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Medial septum modulates hippocampal gamma activity and prepulse inhibition in an *N*-methyl-D-aspartate receptor antagonist model of schizophrenia

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ABSTRACT

We reviewed the participation of the septohippocampal system in an animal model of schizophrenia that was acutely induced by systemic injection of an *N*-methyl-D-aspartate (NMDA) receptor antagonist such as phencyclidine, MK-801 and ketamine. The NMDA receptor antagonist-induced model of schizophrenia is characterized by behavioral and electrophysiological disruptions, including a decrease in prepulse inhibition of the acoustic startle response (PPI), hyperlocomotion, decrease in gating of hippocampal auditory evoked potentials and robust increase in hippocampal gamma (30–100 Hz) oscillations. Similar disruptions were also induced by a single electrographic seizure in the hippocampus. The behavioral and electrophysiological disruptions induced by an NMDA receptor antagonist can be reduced by inactivation or lesion of GABAergic neurons in the medial septum, deep brain stimulation of the medial septum or nucleus accumbens, or positive modulation of $GABA_B$ receptors. Our results suggest a close association between high-amplitude hippocampal gamma oscillations and psychosis-relevant behaviors including PPI loss, behavioral hyperactivity and loss in auditory gating. Abnormal electrophysiology suggests a disruption of somatic and apical dendritic inhibition in the hippocampus, resulting in distorted sensory integration, and impaired cognitive and memory processing. The hippocampus is suggested to be a hub in a brain network that participates in psychosis-relevant behaviors, through its direct projection to the nucleus accumbens, or through indirect connections via the entorhinal, cingulate and prefrontal cortices.

1. Introduction

1.1. Schizophrenia as a brain network disorder

Schizophrenia is recognized as a brain network disorder associated with positive and negative symptoms (Tandon et al., 2013). Functional neuroimaging has revealed involvement of the prefrontal cortex, medial temporal lobe including the hippocampus, and basal ganglia (Liddle et al., 1992; Silbersweig et al., 1995). Postmortem tissues of the temporal and frontal lobe show pathology of glutamate receptors (Harrison et al., 2003) and loss of GABAergic inhibitory neurons, particularly those expressing the calcium binding protein parvalbumin (Benes and Berretta, 2001; Gonzalez-Burgos and Lewis, 2012). Medial temporal lobe and the hippocampus in schizophrenia patients show increases in baseline blood perfusion and decreases in task-related activation (Heckers et al., 1998; Tamminga et al., 2012). CA3, a hippocampal area proposed to perform associative memory and pattern completion, has been suggested to mediate hallucinations in schizophrenia (Behrendt, 2016). In one study, relief of schizophrenia symptoms by risperidone treatment has been reported to be associated with decreased metabolism in the hippocampus (Liddle et al., 2000).

Abnormal electrical activity in electroencephalogram, in particular in the gamma frequency (30–100 Hz) band, has been reported in schizophrenia patients (Baldeweg et al., 1998; Gonzalez-Burgos and Lewis, 2012; Itil and Itil, 1986; Lee et al., 2003; Uhlhaas and Singer, 2010; Spencer et al., 2003). Schizophrenia patients show impairments of sensory gating and sensorimotor gating (Adler et al., 1985; Braff et al., 2001), two endophenotypes that have been studied by means of animal models. Lack of sensory or sensorimotor gating provides an intuitive view that schizophrenia patients cannot automatically habituate to ongoing sensory inputs. Sensory gating can be measured by paired-pulse sensory stimulation, and gating is the suppression of the response to the second pulse as compared to that of the first pulse. Sensorimotor gating is the gating of motor response by a sensory stimulus, and can be measured by prepulse inhibition (PPI), the ability of a preceding low-intensity sensory signal in attenuating a startle response. While not used as a diagnostic tool in schizophrenia, PPI provides a quantitative and reproducible measure that is reduced in many schizophrenia patients (Braff et al., 2001). PPI studies in animals have elucidated the

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neurobiological mechanisms underlying sensorimotor gating (Swerdlow and Geyer, 2001; Swerdlow et al., 2008).

