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An examination of the roles of glutamate and sex in latent inhibition: Relevance to the glutamate hypothesis of schizophrenia?

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ABSTRACT

The present study examined the effects of the glutamate receptor antagonist MK-801, the glutamate receptor agonist *N*-methyl-D-aspartate (NMDA), and sexual dimorphism on latent inhibition to elucidate the glutamate hypothesis of schizophrenia. During the pre-exposure phase, 56 male and 65 female Wistar rats were intracerebroventricularly administered normal saline, MK-801 or NMDA, in the left ventricle and then exposed to a passive avoidance box (or a different context) in three trials over 3 days. Then, all of the rats were placed in the light compartment of the passive avoidance box and were allowed to enter the dark compartment, where they each received a footshock (1 mA, 2 s) in five trials over 5 days. Injections of the glutamate drugs NMDA and MK-801 did not affect latent inhibition. Sexual dimorphism did not occur in latent inhibition. The present data on the male rats indicated that the glutamate system did not affect latent inhibition, indicating that the glutamate system was not like the dopamine system in terms of mediating the positive symptoms of schizophrenia. The glutamate system might be involved in the negative and cognitive symptoms of schizophrenia. The results may provide information for novel treatments of the negative and cognitive symptoms of schizophrenia.

1. Introduction

Schizophrenia has three major symptoms: positive, negative, and cognitive (Labrie et al., 2008; Weiner, 2003). Previous studies on the positive symptoms of schizophrenia often used the latent inhibition model (Gray et al., 1995). They also predominantly investigated the involvement of the mesocorticolimbic dopamine system, suggesting that the dopamine system is involved in the positive symptoms of schizophrenia (Feldon and Weiner, 1992; Gray et al., 1997). Some studies reported that the glutamate system also plays a crucial role in latent inhibition, representing the negative and cognitive symptoms of schizophrenia (Weiner and Arad, 2009). Latent inhibition appears to be an important model for assessing the symptoms of schizophrenia.

In the latent inhibition model, a conditioned stimulus (CS) is pre-exposed alone without any consequences (i.e., unconditioned stimulus [US]) in the pre-exposure phase. The CS is then associated with a US to form a CS-US association. The strength of the CS-induced response in the pre-exposure group is less than that in the non-pre-exposure group, referred to as latent inhibition (Escobar et al., 2002; Weiner and Feldon, 1997). Schizophrenia patients do not obtain latent inhibition (Lubow and Gewirtz, 1995) and cannot learn the CS-nothing association, which consequently interferes with subsequent CS-US conditioning (Escobar et al., 2002). One important issue is the involvement of glutamate neurotransmission in latent inhibition associated with schizophrenia. Numerous studies on this subject have reported discrepant results. For example, some studies suggested that glutamate antagonism in the brain disrupts the formation of latent inhibition (Davis and Gould, 2005; Razoux et al., 2007; Schauz and Koch, 2000; Traverso et al., 2010, 2003). *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine injections impaired latent inhibition when it was administered in the pre-exposure phase (Aguado et al., 1994; Razoux et al., 2007). Rats that receive injections of the noncompetitive NMDA receptor antagonist MK-801 after the pre-exposure phase exhibit a disruption of latent inhibition in the conditioned taste aversion paradigm (Traverso et al., 2003) and the cued fear conditioning paradigm (Davis and Gould, 2005). Infused D,L-2-amino-5-phosphonopentanoic acid (AP5; an NMDA receptor antagonist) in the basolateral nucleus of the amygdala prior to CS pre-exposure could abolish latent inhibition in the footshock-induced fear conditioning (Schauz and Koch, 2000) and conditioned taste aversion (Traverso et al., 2010) paradigms. A high (but not low) dose of phencyclidine (PCP), which is an NMDA receptor antagonist, appeared to disrupt latent inhibition when PCP was administered in the pre-exposure and conditioning phases (Turgeon et al., 2000, 1998). However, another research indicates that glutamate

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antagonism may potentiate latent inhibition (Gaisler-Salomon et al., 2009), and glutamate agonism may disrupt latent inhibition (Gaisler-Salomon et al., 2009; Gaisler-Salomon and Weiner, 2003). For example, a recent study on latent inhibition showed that glutaminase-deficient mice, which reduced glutamate transmission, potentiated latent inhibition (Gaisler-Salomon et al., 2009). A systematic administration of MK-801 appeared to be a persistent effect of latent inhibition, suggesting that glutamate antagonists might play a role in the facilitation or persistence of latent inhibition (Gaisler-Salomon and Weiner, 2003). In addition, the third hypothesis suggests that NMDA receptors do not govern latent inhibition and that NMDA antagonists do not affect latent inhibition (Palsson et al., 2005; Tenn et al., 2005; Weiner and Feldon, 1992). For example, a behavioral sensitization study showed that rats that were repeatedly exposed to amphetamine-induced sensitization exhibited an attenuation of latent inhibition, but PCP-sensitized rats did not present impairment in latent inhibition (Tenn et al., 2005). A similar study indicated that PCP did not affect latent inhibition when it was injected in the pre-exposure phase, although it was shown to potentiate latent inhibition when it was administered prior to the conditioning phase (Palsson et al., 2005). Furthermore, a behavioral pharmacology study found that low and high doses of PCP did not affect latent inhibition when PCP was injected during the pre-exposure, conditioning, and test phases, respectively (Weiner and Feldon, 1992). Therefore, the present study used glutamate antagonist MK-801 and glutamate agonist NMDA to examine whether the glutamate system influences latent inhibition in the animal model of schizophrenia.

