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MK-801 suppresses muricidal behavior but not locomotion in olfactory bulbectomized rats: involvement of NMDA receptors

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Abstract

In rats, olfactory bulbectomy (OBX) causes changes in glutamatergic function in the amygdala (AMG) and induces mouse-killing behavior (MKB). The medial AMG (mAMG) plays an important role in the initiation and maintenance of OBX-induced MKB. In the present study, systemic injection or intra-mAMG perfusion of (+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate (MK-801) was used to determine the effects of MK-801, a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, on the expression of OBX-induced MKB in male Wistar rats that had undergone OBX 1 month previously. The effects of MK-801 on locomotion in OBX rats were also examined using the open-field test. Intraperitoneal injection of MK-801 at doses of 0.10 and 0.15 mg/kg resulted in reversible suppression of MKB, the effect being maximal within 1 h after drug treatment, then gradually disappearing over 6 h. Locomotor distance in OBX rats was not affected using 0.10 mg/kg of MK-801, but increased after treatment with 0.15 mg/kg of MK-801; both doses, however, caused the rats to spend longer in the central area of the open field. MKB was also reversibly suppressed by local perfusion of 1 mM MK-801 at a rate of 1 μl/min into the mAMG through microdialysis probes. These results suggest that NMDA receptors, at least, in the mAMG, are involved in the expression of OBX-induced MKB.

Keywords: Olfactory bulbectomy; NMDA receptor; MK-801; Mouse-killing behavior; Amygdala; Glutamate

1. Introduction

The olfactory bulbs project nerve fibers widely through the lateral olfactory tract to the olfactory cortex, including the amygdaloid complex (Lowell and White, 1965). Since glutamate is an important neurotransmitter in the lateral olfactory tract (Godfrey et al., 1980), olfactory bulbectomy (OBX) causes substantial changes in glutamatergic functions, such as a reduced glutamate content in the olfactory cortex (Collins, 1984), a decreased affinity of glycine for *N*-methyl-D-aspartate (NMDA) receptors in the cerebral cortex (Nowak, 1996), and a lowered NMDA receptor density in the cerebral cortex and the amygdala (AMG) (Ho et al., 2001; Robichaud et al., 2001). NMDA receptors are involved in the neuronal activity of the olfactory cortex (Collins, 1982; Nakanishi et al., 1990). In addition, chronic treatment with (+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate (MK-801), a noncompetitive NMDA receptor antagonist, inhibits the hyperactivity of OBX rats in open-field tests (Redmond et al., 1997). These results suggest that NMDA receptors are related to certain behavioral changes in OBX rats.

After OBX, terminal degeneration is seen in the medial AMG (mAMG) (Lowell and White, 1965), neuronal activity in the mAMG shows hyperexcitability (Nakanishi et al., 1990), and the AMG electroencephalogram (EEG) changes to an arousal pattern (Watanabe et al., 1980). Furthermore, it has been reported that lesioning of the mAMG before, at the same time as, or after, OBX inhibits the expression of OBX-induced mouse-killing behavior (MKB) in rats, suggesting that the mAMG plays an important role in the initiation and maintenance of OBX-induced MKB (Shibata et al., 1982a,b). Although it is now known that the mAMG contains a high density of NMDA receptors (Cotman et al.,

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1987), it is still unclear whether these receptors are involved in MKB expression.

Since OBX transects glutamatergic fibers from the olfactory bulbs and causes extensive changes in NMDA receptor-mediated function in the brain, especially in the mAMG, we hypothesized that the expression of OBX-induced MKB may be related with such changes. In the present study, MK-801 was administered either by systemic injection (0.05, 0.10, or 0.15 mg/kg ip) or by local perfusion (1 mM in artificial cerebrospinal fluid; aCSF) into the mAMG through microdialysis probes to clarify the role of NMDA receptors in MKB expression. The effects of the same three doses of MK-801 on locomotor activity were also investigated using the open-field test.

