videotape, and only the behaviors during the second hour were analyzed by playback of the videotape. The duration of "social contact" was defined as the time that the rat occupied the same square with another rat, and the duration of "social isolation" as the duration of the rat stayed alone in one square with complete absence of body contact with any rats. An episode of climbing was defined as a rat grasping the top edge of the wall of the open field with its forepaws, with its hind paws lifted up from the floor.

Porsolt forced swimming test is a test of behavioral despair and depression in animals [8,35,45]. A rat was placed in a plastic tank (100 cm × 50 cm) containing 24 °C water at a depth of 50 cm. The time spent in immobility (motionless floating on the surface of the water) and struggling (vigorously breaking the water surface with the head and forepaws) were measured. After 15 min in the tank, the rat was removed and allowed to dry in a warm environment (28 °C) before being returned to its home cage.

Horizontal movements (locomotion) of a rat were measured by the number of interruptions of infrared beams in a plastic chamber (69 cm × 69 cm × 49 cm). Four independent infrared sources, at 23 cm intervals, were located on a horizontal plane 5 cm above the floor, with photodiode detectors on the other side. Interrupts of the beams were counted and transferred to a microcomputer via an interface (Columbus Instruments).

An 8.2 cm diameter Plexiglas cylinder served as the startle chamber (SR-LAB, San Diego Instruments, San Diego, CA). A piezoelectric accelerometer was used to detect startle amplitude, and bursts of acoustic noise were given by a loudspeaker mounted 24 cm above the rat. An IBM-compatible microcomputer with SR-Lab software and interface was used to present acoustic stimuli and to record data. During PPI testing, a rat was put in the startle chamber for a 5 min acclimation period with a 68 dB background noise. After the acclimation period, the rat was given four types of stimuli: (i) startle pulse (120 dB 40 ms broadband burst), (ii) prepulse of three different intensities of 73, 75, or 80 dB (20 ms broadband) presented 100 ms prior to startle pulse. The session was designed with five trial types: startle pulse alone, each of three prepulses followed by a startle pulse or a period of no acoustic stimulation. For each test session, 50 trials (10 startle pulse, 10 no stimulation, 10 of each prepulse trial types) were given in randomized order. Intertrial interval was 15 s. Two test sessions were run continuously and the results of two test sessions were pooled for final data. In this study, mean values of the prepulse intensity of 73, 75, 80 dB (integrated prepulse intensity) and each of the three types of

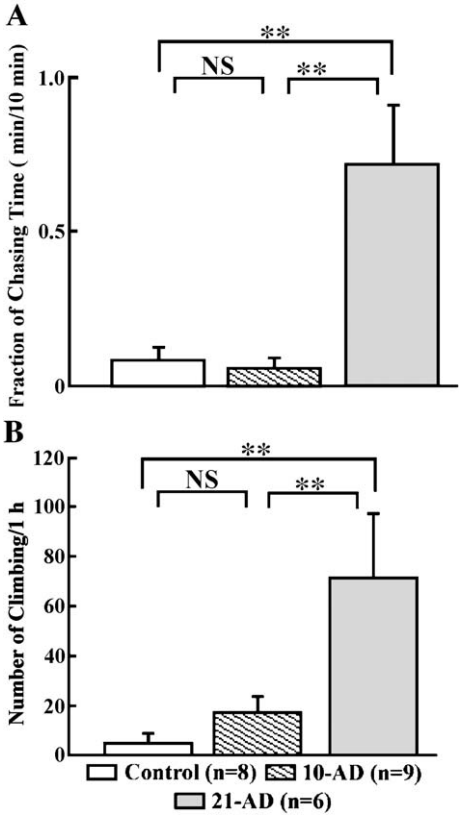

Fig. 2. Effects of 10- and 21-hippocampal AD on chasing (A) and climbing (B) behavior in an open field measured 3 days after last kindling. $^{**}P < 0.01$, difference between two groups (Newman–Keuls post hoc test after one-way ANOVA). NS, no significance.

intensity was used for calculation of the percentage of the PPI as follows:

$$\text{PPI (in percent)} = 100\left\{1 - \frac{\text{mean response amplitude in startle trials with prepulse}}{\text{mean response amplitude to startle alone}}\right\}$$

Statistical analyses were performed using paired *t*-test (two-tailed), one-way or two-way repeated measure analysis of variance (ANOVA), followed by Newman–Keuls post hoc test. *P*-values of <0.05 were considered to be statistically significant.

