

Effects of Alcohol on the Mouse-Killing Behavior of Olfactory Bulbectomized Rats

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Abstract

The purpose of the current study was to evaluate the effects of chronic administration of alcohol on the olfactory bulbectomy (OBX)-induced mouse-killing behavior (MKB), an animal model for screening antidepressants. The rats were divided into three groups, which were given alcohol (0, 0.5, or 1 g/kg/day) orally for 28 days. MKB was analyzed before and at the end of each week of the alcohol treatment. The results showed that chronic alcohol treatment produced a significant increase in the latency of MKB, implying that alcohol may have an antidepressant-like activity. This suggests that alcohol dependence or abuse in depressed patients may result from "self-medication". Since it has been reported that OBX causes a decrease in the density of N-methyl-D-aspartate (NMDA) receptors in the brain and that alcohol is a potent and selective inhibitor of NMDA receptors, the possible role of NMDA receptors in this effect is discussed.

Key Words: alcohol, depression, mouse-killing behavior, olfactory bulbectomy

Introduction

In the 21st century, depression, an affective disorder, has a higher prevalence than other psychiatric disorders (15). Elucidation of its pathophysiological mechanism would be helpful in developing effective ways to control this important public health issue. Comorbidity of depression and alcohol dependence is high (31), suggesting a close relationship (1, 5). Alcohol drinking may be one way for some depressed patients to relieve their negative emotions, suggesting that alcohol might have antidepressant-like activities. However, this has not yet been tested in animal models.

Olfactory bulbectomy (OBX)-treated rodents have long been used as an animal model of depression (22,

32, 36, 38), as OBX causes neurological, immunological, endocrine, and behavioral changes that are similar to the symptoms in depressed patients (33, 34). The mouse-killing behavior (MKB) induced by OBX is responsive to antidepressant treatment and has been used as an indicator for screening antidepressants (14, 16). However, in the original model, only a few parameters can be used to analyze the MKB, since it occurs very quickly with an experienced killer rat, which takes only a few seconds to kill a mouse. We reported earlier that cutting the incisors of killer rats does not impair the expression of MKB, but effectively prolongs attack duration and results in more attacks towards the mouse before it is killed (12). Thus, the incisor cutting method is ideal for studying the effect of drugs on MKB.

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In this study, MKB induced by OBX was used to evaluate the effects of chronic administration of alcohol on this behavior. This behavior was analyzed before and at the end of each week of alcohol treatment.

Materials and Methods

Animals

Male Long-Evans rats weighing 300 ± 50 g (purchased from the Animal Center of the National Science Council, Taipei, Taiwan, ROC) and ICR mice weighing 25 ± 5 g (purchased from the Animal Center of the National Taiwan University, Taipei, Taiwan, ROC) were used. All the animals were housed in groups of 4 in conventional metal cages ($31 \times 30 \times 21$ cm) with wire mesh floors in an animal room with a 12-h light-dark cycle (lights on at 5:00 a.m.; room temperature $22 \pm 1^\circ\text{C}$; humidity controlled as $55 \pm 10\%$). Food and water were provided *ad libitum*. All experimental procedures used conformed to the NIH Guidelines for the Care and Use of Laboratory Animals.

Surgery and Behavioral Test

OBX. OBX was performed when the rats were 8- to 10-week-old, as described previously (9, 12). Briefly, the rat was anesthetized with 3.5% sodium pentobarbital (10 mg/kg, i.p.), then placed in a stereotaxic instrument. Two 2 mm diameter holes were drilled in the skull (5-7 mm rostral to the bregma and ± 1.5 mm lateral to the central fissure), then a 27 gauge needle was used to cut the olfactory tract and the olfactory bulbs were removed by suction. Since OBX can also cause hyperirritability (10), the rats were housed individually in the metal cages after the surgery.

