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Research report

Latent inhibition in rats neonatally treated chronically with MK-801: Differential effects on conditioned taste aversion and conditioned emotional response

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HIGHLIGHTS

- Effects of chronic neonatal NMDA receptor blockade were tested in adulthood rats.
- Treatment impaired latent inhibition of conditioned taste aversion without affecting conditioning.
- Treatment impaired neither conditioned emotional response nor its latent inhibition.
- Deficit in latent inhibition of conditioned taste aversion reflects abnormal development after treatment.

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ABSTRACT

Chronic neonatal blockade of *N*-methyl-D-aspartate (NMDA) receptors produces various abnormal behaviors in adulthood animals. This study investigated the effects of neonatal treatment chronically with MK-801 in rats on the preexposure-induced retardation of CS-US association, i.e. latent inhibition (LI), of two aversive classical conditioning tasks in adulthood. In conditioned taste aversion (CTA) using sucrose taste and LiCl, neonatal chronic MK-801 (0.4 mg/kg twice/day) treatment attenuated the inhibitory effect of sucrose preexposure on the aversive conditioning, although the treatment did not affect CTA conditioning itself. On the other hand, in conditioned emotional response (CER) using tone and electrical foot shock, rats neonatally treated with MK-801 showed the same degree of inhibitory effect of tone preexposure on the aversive conditioning compared with neonatally vehicle-treated rats, and also showed the same level of CER conditioning itself. Thus, the effect of chronic neonatal blockade of NMDA receptors on the LI of classical conditioning in adulthood was differentiated by the task employed. Results suggest that LI of CTA paradigm compared with that of CER is more sensitive to abnormal development after chronic neonatal blockade of NMDA receptors as an index of cognitive/attentional deficits caused by the treatment.

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1. Introduction

N-Methyl-D-aspartate (NMDA) receptors are a type of ionotropic glutamate receptors which mediate excitatory neurotransmission, and function as a predominant molecular device for controlling synaptic plasticity. Furthermore, in the early stage of life that is called brain growth spurt period [1], NMDA receptors also play an important role for development of the central nervous system, which is essential for neuronal differentiation and establishment or elimination of synapses [2–4]. Neonatal treatment of rats and mice with various NMDA receptor antagonists produces neurophysiological and anatomical alterations such as apoptotic neurodegeneration [5–9].

Prolonged behavioral alterations have been reported caused by early life chronic NMDA receptor blockade in rodents [10,11]. First, these include spatial learning impairment of adult rats in water maze [12], impaired spontaneous spatial alternation in a four-arm elevated maze [13], deficit of food-rewarded spatial learning in a maze [14], learning deficit of radial maze task [15] after chronic neonatal treatment with 5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepten-5,10-imine (MK-801), slower acquisition of delayed spatial alternation in T maze after chronic neonatal phencyclidine (PCP) treatment [16]. Thus, neonatal NMDA receptor blockade consistently disrupted spatial learning in

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previous studies. Second, locomotor activity is also one of the most investigated behavioral items in animals neonatally treated with NMDA receptor antagonists. In many cases, rodents with neonatal NMDA receptor blockade showed hyperactivity in various situations such as open-field and activity box [8,14,17–19], but in some reports there were not significant effects of the neonatal treatment [15,20–22]. Third, pre-pulse inhibition (PPI), a neurological inhibitory phenomenon induced by weaker pre-stimulus just before salient startle stimulus, has been also disturbed in animals neonatally treated with NMDA receptor antagonists [17,21,22] suggesting impairment of ability in sensory gating. It is well known that schizophrenics frequently show deficits of PPI function [23]. Thus the fact that animals neonatally treated with NMDA receptor antagonists show deficits in PPI suggests these animals could be suitable for an animal model of schizophrenia. On the other hand, it has been reported that schizophrenic patients suffer from selective attention deficit, especially with ignoring irrelevant stimuli [24,25].

Latent inhibition (LI) is a phenomenon that can be explained as a decrease in attention to or in the functional salience of the conditioned stimuli (CS) in classical conditioning, and is widely accepted as an index of the ability to ignore irrelevant stimuli [26]. In the context of classical conditioning, subjects given repeated exposure to a neutral stimulus (to-be-CS) without reinforcer (unconditioned stimulus: US) prior to CS-US pairing provide retarded acquisition or expression of subsequent CS-US association shown as reduction of conditioned response. Several studies reported abnormality of LI in schizophrenic patients [24,27,28]. It is well known that an acute systematic administration of NMDA receptor antagonist such as ketamine, PCP and MK-801 alter LI performance depending on the timing of treatment [24,29]. However, the effect of neonatal treatment with NMDA receptor antagonists on LI in adulthood has not been investigated.