2. Methods

2.1. Animals and surgery

Male Wistar rats (350 ± 50 g) that had not shown spontaneous MKB when tested individually for 30 min with an ICR mouse (22 ± 4 g) in a plastic cage (20 × 27 × 40 cm) were used. After being housed individually for a further day in the same cage used for testing, the rats were randomly assigned to undergo OBX or sham operation. OBX were performed as described previously (Ho et al., 2000). Briefly, after anesthesia by intraperitoneal injection of sodium pentobarbital (10 mg/kg) plus ketamine (45 mg/kg), the rats were placed on a stereotaxic instrument, then two 2-mm-diameter holes were drilled in the skull (5.0 mm rostral to the bregma and 1.5 mm lateral to the midline) and the olfactory bulbs removed by suction. The sham-operated group underwent the same surgical procedures except for the removal of the olfactory bulbs. For recovery, the rats were returned to their home cages and kept in an animal room on a 12-h light–dark cycle (lights on at 2200 h). Food and water were provided ad libitum. All the behavioral observations were started 2 h after lights off. All experimental procedures involving animals conformed to the National Institute of Health's Guide for the Care and Use of Laboratory Animals.

2.2. Mouse-killing behavior test

Five days after the OBX surgery, killer rats were selected by testing muricidal behavior every other day. Rats that killed mice within 5 min after their introduction into the rat's home cage in at least five consecutive tests were used to test the effects of MK-801. The MKB test was performed between 1400 and 1700 h. One month after OBX, 67% of the rats met this criterion and were used in the experiments below.

2.3. Intraperitoneal injection

Rats showing MKB were injected intraperitoneally with either saline (1 ml/kg) or MK-801 (1 ml/kg of saline containing 0.05, 0.10, or 0.15 mg/ml MK-801; RBI, Natick, MA). MKB tests were carried out 30 min before and 0.5, 1, 2, 4, and 6 h after injection, and the percentage of rats that killed mice within 5 min was recorded.

2.4. Drug perfusion

The MK-801 local perfusion experiment was also performed 1 month after OBX. Microdialysis probe implantation surgery was carried out in the OBX-induced killer rats 2 h after lights off on a stereotaxic instrument under anesthesia. Two microdialysis probes (1.5 mm in tip length; molecular weight cut-off 5000 Da) were bilaterally implanted into the mAMG (A −2.6, L ±3.0, V −9.4 mm from the bregma, midline, and skull surface, respectively), attached to the skull with dental cement, and continuously perfused with aCSF (NaCl 140 mM, $CaCl_2$ 1.2 mM, KCl 3.0 mM, $MgCl_2$ 1.0 mM) at a rate of 1 μl/min. For recovery and habituation, the animal was then placed in an observational bowl (diameter 41 cm, depth 36 cm) in which it could move freely. Starting 24 h after implantation of the microdialysis probes, MKB tests were performed repeatedly at 30-min intervals by introducing a mouse into the observational bowl, each test taking 5 min. After three tests, MK-801 (1 mM in aCSF) was locally perfused into the mAMG via the microdialysis probe for 2 h, during which time, four MKB tests were carried out. The perfusion medium was then changed back to aCSF, and two more MKB tests were performed. The control group was perfused with aCSF throughout the experiment. After the experiment, histological sections of the brain were made to confirm the accuracy of probe placement (Fig. 1).