Screening of MKB and alcohol treatment. Five days after OBX, an ICR mouse was placed in the rat's home cage to induce and establish the MKB. Since not all the rats showed MKB at the first testing, if the rat did not kill the mouse within 5 min, the mouse was left in the cage until the next day to see whether the rat showed muricidal behavior. The MKB screening was performed once a day. Rats that killed mice within 5 min after their introduction into the rat's home cage in at least five consecutive tests were defined as "killer rats". Eighty percent of OBX rats met the killer criterion and were used for further studies, *i.e.* 6 rats were discarded from this study.

Around 2 weeks after OBX, the killer rats were randomly divided into three groups, which were given alcohol (0.5 or 1 g/kg/day; $n = 8$ and 6, respectively) or distilled water (1 ml/kg/day, control group; $n = 8$) *via* oral gavage once a day, for 28 days. The alcohol dosage of 0.5 and 1 g/kg used was equivalent to the alcohol concentration of 23.75% and 47.5% (vol/

vol), respectively. The concentrations chosen in the present study were in the range routinely used in rats for oral alcohol gavage (2, 27). Previous reports show that acute administration of alcohol at the dose of 0.5-2 g/kg *via* oral gavage has no effects on motor coordination (27) or the latency to make the lever-press response in alcohol seeking and self-administration in rats (4).

Incisor cutting. Starting on day 6 of alcohol treatment, incisor cutting was performed on the killer rats every 7 days (at 6:00-7:00 p.m.) under anesthesia with 3.5% sodium pentobarbital (10 mg/kg, i.p.). The rats' upper and lower incisors were cut off at the gum line using a diamond disk. The rats recovered from the anesthesia in one hour after the cutting surgery. The procedures were the same as those in our previous study, where we found that 28 h after incisor cutting was suitable for MKB testing and that the incisors recovered in 4 days (12). The food pellets were cut into small pieces for easier chewing. The body weight of rats after incisor cutting was monitored and no changes were observed.

MKB test. The MKB test was performed at 7:00-10:00 pm one day after the incisor cutting before the oral gavage for that day. Before the test, each rat was placed in an acrylic observational cage ($35 \times 56 \times 19$ cm) with sawdust on the floor for 5 min to allow it to accommodate to the cage. Then mouse was placed in the cage and the parameters of MKB were recorded for 5 min. If the rat killed the mouse within 5 min, other mice were sequentially placed in the cage and observations continued for the full 5 min period.

Parameters of MKB. To record the parameters of MKB, a naive mouse was placed in the rat's cage. According to the report of Miczek (21), an attack was defined as continuous body contact between the rat's forepaws or snout and any part of the mouse's body, including chasing, biting, and pushing the mouse. The end of an attack was denoted by the appearance of non-aggressive behavior, such as grooming, feeding, or exploration. Six parameters, described previously (12), were used to evaluate MKB in this study: [1] attack latency, the time between the introduction of the mouse into the rat's home cage and the rat's first attack response; [2] killing latency, the time for a rat to successfully kill the first mouse after it was placed in the rat's cage. If the rat did not kill the mouse within 5 min, the killing latency was recorded as 300 sec; [3] attack frequency, the number of attacks during the 5 min trial; [4] total attack duration, the time a rat spent attacking mice during the 5 min observation period; [5] mean attack duration, the total attack duration divided by the number of attacks and [6] number of killed mice, the number of mice killed by the killer rat during the 5 min observation period.