On the other hand, sexual dimorphism has been investigated in latent inhibition (Bethus et al., 2005; Wang et al., 2012; Weiner et al., 1985). For example, a previous study showed that female rats exhibited latent inhibition regardless of the handling/non-handling conditions. Meanwhile, male rats exhibited latent inhibition in the handling condition but not in the non-handling condition (Weiner et al., 1985). Male rats that were not exposed to stress exhibited less latent inhibition than did female rats that were not exposed to stress. However, prenatal stress was shown to increase the magnitude of latent inhibition only in male rats and not in female rats (Bethus et al., 2005). Sex differentially affects the involvement of the brain's dopamine system in latent inhibition (Wang et al., 2012). Therefore, whether sex difference exhibits sexual dimorphism in the glutamate's latent inhibition model needed to be scrutinized in the present study.

Altogether, the glutamate compounds (including glutamate agonist NMDA and antagonist MK-801 injections, respectively) were microinjected in the left ventricle during the pre-exposure phase in different sex (male and female rats) to examine how the glutamate system and sex difference affect the pre-exposure effect of fear conditioning (latent inhibition). According to the data, the present study examined which glutamate hypothesis of schizophrenia as described above was supported.

2. Methods and materials

2.1. Animals

Fifty-six male and 65 female Wistar rats were purchased from the Laboratory Animal Center, National Taiwan University College of Medicine, Taipei, Taiwan. All of the rats weighed 220–350 g at the beginning of the experiment. They were raised in pairs in a group-housed plastic cage under a controlled temperature (22 ± 2 °C) and in a 12 h/12 h light/dark cycle (lights on from 6:00 AM-6:00 PM) with food and water available ad libitum. The study was performed in compliance with the Animal Scientific Procedures Act of 1986. The experimental protocol was approved by the Committee on the Ethics of Animal Experiments and Administrations of Fo Guang University.

2.2. Apparatus

The passive avoidance apparatus (95-cm length × 54-cm width × 39-cm height) had a one-step-through down alley and consisted of a light/safe compartment (35 cm; illuminated by a 25-W light) and dark/shock compartment (60 cm; no light with a footshock). These two compartments were divided by a guillotine door. The rat's latency to go from the light compartment to the dark compartment was recorded by a timer (Liang et al., 1994). The different box (45 cm length × 43 cm width × 43 cm height) had a white compartment with wood bedding.

2.3. Procedure

All of the rats underwent adaptation in their home cages in the colony room for 7 days and then underwent surgery. During the surgery phase, they were injected with atropine sulfate (0.1 mg/ml/kg, i.p.) and gentamicin (6 mg/ml/kg, i.p.) 20 min prior to anesthesia. They were then anesthetized with sodium pentobarbital (50 mg/ml/kg, i.p.), and their skulls were mounted in a stereotaxic apparatus. All of the rats were surgically implanted with an intracerebroventricular (i.c.v.) cannula in the left lateral ventricle (anterior/posterior, +1.68 mm; medial/lateral, −1.00 mm; dorsal/ventral, −4.6 mm) according to a rat brain atlas (Paxinos and Watson, 2007). The injection cannula remained in the left ventricle for an additional 1 min after the injection ended to allow for diffusion. The microinjection time was 4 min.

After 7 days of surgery recovery, the present experimental procedure was conducted according to our previous study (Wang et al., 2012). In the pre-exposure phase, all of the groups were given their respective microinjections and were exposed to the passive avoidance box (including the light and dark compartments) or to a different box. They were allowed to move from one compartment to the other compartment. The non-pre-exposure group was given normal saline, MK-801, and NMDA injections (i.c.v.) and was exposed to a different box. Then, the pre-exposure group was injected with normal saline, MK-801, and NMDA solutions (i.c.v.) and placed in the passive avoidance box. Therefore, all male and female rats formed 12 groups: the non-pre-exposure/saline/male (n = 8), the non-pre-exposure/MK-801/male (n = 12), the non-pre-exposure/NMDA/male (n = 12), the pre-exposure/saline/male (n = 8), the pre-exposure/MK-801/male (n = 8), the pre-exposure/NMDA/male (n = 8), the non-pre-exposure/saline/female (n = 11), the non-pre-exposure/MK-801/female (n = 10), the non-pre-exposure/NMDA/female (n = 12), the pre-exposure/saline/female (n = 11), the pre-exposure/MK-801/female (n = 13), and the pre-exposure/NMDA/female (n = 8) groups. Each group underwent three trials for 5 min without a footshock.

All of the rats were randomly assigned to the abovementioned groups. In the conditioning phase, they were then placed in the light compartment, and the latency to enter the dark compartment was recorded. When the rats moved to the dark compartment, they each received a footshock (1 mA for 2 s). This treatment was performed for 5 days with one trial per day. If the rat spent more than 10 min in the light compartment, then it was placed in the dark footshock compartment, and the latency time was recorded as 10 min (see Fig. 1).

2.4. Drugs

MK-801, NMDA, and sodium chloride were obtained from Sigma (Taipei, Taiwan). Sodium chloride powder was dissolved in distilled water to a final concentration of 0.9% sodium chloride solution (i.e., normal saline solution) for the pre-exposure and non-pre-exposure groups. MK-801 (2 μg/3 μl) and NMDA (1 μg/3 μl) were prepared in normal saline solutions. All of the injections were administered intracerebroventricularly in a total volume of 3 μl. The concentrations of glutamate antagonist MK-801 (Tian and Hartle, 1994) and glutamate agonist NMDA (Harkany et al., 2001; Pouzet et al., 2004) were modified with the previous data and tested via our pilot study

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