2.5. Locomotion test

To investigate the locomotor effects of MK-801 at the dosages used in the MKB study, automated open-field equipment (40 × 40 × 54 cm; Digiscan-16 Animal Activity Monitor System; model RXYZCM, Omnitech Electronics, Columbus, OH) was used to measure the

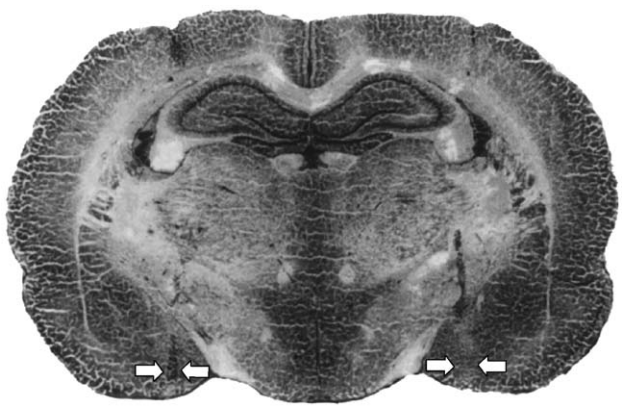

Fig. 1. Histological section showing the location of the dialysis probes in the mAMG. The arrows indicate the placement of the probe tips.

behavioral activity of the rats. The variables examined were (1) total distance (total distance traveled by the animals, in centimeters) and (2) center time (time that the body of the rat was in the central area [20 × 20 cm], in seconds) of the equipment. Ten rats were randomly divided into two groups and underwent OBX ($n = 5$) or sham operation ($n = 5$). After recovery for 1 month in individual cages, locomotor activity in the open field was monitored for 5 min, then saline was injected (1 ml/kg) intraperitoneally, and locomotion was recorded at 0.5, 1, 2, 4, and 6 h after injection, each recording lasting 5 min. Subsequently, the animals received three increasing single doses of MK-801 (0.05, 0.10, or 0.15 mg/kg) by intraperitoneal injection at weekly intervals and the locomotor activity recorded as above. The protocol of one saline injection, followed by a series of three increasing doses of MK-801 was used to prevent a residual effect of a higher dose of the drug.

2.6. Data analysis

MKB was expressed as the percentage of killers at a given time-point and differences between groups were evaluated using Fisher's exact probability test. The behavioral data of locomotor distance and center time in the open field were analyzed by repeated measures ANOVA with the preinjection value as a covariate. P values less than .05 were taken as statistically significant.

3. Results

As shown in Fig. 2, intraperitoneal injection of saline or 0.05 mg/kg MK-801 did not affect OBX-induced MKB. However, 30 min after treatment of 0.10 or 0.15 mg/kg of MK-801, only 44% (8/18; $P < .05$) or 27% (5/18; $P < .01$) of rats, respectively, showed MKB, this effect being gradually lost over the next 6 h. As shown in Fig. 3, MKB was not affected by local perfusion of aCSF into the mAMG, but was reversibly suppressed by perfusion of 1 mM MK-801. Thirty minutes after the start of MK-801 perfusion into the mAMG, 67% (6/9) of rats showed MKB, but this percentage fell to 11% (1/9; $P < .01$) 1 h after the start of perfusion and remained at this level until 30 min after the end of perfusion, increasing to 44% (4/9) 1 h after the cessation of MK-801 perfusion.

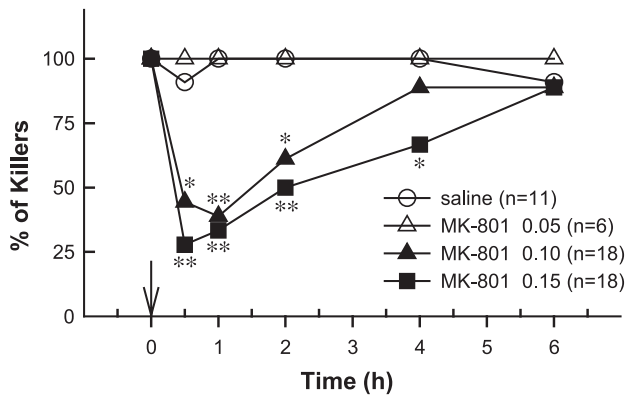

Fig. 2. Effect of MK-801 (0.05, 0.10, or 0.15 mg/kg) on the expression of OBX-induced MKB in rats. * $P < .05$, ** $P < .01$ compared with the saline control group at the same time-point. The arrow indicates the time of injection.