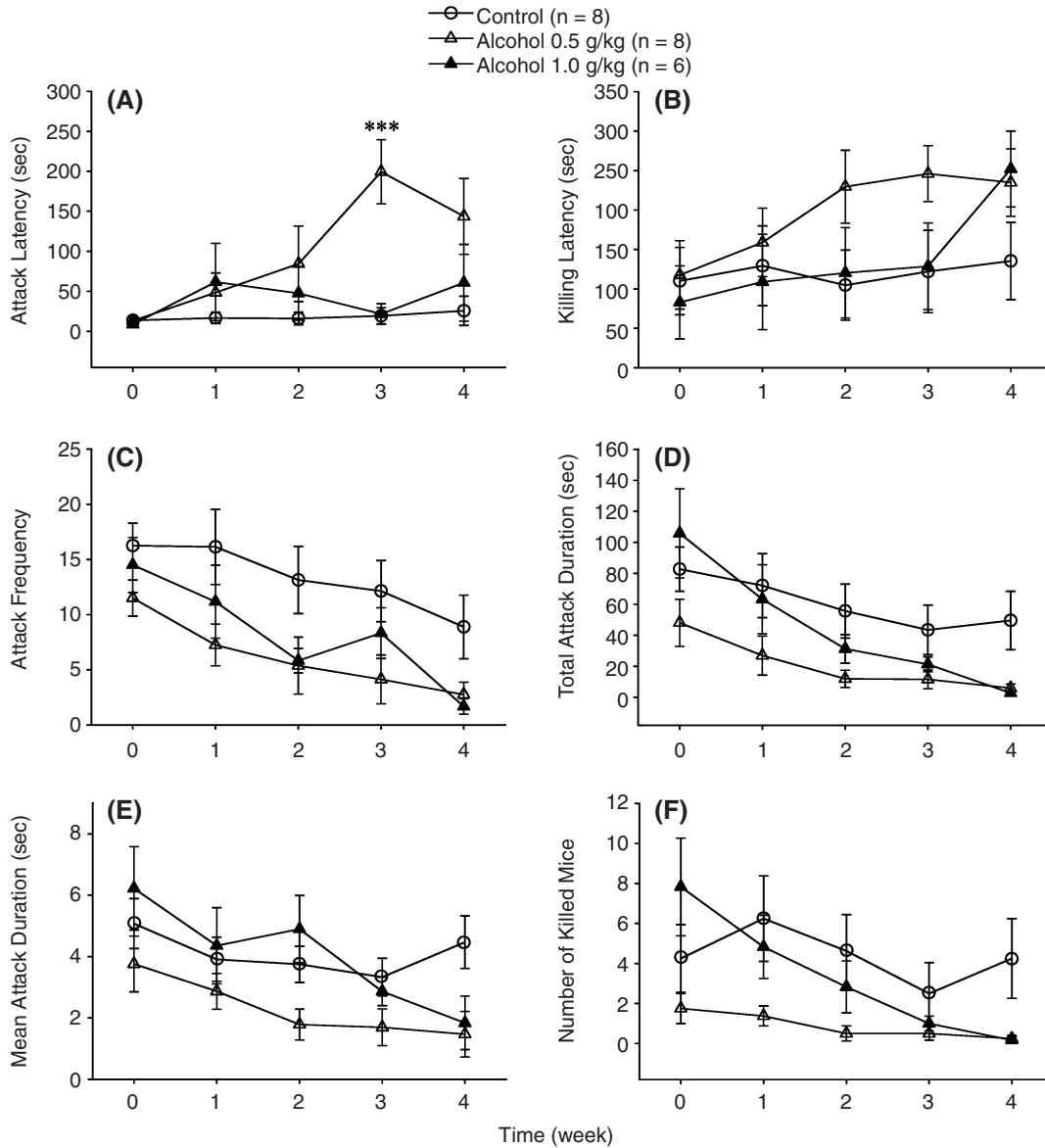


Fig. 1. Effects of chronic alcohol administration on the parameters of the mouse-killing behavior: attack latency (A), killing latency (B), attack frequency (C), total attack duration (D), mean attack duration (E), and number of killed mice (F) during the 5 min observation period in olfactory bulbectomized rats. Alcohol (0, 0.5, or 1 g/kg) was administered everyday *via* oral gavage for 4 weeks. Behavioral tests were performed weekly. *** $P < 0.001$ compared to vehicle control. The data are expressed as the means \pm SEM.