3. Results

3.1. Stages of seizure-induced by kindling and duration of hippocampal AD

Of 16 rats used for 10- or 21-times kindling, no convulsions were observed except in one rat, which developed stage three seizures with unilateral forepaw clonus [37] on the 21st AD. All other rats showed a typical electrographic seizure followed by postictal hyperlocomotion. Average durations of AD at the 1st, 5th, 10th, 15th and 21st AD were shown in Table 1. For each group of animal (10- or 21-AD groups), the duration of AD progressively increased with the number of AD given [$F(2,18)=58.46$, $P<0.0001$ in 10-AD group, and $F(4,28)=63.22$ in 21-AD group, $P<0.001$, one-way ANOVA]. The AD durations up to the 10th AD were not different between the 10- and 21-AD groups.

3.2. Social contact and isolation in open field test

Social contact and isolation in an open field test were examined 3 days after the last AD of each group. The time of social contact was significant different among the groups [$F(2,20)=4.70$, $P<0.05$, one-way ANOVA]. Post hoc Newman–Keuls test showed that rats kindled with 21 ADs showed a significant decrease in social contact as compared to control and 10-AD rats (Fig. 1A, B). Similarly, the time of social isolation was different among groups [$F(2,20)=6.41$, $P<0.01$, one-way ANOVA], and post hoc Newman–Keuls test showed that the 21-AD group had significantly higher time of social isolation compared to control and 10-AD rats (Fig. 1C, D). Post hoc tests did not reveal differences between control and 10-AD groups in social contact or social isolation.

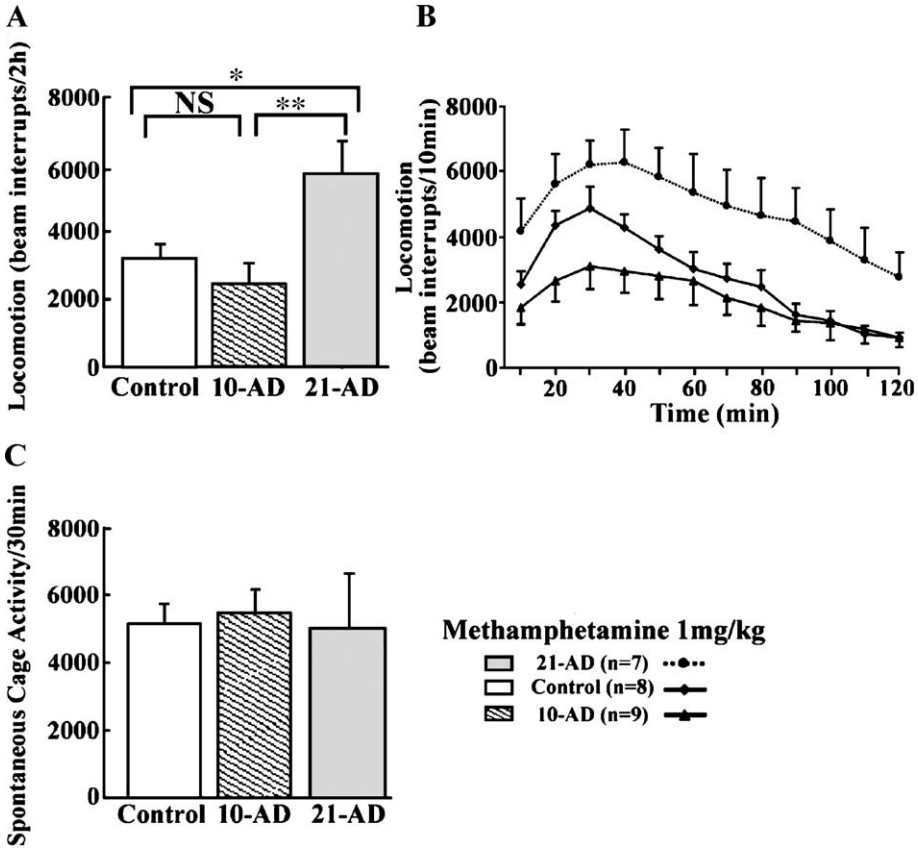

Fig. 3. Effects of 10- and 21-times hippocampal kindling on methamphetamine-induced behavioral hyperactivity (A and B) and spontaneous cage activity (C) measured by an activity counter 2 weeks after kindling. *$P<0.05$; **$P<0.01$; difference between two groups (Newman–Keuls post hoc test after one-way ANOVA). NS, no significance.