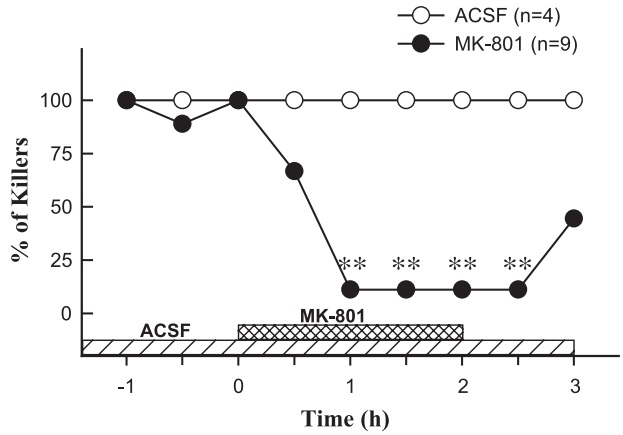

Fig. 3. Effect of MK-801 (1 mM in aCSF) perfused through microdialysis probes into the mAMG on the expression of OBX-induced MKB in rats. ** $P < .01$ compared with the aCSF control group at the same time-point.

The preinjection locomotor distance recorded before injection of 0, 0.05, 0.10, and 0.15 mg/kg of MK-801 on Days 0, 7, 14, and 21, respectively, showed a significant within-subjects effect [$F(3,24) = 5.38$, $P < .01$], but no Time × Surgery interaction [$F(3,24) = 0.54$, $P = .66$] or between-subjects effect [$F(1,8) = 3.27$, $P = .11$]. The preinjection values for locomotor distance in sham-operated rats were significantly lower on Days 7 and 14 compared with Day 0 by the within-subjects contrasts test ($P < .05$). Similar habituation was found in the OBX rats, in which the locomotor distance was lower on Days 7 [$F(1,4) = 8.65$, $P < .05$] and 21 than on Day 0 [$F(1,4) = 37.30$, $P < .01$] (Table 1). The preinjection center time values also showed a significant within-subjects

Table 1
Preinjection spontaneous locomotion in sham-operated and OBX rats in a 5-min open-field test

	Day 0	Day 7	Day 14	Day 21
Locomotor distance (cm)				
Sham-operated	1345 ± 178	871 ± 181 *	868 ± 264 *	1072 ± 148
OBX	1642 ± 115	925 ± 154 *	1282 ± 270	1329 ± 110 **
Center time (s)				
Sham-operated	156 ± 22	195 ± 29	171 ± 26	208 ± 19 *
OBX	182 ± 18	149 ± 24	220 ± 23	212 ± 21 *

The data, expressed as the mean ± S.E.M. for five rats, were obtained immediately before intraperitoneal injection with saline (Day 0), 0.05 (Day 7), 0.10 (Day 14), or 0.15 (Day 21) mg/kg of MK-801.

* $P < .05$, compared to Day 0.

** $P < .01$, compared to Day 0.

effect [$F(3,24)=3.11$, $P<.05$], but no Time × Surgery interaction [$F(3,24)=2.47$, $P=.086$] or between-subject effect [$F(1,8)=0.017$, $P=.90$]. The preinjection center time values were increased in both sham-operated and OBX rats on Day 21 compared with Day 0 ($P<.05$) (Table 1).