Statistical Analysis

Two-way mixed analysis of variance (ANOVA) of time (week, 5 levels, 0-4) by treatment (dose, 3 levels, 0, 0.5, and 1 mg/kg) was conducted to analyze the behavioral data, where time and treatment were within- and between-subjects factors, respectively. Scheffé's test or Dunnett *t*-test against baseline values was used as post-hoc test. Experimental data are presented as the means \pm SEM. Statistical significance was defined when P was < 0.05 .

Results

The effects of alcohol administration on the parameters of the MKB are shown in Fig. 1. During the MKB observation, ANOVA tests showed a significant overall difference for changes in attack latency between alcohol-treated groups and control group ($F(2,19) = 5.25$, $P < 0.05$), a significant time effect ($F(4,76) = 3.73$, $P < 0.01$), and a significant interaction between time and treatment ($F(8,76) = 3.17$, $P < 0.01$). One-way ANOVA followed by Scheffé's post-hoc test showed

that the attack latency was significantly prolonged in the group treated with 0.5 g/kg alcohol for 3 weeks when compared to the vehicle control group ($F(2,19) = 15.36, P < 0.001$) (Fig. 1A).

As shown in Fig. 1B, ANOVAs revealed a significant time effect ($F(4,76) = 4.10, P < 0.01$) for the killing latency, but no significant treatment effect or time \times treatment interaction.

The attack frequency in all three groups was attenuated as treatment time progressed ($F(4,76) = 14.18, P < 0.001$). Besides, ANOVAs showed also a treatment effect for the attack frequency ($F(2,19) = 4.00, P < 0.05$). Subsequent post-hoc comparison by Dunnett *t*-test showed a significant difference in the attack frequency between the control group and the rats treated with 0.5 g/kg of alcohol ($P < 0.05$) (Fig. 1C).

As shown in Fig. 1D, ANOVAs revealed a significant time effect ($F(4,76) = 15.57, P < 0.001$), but no treatment effect ($F(2,19) = 3.29, P = 0.059$) for the total attack duration. In contrast, a significant time effect ($F(4,8) = 5.94, P < 0.001$) and treatment effect ($F(2,19) = 4.33, P < 0.05$) for the mean attack duration were detected ($P < 0.001$). Subsequent post-hoc comparison by Dunnett *T*-test showed a significant difference in the mean attack duration between the control group and the rats treated with 0.5 g/kg of alcohol ($P < 0.05$) (Fig. 1E).

ANOVA tests showed a significant main effect of time ($F(4,76) = 9.19, P < 0.001$) and time \times treatment interaction ($F(8,76) = 3.35, P < 0.01$) for the number of killed mice, but no significant treatment effect was found ($F(2,19) = 2.62, P = 0.099$). Further analysis of the significant two-way interaction, by using simple effect under the control of Dunnett *t*-test, showed that the treatment of alcohol (0.5 g/kg) had a trend to decrease the number of killed mice at 2nd and 4th week (both P values < 0.059) (Fig. 1F).

Discussion

Since the alcohol treatment at the dose of 0.5 and 1 g/kg i.p. is neither sedative nor ataxic in rats (3) and each MKB test was performed before the oral administration of alcohol for that day, the suppressive MKB caused by the alcohol treatment in the present study is unlikely to be due to sedation or ataxia. Cessation of chronic administration of high dose alcohol (for example 3 g/kg/day, for 30 days) is reported to be associated with withdrawal syndrome, including hyperactivity, tail rigidity, and tremor (18), but, may be due to tolerance, no such signs were observed in this study. If the incisors of killer rats are not removed, MKB can be over in seconds, as the mouse is rapidly killed. In this case, researchers can only analyze this complicated behavior using a few parameters, such as attack latency, killing latency, and the number of killed

mice. In the present study, the incisor cutting method was used to prolong the attack without disturbing the attack components (12) and the MKB could be analyzed in more detail than in previous studies. Previous studies reported that only 40% (6) and 67% (11) of male Wistar rats showed muricidal behavior 2 and 4 weeks after OBX, respectively. Since all the rats used in the present incisor-cutting experiment were selected to be able to show killing behavior, it implies that the bulbectomy surgery was adequate. A histological confirmation would be helpful for determining the completeness of the surgery.