The finding that non-competitive NMDA receptor (NMDAR) antagonists, phencyclidine (PCP) and ketamine, induce schizophrenia symptoms in humans provided a paradigm shift in schizophrenia research (Javitt and Zukin, 1991; Moghaddam and Krystal, 2012). Ketamine induces both positive and negative schizophrenia symptoms in normal humans, and it reproduces and aggravates the symptoms already present in schizophrenia patients (Krystal et al., 1994: Lahti et al., 1995). Previously, dopaminergic agonists were known to induce positive schizophrenia symptoms, and dopaminergic antagonists could serve as antipsychotics (Javitt, 2007). A current hypothesis is that glutamatergic NMDARs are the primary cause of schizophrenia, and dysfunctional dopaminergic mechanisms may be activated secondarily (Moghaddam and Krystal, 2012).

1.2. NMDA receptor antagonist model of schizophrenia in animals

In animals, PCP, ketamine, MK-801 and similar NMDAR antagonists induce psychosis-relevant behaviors, such as an increase in locomotor activity and a decrease in PPI (Javitt and Zukin, 1991; Mansbach and Geyer, 1989, 1991). Deficits in sensory gating (Miller et al., 1992) and abnormal gamma frequency activities (Leung, 1985; Ma and Leung, 2002; Uhlhaas and Singer, 2010) also validate the NMDAR antagonist model of schizophrenia in animals.

PCP, ketamine, and MK-801 are non-competitive antagonists that bind to a site different from glutamate on the NMDARs. NMDARs are expressed with high density in the hippocampus (Cotman et al., 1988), highest in the CA1 area. NMDARs are also abundant in the frontal cortex and nucleus accumbens (NAc). NMDAR antagonists more readily block excitation of inhibitory interneurons as compared to pyramidal cells (Grunze et al., 1996). In awake animals, NMDAR antagonists decrease firing of fast-spiking interneurons, which results in increased firing (disinhibition) of pyramidal cells in the prefrontal cortex (Homayoun and Moghaddam, 2007). Blockade of NMDARs disrupts synaptic plasticity, which plays a role in the acquisition of hippocampal-dependent and other types of memory (Morris, 2007).

C^{14} 2-deoxyglucose labeling in the brain has revealed that PCP (5 mg/kg i.p.) increases glucose metabolism in the limbic system, with the highest label in the molecular layer of hippocampal CA1, followed by posterior and anterior cingulate cortices (Meibach et al., 1979). The same brain areas, and other limbic areas such as the entorhinal cortex, mediodorsal thalamus, and cortical amygdaloid nucleus, also show an increase in glucose metabolism after MK-801 (Sharkey et al., 1996) and ketamine (Nelson et al., 1980; Oguchi et al., 1982). Subcortical and cortical auditory areas, such as the inferior colliculus, medial geniculate, and auditory cortex show a decrease in glucose metabolism after injection of an NMDAR antagonist (Meibach et al., 1979; Nelson et al., 1980; Oguchi et al., 1982; Sharkey et al., 1996).

Pathology in the anterior and posterior cingulate cortices was suggested to be a correlate of the NMDAR-antagonist induced behavioral disruptions in rats (Olney et al., 1989). The doses of PCP (2.8 mg/kg s.c.) and MK-801 (0.18 mg/kg s.c.) required to induce cingulate pathology are similar to those that induce PPI disruption. However, a 40 mg/kg s.c. dose of ketamine required for pathology (Olney et al., 1989) is >10 times that needed for PPI disruption (below).

We advocate the study of brain-behavior relations by using electrophysiological recordings in behaving animals. Gamma oscillations of 30–100 Hz in the hippocampus stand out as a prominent correlate of the behavioral disruptions induced by an NMDAR antagonist. The present review focuses on the relation between hippocampal gamma oscillations and PPI deficit, and the role of the medial septum, in the NMDAR antagonist model of schizophrenia.