The present study, therefore, investigated the long lasting behavioral effects of systemic administration of a NMDA receptor antagonist during the critical period for development of the central nervous system on LI in rats. In order to block NMDA receptor functions, we used a potent and selective, noncompetitive NMDA receptor antagonist, MK-801. Neonatal drug administration was conducted 14 days between postnatal day (PND) 7 and 20, corresponding to the period of the third trimester of gestation up until the first two years after birth for human [30]. The effects of neonatal repeated treatment of MK-801 on LI were assessed in two aversive classical conditioning paradigms, conditioned taste aversion (CTA) and conditioned emotional response (CER), since these two tasks have been most frequently used in animal studies of LI.

2. Materials and methods

2.1. Subjects

Fifty-three female Wistar–Imamichi rats were used as breeders. To avoid single-sex rearing, 5–8 male and 2–5 female rats bone from the same mother were raised in one nest, and only males were treated with MK-801 or saline (SAL). Totally 293 male rats were treated.

The day of birth was defined as PND 0. On PND 6, to avoid malnutrition, we allotted 10 rats to a nest and the rest was eliminated. On PND 7–20, animals were subcutaneously (s.c.) injected with MK-801 maleate (Sigma, MO; 0.2 or 0.4 mg/kg) dissolved in SAL, or an equal volume of SAL (1 ml/kg) twice a day. Each animal was randomly assigned to one of the three groups (two groups in additional CER experiments) of different doses. Every daily treatment was interposed by an interval of more than 8 h. The animals were weaned at PND 28, and housed in a group (4–5 rats in each cage) with water and food ad libitum. They were moved into individual cages at postnatal week (PNW) 10. During the behavioral experiments, animals were restricted to water access.

Throughout the experimental periods, they were maintained on a 12:12 h light–dark cycle. All behavioral experiments were conducted in the light phase. Animal experiments were approved by the University of Tsukuba Committee on Animal Research.

2.2. Conditioned taste aversion (CTA)

2.2.1. Apparatus

CTA procedure was carried out in individually separated stainless-steel mesh cages (15 × 21 × 15 cm). There were two holes on the roof of each cage, into which stainless tubes could be inserted to provide the rat free access to drinking solutions. Animals were kept in this mesh cage throughout the experiment.

2.2.2. Procedure

On PNW 11, CTA task was carried out. The procedure comprised the following five stages: (1) Water-deprivation (4 days). Rats were trained to drink tap water from a single tube inserted into one of the holes on the cage in a counterbalanced pseudo-random sequence. Time permitted for drinking was progressively reduced, and it was finally only 30 min a day. (2) Preexposure (3 days). With the same procedure as water-deprivation, half of rats were allowed to drink 5% sucrose solution for 15 min (preexposure (PE) groups), and the other half (non-preexposure (NPE) groups) were allowed to drink water for the same duration. (3) Conditioning (1 day). All rats were first allowed to drink 5% sucrose solution for 15 min. This was immediately followed by intraperitoneal (i.p.) injection of LiCl (1.5 M, 10 ml/kg). (4) Recovery (1 day). With the same procedure as in water-deprivation stage, rats were allowed to drink water for 15 min. (5) Testing (1 day). Rats were allowed to choose to drink between two kinds of liquid from double tubes that were inserted into two holes on the cage for 15 min. The amount of liquid consumption was weighted and the percentage sucrose solution consumption of the total liquid consumption was calculated. The combination of two factors, neonatal treatment (SAL, MK-801 0.2 mg/kg, 0.4 mg/kg) × preexposure to sucrose, produced six groups: SAL-PE (n = 16), SAL-NPE (n = 15), MK0.2-PE (n = 15), MK0.2-NPE (n = 17), MK0.4-PE (n = 16), and MK0.4-NPE (n = 17).

2.3. Conditioned emotional response (CER)

2.3.1. Apparatus

CER procedure was carried out in a conditioning chamber (24 × 29 × 25 cm) made of Plexiglas that was placed in a sound attenuation box provided with a fan being the source of a background noise (70 dB). The floor consisted of stainless steel bars, connected to a shock generator (BRS/LVE Inc., MD) set to deliver 0.5 mA scrambled foot shock lasting 1.0 s. A licking spout, placed into the chamber through a hock in the middle of a lateral wall, 5 cm above the grid floor, provided the rat with water. A loudspeaker was placed at the back side of the chamber. This allowed to deliver a tone (2.8 kHz, background + tone = 90 dB) when required. A personal computer was programmed to activate the loudspeaker and the shock generator as well as to record the number of licks during the experiment.

2.3.2. Procedure

On PNW 11–13, CER task was carried out. The procedure comprised the following five stages: (1) Water intake training (10 days). After three-day handling and water-deprivation period in which animals were allowed to access water 30 min a day while food intake was free, rats were placed in the conditioning chamber, and given access to the drinking tube for 15 min. Then rats were allowed to access water 15 more min in their home cage. (2) Preexposure (1

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