OBX-induced MKB in control animals did not change over the time of this experiment. After chronic administration of alcohol, the attack latency in killer rats was significantly prolonged, but the attack frequency and total attack duration decreased. In addition, killing latency was increased, while the number of killed mice decreased. These results show that chronic alcohol treatment attenuated MKB, indicating that alcohol may have an antidepressant-like activity. In some cases of drug effects, the dose-response curve is biphasic or inversely U-shaped (8). It is possible that the effects of alcohol on OBX-induced MKB may have such phenomenon because the lower but not higher dose showed behavioral effects. Although acute but not chronic administration of anxiolytics can diminish MKB with several hours of duration (35), the MKB suppression seen in the present study is unlikely due to acute anxiolytic effects of alcohol because the drug was chronically administered and that the behavioral test was performed one day after the last gavage.

Since the olfactory system in the rat is involved in the emotional components of behavior, OBX causes a major dysfunction of the neuronal circuit that underlies the behavioral and other changes. Several studies have demonstrated that OBX results in changes not only in behavior, but also in the endocrine, immune, and neurotransmitter systems, which simulates many of those seen in patients with major depression (34). Chronic rather than acute treatment of antidepressants largely corrects most of these changes that occur after OBX (16). Thus, the OBX-treated rat has been used for an antidepressant screening assay. When one considers the role of MKB in behavioral neuroscience, it should be noticed that there is a distinction between being a model of depression per se vs. being a test for assessing antidepressant activity (22, 32, 36, 38). MKB is the most unique and complex behavior in OBX rats, whereas other behavioral, neuronal, and endocrine parameters should also be taken into account in the future study.

The nature of the relationship between depression and alcohol dependence is still controversial. Some results imply that depression causes alcohol dependence or abuse (26, 28), while another study suggests that

depressed patients may try to “self-medicate”, using alcohol to relieve their symptoms (17). Moreover, some data suggest that depression and alcohol abuse are mutually independent diseases and that the comorbidity of these two diseases is due to their relatively high prevalence (37). Our result which demonstrates that chronic alcohol treatment significantly attenuated OBX-induced MKB shows that alcohol may induce an antidepressant-like activity. In addition, the fact that the amount of alcohol intake correlates with the depression-like symptoms (25) suggests that alcohol dependence or abuse in depressed patients may result from “self-medication”.

Several lines of research have provided evidence for the hypothesis that deficits of neurotransmission, similar to the pathophysiological changes in depression, may underlie OBX-induced MKB. Administration of antidepressants suppresses MKB in OBX-treated rats (19, 36, 38). This result is consistent with the present result which shows that chronic alcohol administration attenuated MKB. Furthermore, MKB is related to a decrease in noradrenergic and/or serotonergic function in the rat’s brain (14). Some antidepressants diminish MKB by raising the concentration of monoaminergic transmitters in the rat’s brain (13). On the other hand, our previous study showed that the glutamatergic system is involved in OBX-induced neuronal and behavioral changes in the rats (9-11). OBX causes a decrease in the density of N-methyl-D-aspartate (NMDA) receptors in the cortex and amygdala (10). OBX-induced MKB and hyperactivity are suppressed by MK-801, an NMDA receptor antagonist (11, 29, 30). Based on the fact that alcohol is a potent and selective inhibitor of NMDA receptors (23) and that blockade of NMDA receptors can alleviate depressive behavior in a chronic mild stress model (24), it deserves pharmacological manipulation, for example, by using selective agonist or antagonist, to address the role of NMDA receptors in the current result. The participation of many other neurotransmitters certainly cannot be ruled out (7, 20).