3.3. Climbing and chasing behavior in an open field

The control, 10- and 21-AD groups of rats showed a significant difference in chasing behavior [$F(2,20)=14.61$, $P<0.0001$, one-way ANOVA]. Rats with 21 ADs were found to spend a longer time in chasing behavior as compared to control rats and to rats with 10 ADs ($P<0.01$, post hoc Newman–Keuls; Fig. 2A). Similarly, the number of episodes of climbing in rats was different among the three groups of rats [$F(2,20)=6.88$, $P<0.01$], and post hoc Newman–Keuls test showed that rats with 21 ADs had significantly higher number of climbing than controls and 10-AD rats (Fig. 2B). Climbing episodes and chasing behavior was not significantly different between 10-AD and control rats (Fig. 2).

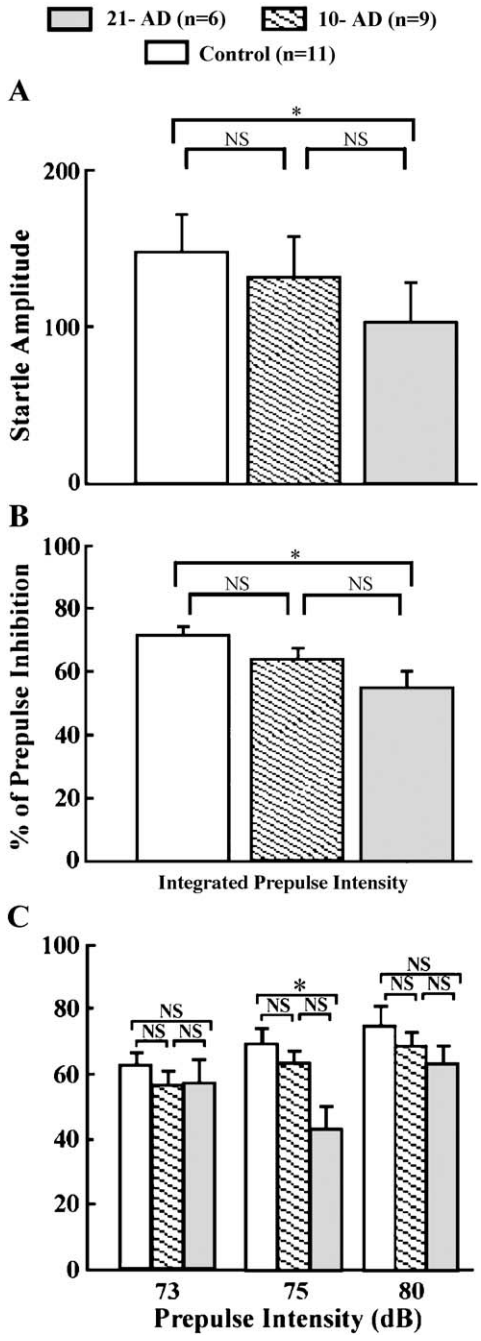

Fig. 4. Effects of 2 weeks after 10- and 21-times hippocampal kindling on startle amplitude (A) and prepulse inhibition to an acoustic startle stimulation calculated by integrated (B) and individual (C) prepulse inhibition. 21-AD group had six rats only, since data from one rat could not be retrieved because of technical problems. *$P<0.05$; difference between two groups (Newman–Keuls post hoc test after one-way ANOVA). NS, no significance.

3.4. Porsolt forced swimming test and locomotion induced by methamphetamine

Time of struggling and immobility of Porsolt forced swimming test was examined 3 days after kindling. Neither the time of struggling [$F(2,21)=1.82$, $P=0.19$] nor the time of immobility was significantly different among controls, rats with 10 ADs, and rats with 21 ADs [$F(2,21)=0.14$, $P=0.67$).

Methamphetamine (1 mg/kg i.p.) challenge was given 2 weeks after kindling or control treatment. The number of infrared beam interruptions after metamphetamine showed a significant main effect between kindled and control groups [$F(2,20)=5.82$, $P<0.02$, one-way ANOVA] (Fig. 3A, B). Post hoc Newman–Keuls test revealed a significant difference ($P<0.05$) between control and 21-AD, or between 10- and 21-AD groups, but not between control and 10-AD groups. When placed in a novel cage, there was no difference in the spontaneous locomotor activity among control, 10- and 21-AD groups of rats in the infrared beam chamber (novel environment) before methamphetamine (Fig. 3C).

3.5. Prepulse inhibition test

Prepulse inhibition was tested 2 weeks after last day of kindling. There was no significant difference in the startle amplitude among the three groups [$F(2,23)=0.66$, $P=0.52$, one-way ANOVA] (Fig. 4A). Rats with 21 ADs showed a significantly different PPI from controls and rats with 10 ADs (Fig. 4B,C), as calculated by integrated prepulse intensity [$F(2,23)=5.30$, $P<0.05$] (Fig. 4B). The latter difference in PPI was only significant for prepulse intensity of 75 dB [$F(2,23)=5.97$, $P<0.01$], but not for 73 and 80 dB [$F(2,23)=0.55$ and 1.15, respectively; $P>0.05$] (Fig. 4C). There was no difference in PPI between control and 10-AD groups.