2. Septohippocampal system, electrophysiology and psychosis-relevant behaviors

2.1. Systemic NMDAR antagonist injection induces behavioral disruptions

PPI disruption in Sprague-Dawley rats by an NMDAR antagonist (PCP, MK-801 or ketamine) was first reported by Mansbach and Geyer (1989, 1991). Our own studies used adult (2–4 months old) male Long-Evans rats, in which PPI and other behavioral and electrophysiological measures were recorded. The NMDA antagonists included PCP (1–5 mg/kg i.p.), ketamine (3–6 mg/kg s.c.), and MK-801 (0.5 mg/kg i.p.) (Table 1). The decrease in PPI was generally not different among different prepulse intensities (73, 75 and 80 dB noise pulses, delivered 100 ms preceding the 120-dB startle pulse), and the integrated PPI (averaged over 3 prepulse intensities) was used with units of % PPI (percent inhibition of the startle response amplitude). A group of rats following saline (i.p. or s.c.) injections showed an average 65–70% PPI, as compared to a large decrease of PPI to 20–30% following PCP (5 mg/kg i.p.), MK-801 (0.5 mg/kg i.p.) or ketamine (6 mg/kg s.c.) (Table 1; Fig. 1A2, Fig. 2A2). Lower dose of PCP (3 mg/kg i.p.) and ketamine (3 mg/kg s.c.) decreased PPI to a lesser degree of 35–50%, which was still significantly smaller than that after saline injection (Table 1). These PPI changes induced by different NMDAR antagonists were similar to those reported in Sprague-Dawley rats tested with similar parameters (Swerdlow et al., 1998).

Robust and prolonged increase in locomotor activity was found after PCP and MK-801 injection, and for a shorter duration after ketamine injection (Ma and Leung, 2000, 2007). Disruption of sensory input to the hippocampus can be demonstrated by an impaired gating of auditory

Table 1
Systemic and local drug injections or other animal models that showed hippocampal gamma activity increase and psychosis-relevant behaviors. NA = not available; # mean integrated PPI% in brackets.

Model	Dose	Hippocampal gamma	Locomotor activity	Prepulse inhibition#	References/comments
Ketamine s.c.	3 mg/kg	↑ (62–100 Hz)	↑	↓ (30%)	Ma and Leung, 2014
Ketamine s.c.	6 mg/kg	↑ (30–100 Hz)	↑	↓ (20%)	Ma and Leung, 2007
Saline s.c.	0.3 mL/kg	No change	No change	No change (70%)	
Phencyclidine i.p.	3 mg/kg 5 mg/kg	↑ (40–100 Hz)	↑	↓ (52%) ↓ (28%)	Ma et al., 2004
MK801 i.p.	0.5 mg/kg	↑ (40–100 Hz)	↑	↓ (22%)	Ma and Leung, 2007
Meth-amphetamine i.p.	1.5 mg/kg	No change	↑	NA	Ma and Leung, 2000
Carbachol intra-DG, ventral CA1, ventral SUB	0.4 μg/0.5 μL/side; bilateral	Not recorded	NA	↓ (60 ms interval)	Caine et al., 1991, 1992 PPI deficit not reversed by D2 antagonist spiperone 0.1 mg/kg s.c.
$GABA_B$ receptor antagonist CGP35348 or CGP56999A	Intra-hippocampal	↑ (30–60 Hz)	NA	↓	Leung and Shen, 2007; Ma and Leung, 2011
Hippocampal afterdischarge	>15 s duration	↑ (40–80 Hz)	↑	↓	Ma et al., 1996, 2004
Intra-hippocampal & amygdala MK-801	6.25 μg/0.5 μL/side; bilateral	NA	NA	↓	Bakshi and Geyer, 1998 (no PPI change for ventral hippocampus and medial prefrontal cortex infusion)

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