In summary, chronic alcohol administration suppresses OBX-induced MKB. Since the behavioral and biochemical changes seen after OBX are similar to those in depressed patients and since MKB is used to screen antidepressants, we suggest that chronic alcohol treatment may have an antidepressant-like activity and that NMDA receptors may be involved in the mechanism.

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References

1. Boyd, J.H., Burke, J.D., Gruenberg, E., Holzer, C.E., Rae, D.S.,

- George, L.K., Karno, M., Stoltzman, R., McEvoy, L. and Nestadt, G. Exclusion criteria of DSM-III. A study of co-occurrence of hierarchy-free syndromes. *Arch. Gen. Psychiatry* 41: 983-989, 1984.
2. Chester, J.A., Blöse, A.M. and Froehlich, J.C. Effects of chronic alcohol treatment on acoustic startle reactivity during withdrawal and subsequent alcohol intake in high and low alcohol drinking rats. *Alcohol Alcohol* 40: 379-387, 2005.
3. Chuck, T.L., McLaughlin, P.J., Arizzi-LaFrance, M.N., Salamone, J.D. and Correa, M. Comparison between multiple behavioral effects of peripheral ethanol administration in rats: sedation, ataxia, and bradykinesia. *Life Sci* 79: 154-161, 2006.
4. Czachowski, C.L., Prutzman, S. and DeLory, M.J. Volume and dose effects of experimenter-administered ethanol preloads on ethanol seeking and self-administration. *Alcohol* 40: 35-40, 2006.
5. Davidson, K.M. and Ritson, E.B. The relationship between alcohol dependence and depression. *Alcohol Alcohol* 28: 147-155, 1993.
6. Gomita, Y., Ogawa, N. and Ueki, S. Effect of bilateral olfactory bulbectomy on discrimination avoidance conditioning in rats. *Physiol. Behav.* 32: 1011-1016, 1984.
7. Hirsch, J.D. The neurochemical sequelae of olfactory bulbectomy. *Life Sci* 26: 1551-1559, 1980.
8. Hjorth, S., Engel, J.A. and Carlsson, A. Anticonflict effects of low doses of the dopamine agonist apomorphine in the rat. *Pharmacol. Biochem. Behav.* 24: 237-240, 1986.
9. Ho, Y.J., Chang, Y.C., Liu, T.M., Tai, M.Y., Wong, C.S. and Tsai, Y.F. Striatal glutamate release during novelty exposure-induced hyperactivity in olfactory bulbectomized rats. *Neurosci. Lett.* 287: 117-120, 2000.
10. Ho, Y.J., Liu, T.M., Tai, M.Y., Wen, Z.H., Chow, R.S.S., Tsai, Y.F. and Wong, C.S. Effects of olfactory bulbectomy on NMDA receptor density in the rat brain: [³H] MK-801 binding assay. *Brain Res.* 900: 214-218, 2001.
11. Ho, Y.J., Chen, K.H., Tai, M.Y. and Tsai, Y.F. MK-801 suppresses muricidal behavior but not locomotion in olfactory bulbectomized rats: involvement of NMDA receptors. *Pharmacol. Biochem. Behav.* 77: 641-646, 2004.
12. Hsuchou, H., Ho, Y.J., Shui, H.A., Tai, M.Y., Chen, K.H. and Tsai, Y.F. Effects of incisor-cutting on muricidal behavior induced by olfactory bulbectomy in rats. *Physiol. Behav.* 76: 669-675, 2002.
13. Isel, F., Ciesielski, L., Gobaille, S., Molina, V. and Mandel, P. Alterations of serotonin neurotransmission and inhibition of mouse killing behavior: II. Effects of selective and reversible monoamine oxidase inhibitors of type A. *Pharmacol. Biochem. Behav.* 29: 97-104, 1988.
14. Iwasaki, K., Fujiwara, M., Shibata, S. and Ueki, S. Changes in brain catecholamine levels following olfactory bulbectomy and the effect of acute and chronic administration of desipramine in rats. *Pharmacol. Biochem. Behav.* 24: 1715-1719, 1986.
15. Judd, L.L. and Kunovac, J.L. Diagnosis and classification of depression. In: *Depression: Neurobiological, Psychopathological and Therapeutic Advances*, edited by Honig, A. and Praag, N.M.V., New York: John Wiley & Sons, 1997, pp. 3-16.
16. Kelly, J.P., Wrynn, A.S. and Leonard, B.E. The olfactory bulbectomized rat as a model of depression: an update. *Pharmacol. Ther.* 74: 299-316, 1997.
17. Khantzian, E.J. The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *Am. J. Psychiatry* 142: 1259-1264, 1985.
18. Kim, J.H., Chung, J.Y., Kwon, Y.K., Kim, K.J., Yang, C.H., Hahm, D.H., Lee, H.J., Pyun, K.H. and Shim, I. Acupuncture reduces alcohol withdrawal syndrome and c-Fos expression in rat brain. *Am. J. Chin. Med.* 33: 887-896, 2005.
19. Manev, H., Pericic, D. and Muck-Seler, D. Inhibitory influence of dihydroergosine on the aggressiveness of rats and mice. *Pharmacol. Biochem. Behav.* 32: 111-115, 1989.