As shown in Fig. 4A after saline injection on Day 0, the locomotor distance in both sham-operated and OBX rats measured at each time-point during the 6-h observational period was about 20–50% of the basal level. A significant dose effect of MK-801 [$F(3,21)=6.14$, $P<.01$] and a Dose × Surgery interaction effect [$F(3,21)=3.36$, $P<.05$] on locomotor distance were found. In sham-operated rats, MK-801, at the dose of 0.15 mg/kg, significantly increased locomotor distance [$F(1,3)=13.54$, $P<.05$], compared with the saline controls. A similar trend [$F(1,3)=8.19$, $P=.065$] was found after the 0.10-mg/kg dose. In the OBX rats, an increase in locomotor distance [$F(1,3)=15.86$, $P<.05$] compared with the saline controls was only seen at the dose of 0.15 mg/kg of MK-801. As shown in Fig. 4B, MK-801 treatment had no effect on the center time in sham-operated rats, but significantly increased the center time in OBX rats at both 0.10 [$F(1,4)=10.82$, $P<.05$] and 0.15 mg/kg [$F(1,4)=32.17$, $P<.01$] compared with the saline controls.

4. Discussion

The present study shows that OBX-induced MKB was suppressed by systemic administration of MK-801 at doses of 0.10 and 0.15 mg/kg, whereas locomotor activity was unaffected by 0.10 mg/kg of MK-801, but increased at the dose of 0.15 mg/kg. In addition, local perfusion of MK-801 (1 mM in aCSF) into the mAMG inhibited OBX-induced MKB. These results suggest that NMDA receptors, at least in the mAMG, are involved in OBX-induced MKB.

It has been documented that denervation induces synaptic reorganization, functional changes in postsynaptic receptors, and behavioral abnormality. NMDA receptors are reported to play an important role in such changes (Dunah et al., 1999). Furthermore, the olfactory bulbs heavily project glutamatergic fibers to the AMG (Cotman et al., 1987); OBX causes a decreased NMDA receptor density in the AMG (Ho et al., 2001; Robichaud et al., 2001). The AMG also receives glutamatergic fibers from other brain areas (Sesack et al., 1989); thus, OBX may also result in reorganization of the glutamatergic system in this area. This hypothesis is supported by increased c-Jun expression in the AMG following OBX (Wrynn et al., 2000), since this increased expression is thought to be involved in neuronal regeneration (Brecht et al., 1995). In addition, neuronal

