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Research report

Deep brain stimulation of the medial septum or nucleus accumbens alleviates psychosis-relevant behavior in ketamine-treated rats

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HIGHLIGHTS

- Ketamine induced changes in behaviors and electrophysiology in rats.
- Behavioral changes included hyperlocomotion and loss of prepulse inhibition.
- Physiological changes included enhanced hippocampal gamma and reduced auditory gating.
- Deep brain stimulation of medial septum or n. accumbens normalized the behaviors.
- Medial septal deep brain stimulation normalized hippocampal gamma and auditory gating.

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ABSTRACT

Deep brain stimulation (DBS) has been shown to be effective for relief of Parkinson's disease, depression and obsessive-compulsive disorder in humans, but the effect of DBS on psychosis is largely unknown. In previous studies, we showed that inactivation of the medial septum or nucleus accumbens normalized the hyperactive and psychosis-related behaviors induced by psychoactive drugs. We hypothesized that DBS of the medial septum or nucleus accumbens normalizes the ketamine-induced abnormal behaviors and brain activity in freely moving rats. Male Long-Evans rats were subcutaneously injected with ketamine (3 mg/kg) alone, or given ketamine and DBS, or injected with saline alone. Subcutaneous injection of ketamine resulted in loss of gating of hippocampal auditory evoked potentials (AEPs), deficit in prepulse inhibition (PPI) and hyperlocomotion, accompanied by increased hippocampal gamma oscillations of 70–100 Hz. Continuous 130-Hz stimulation of the nucleus accumbens, or 100-Hz burst stimulation of the medial septum (1 s on and 5 s off) significantly attenuated ketamine-induced PPI deficit and hyperlocomotion. Medial septal stimulation also prevented the loss of gating of hippocampal AEPs and the increase in hippocampal gamma waves induced by ketamine. Neither septal or accumbens DBS alone without ketamine injection affected spontaneous locomotion or PPI. The results suggest that DBS of the medial septum or nucleus accumbens may be an effective method to alleviate psychiatric symptoms of schizophrenia. The effect of medial septal DBS in suppressing both hippocampal gamma oscillations and abnormal behaviors induced by ketamine suggests that hippocampal gamma oscillations are a correlate of disrupted behaviors.

1. Introduction

Schizophrenia is a heterogeneous mental disease that includes both positive and negative syndromes [3,27]. Subanesthetic doses of ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist [4], have been shown to induce schizophrenic like symptoms in normal humans [32] and aggravate psychiatric symptoms in schizophrenic patients [33]. Psychiatric symptoms induced by ketamine were accompanied by increased cerebral blood flow in limbic areas such as the anterior cingulate cortex (including medial prefrontal cortex) and insula [33,34]. Ketamine and other NMDA receptor hypofunction models of schizophrenia have contributed to the understanding of the mechanism and treatment of schizophrenia [25,56], extending beyond theories of dopaminergic hyperfunction [19,26,57].

In animals, a single subanesthetic dose of ketamine induces a spectrum of behavioral abnormalities that model the symptoms of schizophrenia in humans. The symptoms include hyperlocomotion

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[46], deficit of prepulse pulse inhibition (PPI) [31,46,69], and loss of gating of hippocampal auditory evoked potentials (AEPs) [48,49]. In addition, a subanesthetic dose of ketamine increased gamma or high-frequency oscillations in many brain areas in animals, including the hippocampus [50], nucleus accumbens [21,22] and auditory, motor and visual cortices [20,31,59]. Schizophrenia in patients is associated with altered gamma-frequency electroencephalogram (EEG), shown as an increase in spontaneous gamma activity [5,23,24], and a decrease in evoked gamma activity or synchronization in other studies [18,67,72]. Altered gamma activity may be a manifestation of the abnormal local inhibitory networks [36,41,76] that underlie schizophrenia [7,10,72].

A neural circuit involving the medial septum, hippocampus and nucleus accumbens is suggested to mediate some of the psychosis-related symptoms induced by an NMDA receptor antagonist in animals [21,42,55,70]. Infusion of muscimol into the medial septum [44,46–48] or selective lesion of medial septal GABAergic neurons [49] normalized the hippocampal gamma waves and the behavioral symptoms induced by an NMDA receptor antagonist, including hyperlocomotion, PPI and AEP deficit. These findings are consistent with the results that the medial septal neurons control the hippocampal EEG [8,74] and hippocampus-mediated behaviors [9]. Inactivation of the nucleus accumbens suppressed locomotor activity induced by low-dose general anesthetics [45].