4. Discussion

The present study demonstrated that partial hippocampal kindling resulted in long-term changes of a wide range of behaviors including social and aggressive behaviors, climbing, sensorimotor gating and enhanced response to methamphetamine. Immobility in the Porsolt forced swimming test and spontaneous activity in a novel cage remained

unchanged. Changes in behaviors were observed after 21 but not after 10 hippocampal ADs.

Although the precise neural mechanisms mediating the behavioral effects of partial hippocampal kindling are not known, there is evidence that alterations in a circuit involving the hippocampus and nucleus accumbens may mediate the behavioral changes reported in this study. The hippocampus sends dense glutamatergic fibers to the nucleus accumbens [22,49] and activation of the hippocampus may induce dopamine release in the nucleus accumbens [9,10,27]. A hippocampal AD was suggested to induce dopamine release in the nucleus accumbens [30,42]. Dopaminergic D_2 receptors in the nucleus accumbens were also reported to increase 2 weeks after hippocampal kindling [13].

Five behaviors were altered in rats after 21 hippocampal ADs as compared to control rats: (1) increase in climbing episodes, (2) increase in locomotion after methamphetamine, (3) decrease in PPI, (4) decrease in social contact and increase in social isolation, and (5) increase in chasing or aggressive behaviors. An increase in dopamine functions in the nucleus accumbens could explain the first three behaviors. Climbing behavior was presumably mediated by the nucleus accumbens through a dopaminergic mechanism [12,52]. Methamphetamine induces dopamine release in the nucleus accumbens [51], and increased locomotion is mediated by increased dopaminergic functions in the accumbens [32]. One example is the increased sensitivity of dopaminergic receptors in the mesolimbic system after repeated administration of psychotomimetic drugs [36,38]. Enhancing dopaminergic functions in the nucleus accumbens by various means will induce a decrease in PPI [43,50].

The hippocampus may participate in social behavior. Lesion of the hippocampus decreased social interactions in rats [48] and injection of a benzodiazepine into the hippocampus increased social interactions [19]. Neonatal damage of the ventral hippocampus induced a long-term decrease in social contact in a model of schizophrenia [5,6]. However, how kindling may alter social behavior is not known. Hippocampal kindling may alter benzodiazepine and $GABA_A$ receptor functions in the hippocampus [29,46,47] and thus social interactions. However, social behavior may also be controlled by other brain areas, including amygdala [14] and neocortex [48].

Aggressive behavior is typically not associated directly with the hippocampus-accumbens circuit. Instead, the amygdala and its connection to the hypothalamus are well known to mediate aggressive behaviors [2,18,31]. The enhanced chasing behaviors following partial hippocampal kindling may be mediated indirectly through hippocampal connections to the amygdala [34], and a hippocampal AD usually spreads to the amygdala [28].

This study shows that a minimal number of hippocampal ADs (>10) was required for changes related to social behavior. However, convulsive or generalized seizures [20,23,24,26] were not necessary. Cell death, which was only detectable after many generalized seizures [11] cannot be the main cause of behavioral alterations. Previous studies used 99 ADs for the study of aggressive and social behaviors in rats [23,24], but only 21 hippocampal ADs can increase chasing behavior in rats. Similarly, aggressive behaviors in cats were induced by partial kindling (12 ADs) of the ventral hippocampus [2,3].

The hippocampus is one of the structures implicated in schizophrenia [4,7,21]. Repeated hippocampal seizures are suggested to induce long-lasting functional changes in the hippocampal-accumbens circuit that may mediate psychotic behavior. In TLE patients, a cluster of temporal lobe seizures [25,44] or long-term epileptic condition may be associated with psychotic symptoms, such as decreased social interests, aggression, and psychomotor hyperactivity [40,41]. These epileptic related psychiatric symptoms can be relieved by antipsychotic drugs [41]. We have previously shown that systemic or accumbens injection of haloperidol, an antipsychotic drug that acts on dopaminergic receptors, blocked the hippocampal seizure-induced behavioral hyperactivity [30]. The similarities between the psychotic behaviors in humans with TLE and in rats after hippocampal kindling may suggest that similar neural mechanisms mediate these behaviors in humans and rats [1]. A thorough understanding of the alteration of the hippocampal-accumbens circuit and its hyperdopaminergic functions after hippocampal kindling may offer remedy and treatment for the adverse behavioral changes in human TLE.

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