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Effects of hippocampal partial kindling on sensory and sensorimotor gating and methamphetamine-induced locomotion in kindling-prone and kindling-resistant rats

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ABSTRACT

The effects of hippocampal partial kindling on gating of hippocampal auditory-evoked potentials (AEPs), prepulse inhibition (PPI) to an acoustic startle response, and methamphetamine-induced locomotion were examined in selectively bred kindling-prone (Fast) and kindling-resistant (Slow) rats. Ten electrographic seizures (afterdischarges, ADs) induced by high-frequency stimulation of the hippocampal CA1 region resulted in deficits in gating of hippocampal AEP and PPI in Fast, but not Slow, rats. The increase in AD duration with kindling was similar in Fast and Slow rats. Kindling-induced changes in hippocampal AEP and PPI in Fast rats were abolished by pretest injection of CGP7930 (1 mg/kg i.p.), a positive allosteric modulator of $GABA_B$ receptors. Injection of haloperidol (0.1 mg/kg i.p.) daily before kindling also prevented kindling-induced changes in PPI and hippocampal AEP in Fast rats. Interestingly, methamphetamine-induced hyperlocomotion was enhanced by kindling in Slow, but not Fast, rats. However, the methamphetamine-induced hyperlocomotion in Slow rats was not suppressed by daily injection of 0.1 mg/kg i.p. haloperidol before kindling, as compared with kindling without haloperidol. It is concluded that genetic disposition affected the behavioral consequences of repeated seizures. Fast rats required fewer hippocampal ADs to induce sensory (AEP) and sensorimotor (PPI) deficits, while Slow kindled rats were more sensitive to methamphetamine-induced locomotion. Dopaminergic blockade by haloperidol during kindling, or acute injection of CGP7930 before testing, attenuated some of the behavioral deficits induced by repeated hippocampal seizures, suggesting possible therapeutic strategies to treat the schizophrenic-like symptoms associated with temporal lobe epilepsy.

1. Introduction

Prevalence of psychosis in temporal lobe epilepsy (TLE) patients is much higher than in a population without epilepsy [1–3]. The behavioral comorbidity associated with TLE could be more devastating for the patients than the seizures themselves [3,4]. Medial temporal lobe seizures, arising from the hippocampus and amygdala, were shown to increase dopaminergic function and induce schizophrenic-like symptoms in animals [5–7]. This is attributed to dense neural pathways from the hippocampus and amygdala to the nucleus accumbens [8,9] that provide the interface with the mesolimbic dopaminergic system [10].

We have previously demonstrated that a single hippocampal afterdischarge (AD) or electrographic seizure in rats induced behavioral hyperlocomotion [11] and sensorimotor gating deficit [12,13] within 30 min after seizure. Partial kindling of the hippocampus using 21 ADs induced a loss of prepulse inhibition (PPI) to acoustic startle and an increase in methamphetamine-induced locomotion for up to 2 weeks after kindling [14]. The increase in psychosis-relevant behaviors after a single or repeated hippocampal AD suggests that the hippocampus is involved in psychiatric symptoms related to TLE.

In order to study the relation between seizure susceptibility and seizure-induced behavioral and physiological disruptions, we used two strains of rats selectively bred for Fast versus Slow kindling of the basolateral amygdala [15,16]. Fast, as compared with Slow rats, also showed a faster kindling rate in the hippocampus and other areas [16]. Fast rats are associated with an immature pattern of expression of $GABA_A$ receptor subunits as compared with control Long–Evans rats or Slow rats [17,18]. They have learning deficits [19] and manifest symptoms similar to attention deficit hyperactivity disorder without induction of seizures [20]. However, whether Fast rats, as compared with Slow rats, show a higher sensitivity to kindling-induced behavioral and physiological deficits is not known.

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Whether kindling-induced behavioral deficits can be therapeutically treated has not been systematically studied. The kindling-induced schizophrenia-like symptoms suggest activation and sensitization of dopaminergic receptors during kindling [5,7]. Thus, as part of the present study, we attempted to block the activation of both D1 and D2 dopaminergic receptors by haloperidol during kindling. In addition, the $GABA_B$ receptor agonist baclofen was able to suppress schizophrenia-like behaviors [21,22], an effect which was also produced by a positive allosteric modulator of the $GABA_B$ receptor, CGP7930 [23]. Since hippocampal kindling decreased the function of hippocampal $GABA_B$ receptors [24,25], we attempted to normalize kindling-induced behavioral changes by enhancing $GABA_B$ receptor functions with CGP7930. The purpose of the present study was not primarily in treating the seizures but in treating seizure-induced psychiatric symptoms.

We investigated the consequences of partial hippocampal kindling on three psychosis-related phenomena — gating of hippocampal auditory-evoked potentials (AEPs), prepulse inhibition (PPI), and methamphetamine-induced hyperlocomotion. We hypothesized that Fast rats, as compared with Slow rats, need fewer hippocampal ADs to induce psychosis-related behaviors. In addition, we tested whether treatment with the dopaminergic antagonist haloperidol during kindling, or postkindling treatment with CGP7930, a $GABA_B$ receptor positive allosteric modulator, may reduce the behavioral and physiological deficits induced by partial hippocampal kindling.