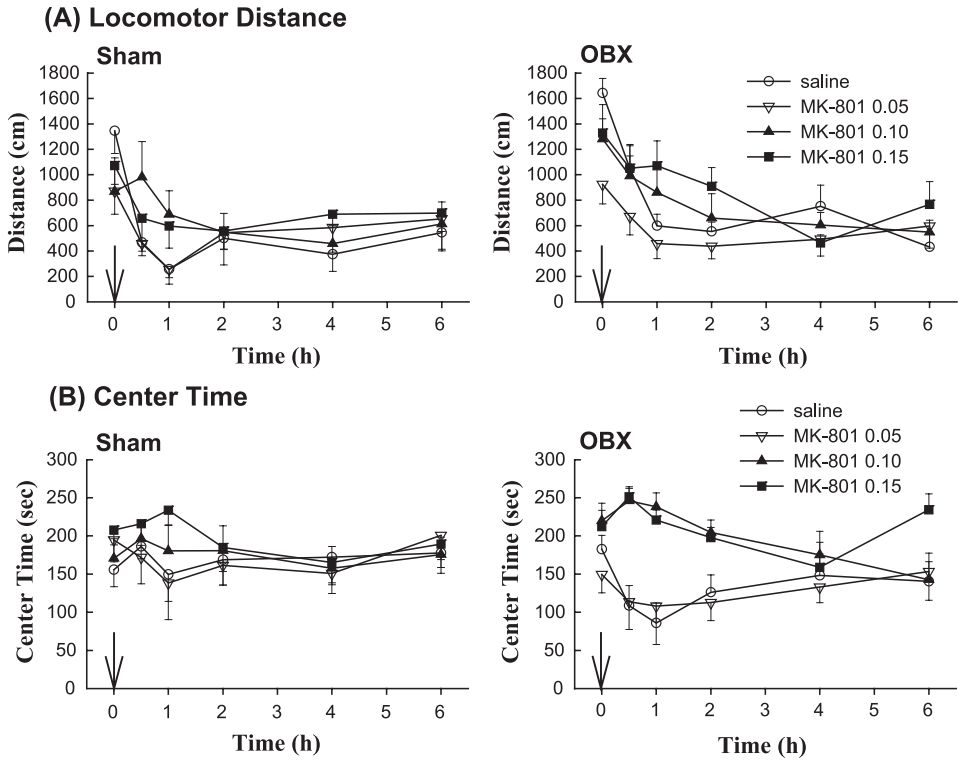

Fig. 4. Effect of MK-801 on locomotor distance (A) and center time (B) for sham-operated and OBX rats in an open-field test. The data are presented as the mean ± S.E.M. for five rats. The arrow indicates the time of intraperitoneal injection of saline (1 ml/kg) or MK-801 (0.05, 0.10, or 0.15 mg/kg). Statistical analysis for the entire curves showed that administration of MK-801 at the dose of 0.15 mg/kg caused a significant ($P<.05$) increase in locomotor distance in sham-operated rats compared with the saline control; a similar trend was found after the 0.10-mg/kg dose ($P=.065$). Whereas, in OBX rats, the effect was only seen at the dose of 0.15 mg/kg ($P<.05$). Center time was unaffected by any dose of MK-801 in sham-operated rats, whereas in OBX rats, an increased center time was seen at MK-801 doses of 0.10 ($P<.05$) and 0.15 mg/kg ($P<.01$).

hyperexcitability in mAMG slices was observed 10 days after OBX (Nakanishi et al., 1990). In these slices, burst discharges were suppressed by NMDA receptor antagonists, suggesting an augmented NMDA receptor-mediated excitatory response of the amygdaloid neurons. Our previous study showing increased release of striatal glutamate during the stress response in OBX rats provides further evidence for enhancement of glutamatergic neurotransmission following OBX (Ho et al., 2000).

At Day 5 after OBX, about 40% of rats displayed MKB, and this percentage increased to 67% at Day 22. Once these behavioral changes are established, they can persist for several months (our unpublished observations). Similar results on the time-course and persistence have been described in a previous study (Cain, 1974). The time-course of OBX-induced behavioral changes is similar to that of denervation-induced synaptic and receptor reorganization (Cotman and Nieto-Sampedro, 1984; Wrynn et al., 2000).

MK-801 blocks NMDA receptor-mediated function (Woodruff et al., 1987), and the topography of its binding sites in the rat brain is consistent with the distribution of NMDA receptors (Monaghan and Cotman, 1989). Thus, the suppression of MKB by systemic administration of MK-801 might be due to extensive antagonism of NMDA receptors in the brain. However, it is more likely to involve the cerebral cortex and AMG, the two regions in which NMDA receptors have been shown to be decreased after OBX (Ho et al., 2001; Robichaud et al., 2001). The AMG, one of the important nuclei in the olfactory cortex, receives glutamatergic afferent fibers from several brain areas (Cotman et al., 1987; Sesack et al., 1989). OBX, which transects afferent fibers from the olfactory bulbs, results in a lower content, and reduced release, of glutamate in the olfactory cortex (Collins, 1984), and also causes substantial changes in the AMG, such as a decreased NMDA receptor density (Ho et al., 2001; Robichaud et al., 2001), enhancement of the NMDA receptor-mediated synaptic potential (Nakanishi et al., 1990), and an arousal EEG pattern (Watanabe et al., 1980). OBX may cause denervation-induced synaptic sprouting and reorganization from other brain regions to the olfactory cortex, which results in supersensitivity of postsynaptic NMDA receptors in the AMG (Nakanishi et al., 1990). Since NMDA receptors in the AMG are involved in the stress response (Adamec et al., 1999; Shors, 1999), they may be associated with OBX-induced abnormalities in the stress response, including the abnormal neurochemical and behavioral responses to stress in an open field (Ho et al., 2000), as well as in MKB directed against intruder mice (Cain, 1974). Thus, OBX-induced functional changes in the AMG may explain the key role played by the AMG in the induction and maintenance of OBX-induced MKB (Shibata et al., 1982a,b). The reversible suppression of MKB by local perfusion of MK-801 into the mAMG suggests that NMDA receptor-mediated glutamatergic function in this area is involved in OBX-induced MKB.