Recently, deep brain stimulation (DBS) has been used as a therapeutic treatment of several neurological and psychiatric diseases. DBS of a brain area may alleviate the symptoms mediated by the local area, such as tremor in Parkinson's disease [6,62]. In other cases, DBS may have an effect in normalizing neural circuitry, such as DBS of the nucleus accumbens may be therapeutic for obsessive-compulsive disorder [68] perhaps by suppressing neural activity in the orbitofrontal cortex [51]. The hippocampus and the nucleus accumbens have been proposed as therapeutic targets for DBS in schizophrenic patients [53], in line with the role of a septohippocampal-accumbens circuit in mediating different psychosis-related behaviors. DBS of the ventral hippocampus relieved the deficit in gating of the auditory evoked potentials in an animal model of schizophrenia [12].

Whether DBS is effective in treating psychosis-related symptoms in freely behaving animals has not been experimentally studied. Based on the role of the septohippocampal-accumbens circuit in mediating hyperlocomotion and PPI/AEP deficit, we hypothesized that DBS of the medial septum or the nucleus accumbens will alleviate the behavioral effects induced by ketamine in rats. Since the medial septum also controls hippocampal EEG, we hypothesized that medial septal DBS will also suppress ketamine-induced hippocampal gamma wave increase.

2. Materials and methods

2.1. Surgery

Under pentobarbital anaesthesia (60 mg/kg i.p.), male Long-Evans rats weighing between 250 and 300 g were implanted with a pair of Teflon-coated stainless steel stimulating electrodes (127 μm) into the medial septum (anterior–posterior (AP) 0.7, lateral (L) 0 or midline, ventral to skull (V) 6.0 and 6.5, all units in mm, according to the atlas of Paxinos and Watson [58]). In order to avoid the midsagittal sinus, a drill hole on the skull was made 0.5 mm lateral to midline and the septal electrode was inserted with a 5° slant from the vertical. In rats for septal stimulation, four pairs of electrodes were implanted bilaterally into the hippocampus (AP-3.2, L ± 1.7; AP-4.6, L ± 2.8; V 3.3 and 2.3) for recordings of hippocampal AEPs or EEG. For accumbens stimulation, a pair of electrodes was implanted into the right accumbens shell region (AP1.5, L1.2, V7.5 and 7.9). Two jeweller's screws were fixed in the skull over the frontal cortex and cerebellum, to serve as reference and ground for recording hippocampal evoked potentials and EEGs. All electrodes and screws were finally anchored to the skull with dental cement. One week was allowed for the animals to recover from surgery. 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.

2.2. Experimental procedures

Experiments were conducted between 9:00 and 18:00 h. A total of 57 rats were used – 28 for septal DBS with ketamine, 17 for accumbens DBS with ketamine, 12 for testing septal or accumbens DBS alone without administration of ketamine; all rats were implanted with electrodes, including those used for experiments without DBS. Four different responses were recorded in the present study – horizontal locomotion, prepulse inhibition (PPI), gating of auditory evoked potentials and EEG recordings in the hippocampus. For each type of measure, the same rat was given three treatments, in random order with at least one week between treatments: (1) ketamine alone, (2) saline alone or (3) ketamine with DBS of one structure (medial septumor nucleus accumbens). When DBS was applied after ketamine injection, the stimulation started immediately after ketamine injection and continued for the whole duration of any experiment. The one-week separation between treatments was considered adequate since no behavioral and EEG effects of ketamine/saline injection could be detected after one week. In addition, randomization effectively removed effects that may depend on treatment order. Separate rats were used to test the effect of DBS alone, without ketamine, on spontaneous locomotion or PPI. In randomized order, locomotion or PPI tests were done, with or without septal or accumbens DBS on the same rats, without administration of any drugs.

For locomotor activity, horizontal movements of a rat in a Plexiglas chamber (69 × 69 × 49 cm) were measured by the number of interruptions of infrared beams (Columbus Instruments), which were transferred to a microcomputer via an interface. For ketamine injection/control experiments, a rat was habituated for at least 1 h in the chamber, and then the number of infrared beam interruptions was counted every minute, for 5 min during baseline (before injection) and 30 min after ketamine injection with or without DBS, or for 30 min after saline injection alone. For experiments to test the effect of DBS alone versus no stimulation, without ketamine injection, a rat was placed into the chamber and infrared beam interruptions were counted for 30 min, without habituating the rat. No habituation ensured the presence of a certain level of locomotor activity, such that a possible suppressive effect of DBS can be tested.

PPI was measured by SR-LAB (San Diego Instruments, San Diego, CA), using a piezoelectric accelerometer to detect startle amplitude [47]. If DBS was applied after ketamine, it was started immediately after placing a rat into the PPI test chamber. After acclimating to 68-dB white noise, the rat was 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. PPI was measured as the difference between the response to the startle pulse alone and the response to the combination of prepulse and 120-dB startle pulse, i.e., PPI (in percent) = 100 × [1 − (mean startle response amplitude after a prepulse/mean amplitude of response to startle alone)]. In this study, the PPI was estimated