2. Animals and methods

Breeding pairs of Fast and Slow kindling Long–Evans hooded rats were transferred from Carleton University to the University of Western Ontario (UWO), as a gift of Dr. Dan McIntyre. The rats were further selectively bred and housed in the animal quarters of UWO. Forty-seven Fast and 27 Slow male rats, of 2–3 months old, were used in this study. The rats were housed in pairs in Plexiglas cages and kept on a 12/12 h light/dark cycle (lights on at 7:00 h), at a temperature of 22 ± 1 °C. Rats were given food and water ad libitum. All experimental procedures were approved by the local Animal Use Committee and conducted according to the guidelines of the Canadian Council for Animal Care. Efforts were taken to minimize the pain and suffering of animals.

2.1. Surgery

Under pentobarbital anesthesia (60 mg/kg i.p.), rats were implanted with a pair of Teflon-coated stainless steel stimulating electrodes (127 μm) into the hippocampal CA1 region, straddling the pyramidal cell layer on both left and right sides (AP −3.5, L ± 2.8; V 3.3 and 2.3, units in mm), according to the atlas of Paxinos and Watson [26]. The dorsal electrode was located near CA1 stratum oriens and the ventral electrode in CA1 stratum radiatum. During surgery, the evoked potentials were monitored to ensure reversed basal dendritic responses across the dorsal and ventral recording electrodes. Two jeweler's screws were fixed in the skull over the frontal cortex and cerebellum to serve as stimulus anode and recording ground, respectively. All electrodes and screws were finally anchored to the skull with dental cement. One week was allowed for the animals to recover from surgery.

2.2. Kindling

A hippocampal AD was induced by a 1-s, 200-Hz train of stimulus pulses (0.1-ms duration) delivered cathodally to stratum oriens of CA1, at an intensity of 3–5× the commissural-evoked potential threshold. Stimulus current was delivered by a photoisolation unit driven by a Grass S88 stimulator. The maximum current used was 400 μA. If the stimulation current intensity that induced hippocampal AD was higher than 400 μA, the rat was excluded for the study. Each rat was kindled 2 times each day for 5 consecutive days, with a minimal 2-hour interval between ADs on each day. In one group of Fast rats, haloperidol was injected at 0.1 mg/kg intraperitoneally (i.p.) daily before the first AD of each day, and a control Fast rat group was injected with an equal volume of saline. For the haloperidol-injected Slow rats, a comparison was made between haloperidol-injected and -noninjected rats after kindling.

2.3. Measurement of gating of hippocampal auditory-evoked potentials (AEPs)

Seven Fast and 7 Slow rats were used for testing hippocampal AEP before and after kindling with or without acute injection of CGP7930. An additional 26 Fast rats were divided into 3 groups of nonkindled (8 rats), saline (9 rats), or haloperidol (9 rats) (injected daily prior to kindling) and only received AEP tests after kindling. Three days after kindling, the implanted electrodes were connected to a flexible cable that led through an opening of the semirestraining chamber. Auditory-evoked potentials (AEPs) were acquired at the stratum radiatum electrode following auditory click pairs separated by a conditioning-test (C-T) interval of 500 ms; each click was a white-noise burst of 20-ms pulse duration and at 75 dB. Click pairs were given 15 s apart. Single sweeps of the auditory-evoked potential were stored on the computer, and those sweeps with clear movement or electrical artifacts were rejected online, and additional sweeps could also be rejected offline. Twenty-five sweeps were averaged for the auditory-evoked potential, from which the ratio of amplitude in response to the test (2nd) pulse and that in response to the conditioning (1st) pulse was used for data analysis. In CGP7930/vehicle-treated rats, AEP recording was started 15 min after injection, and in rats without injection, recording was started immediately after the rat was put into the chamber.

2.4. Prepulse inhibition test

The same rats that were tested with AEP were tested with prepulse inhibition (PPI) 4 h later. The PPI was measured by SR-LAB (San Diego Instruments, San Diego, CA), using a piezoelectric accelerometer to detect acoustic startle amplitude [13]. In rats without drug injection, PPI testing started immediately after a rat was put into the chamber, and the testing session lasted about 25 min. Alternatively, PPI testing started 15 min after CGP7930/saline injection. After acclimating to 68-dB white noise for 5 min, the rats were given different sound stimuli — a startle pulse only (120 dB 40-ms broad band burst) or a startle pulse preceded 100 ms by a prepulse (20-ms broad band noise) of intensity 73, 75, or 80 dB. For each test session, 50 trials were given in randomized order — 10 trials with startle pulse only, 10 trials with no auditory stimulation, and 10 trials with one of the three prepulse intensities followed by a startle pulse. The PPI was measured as the difference between the response to the startle pulse alone and the response to prepulse-startle or PPI (in percent) = 100 × [1 − (mean startle response amplitude after a prepulse / mean amplitude of response to startle alone)].

2.5. Locomotor activity measurement

Thirteen Fast and 20 Slow rats, not previously used for AEP or PPI tests, were used for measurement of locomotion after methamphetamine injection. The Fast rats were divided into kindled (6 rats) and nonkindled groups (7 rats), and the Slow rats were divided into kindled with saline (7 rats), kindled with haloperidol (6 rats), with daily injections prior to kindling, and a nonkindled group (7 rats). Horizontal movements (locomotion) of a rat were measured by the number of interruptions of infrared beams in a Plexiglas 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). Beam interruptions were counted in 5-min bins, starting 15 min after injection of methamphetamine (1 mg/kg i.p.), for a total of 60 min in both Fast and Slow kindled rats. An additional group of Slow rats