Although locomotor activity in naïve Wistar rats is reported to be unaffected by MK-801 at a dose of 0.125 mg/kg (Druhan et al., 1996), other studies have found that MK-801 at doses of 0.05 and 0.1 mg/kg induces hyperactivity (Hargreaves and Cain, 1992; Robledo et al., 1991). In the current study, MK-801 at a dose of 0.15 mg/kg resulted in a significant increase in locomotor distance in sham-operated rats; a similar trend was also found after the 0.10-mg/kg dose. However, only the higher dose, 0.15 mg/kg, increased locomotor activity in OBX rats. These findings support the view that the MK-801 sensitivity of locomotion in OBX rats is lower than that in naïve rats (Redmond et al., 1997; Robichaud et al., 2001), which is consistent with the observed decrease in NMDA receptor density following OBX (Ho et al., 2001; Robichaud et al., 2001). In addition, 0.10 mg/kg of MK-801 effectively inhibited MKB (Fig. 2), but had no effect on locomotor activity (Fig. 4A), suggesting that the suppressive effect of MK-801 on MKB is not due to nonspecific impairment of motor function.

Rats with higher anxiety levels show a decrease in center time in an open field compared with rats with lower anxiety levels (Ho et al., in press) and anxiolytic drugs increase the center time in rats (Treit and Fundytus, 1988). In the present study, the center time for OBX rats was increased after MK-801 administration, suggesting that MK-801 may have anxiolytic-like activity in an open-field test. Avoiding the central area of an open field may be a defensive behavior used by rats to cope with the novelty stress. Rats with low anxiety levels show more active coping behavior in a stressful environment to avoid or escape the aversive stimuli (Ho et al., 2002). The anxiolytic effects of MK-801 may normalize the ability of OBX rats to cope with intruder mouse-induced stress and thus inhibit muricidal behavior.

In the brain perfusion experiment, all the rats in the control group showed MKB throughout the 4-h aCSF perfusion period. In addition, the rats in the MK-801-treated group also showed MKB in the period before MK-801 perfusion, indicating that there was no brain damage effect on behavioral performance. Although no locomotor data were obtained in this experiment, the rats walked around apparently normally in the observational bowl and sometimes used their nose or forepaws to spray bedding toward the introduced mice during the MK-801 perfusion period, suggesting that the inhibition of MKB by perfusion of MK-801 into the AMG did not result from nonspecific motor impairment. Although the method of drug perfusion through microdialysis probes into the brain avoids the behavioral impairment caused by handling stress, it is difficult with this technique to accurately estimate the time and dosage of the drug application.

NMDA receptor blockade can attenuate stress-induced neuronal activity in the AMG and anxiety-like behavior (Adamec et al., 1999; Shors, 1999). In the present study, local perfusion of MK-801 into the mAMG suppressed MKB, indicating that MKB may be related to hyperactivation of NMDA receptor-mediated function in the mAMG.

The growing body of evidence indicating changes in NMDA receptors (Ho et al., 2001) and glutamate release (Ho et al., 2000) after OBX points to abnormality of glutamatergic function in OBX rats, which deserves further study. In conclusion, changes in NMDA receptor-mediated function, at least in the mAMG, may be involved in the expression of OBX-induced MKB in rats. The current findings provide a direct link between the amygdaloid NMDA receptor and OBX-induced behavioral changes.

Acknowledgements

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