20. Masini, C.V., Holmes, P.V., Freeman, K.G., Maki, A.C. and Edwards, G.L. Dopamine overflow is increased in olfactory bulbectomized rats: an *in vivo* microdialysis study. *Physiol. Behav.* 81: 111-119, 2004.
21. Miczek, K.A. The psychopharmacology of aggression. In: Hand book of psychopharmacology, edited by Iversen, L.L., Iversen, S.D. and Snyder, S.H., New York: Plenum Press, 1987, vol. 19, pp. 183-328.
22. Mucignat-Caretta, C., Bondi, M. and Caretta, A. Time course of alterations after olfactory bulbectomy in mice. *Physiol. Behav.* 89: 637-643, 2006.
23. Nagy, J. The NR2B subtype of NMDA receptor: a potential target for the treatment of alcohol dependence. *Curr. Drug Targets CNS Neurol. Disord.* 3: 169-179, 2004.
24. Papp, M. and Moryl, E. Antidepressant activity of non-competitive and competitive NMDA receptor antagonists in a chronic mild stress model of depression. *Eur. J. Pharmacol.* 263: 1-7, 1994.
25. Pare, A.M., Pare, W.P. and Kluczynski, J. Negative affect and voluntary alcohol consumption in Wistar-Kyoto (WKY) and Sprague-Dawley rats. *Physiol. Behav.* 67: 219-225, 1999.
26. Pohorecky, L.A. Stress and alcohol interaction: an update of human research. *Alcohol. Clin. Exp. Res.* 15: 438-459, 1991.
27. Quertemont, E., Green, H.L. and Grant, K.A. Brain ethanol concentrations and ethanol discrimination in rats: effects of dose and time. *Psychopharmacology (Berl)* 168: 262-270, 2003.
28. Quitkin, F.M., Rifkin, A., Kaplan, J. and Klein, D.F. Phobic anxiety syndrome complicated by drug dependence and addiction. A treatable form of drug abuse. *Arch. Gen. Psychiatry* 27: 159-162, 1972.
29. Redmond, A.M., Kelly, J.P. and Leonard, B.E. The NMDA receptor and the olfactory bulbectomised rat model of depression. *Eur. Neuropsychopharmacol.* 6: 87-88, 1996.
30. Redmond, A.M., Kelly, J.P. and Leonard, B.E. Behavioural and neurochemical effects of dizocilpine in the olfactory bulbectomized rat model of depression. *Pharmacol. Biochem. Behav.* 58: 355-359, 1997.
31. Roy-Byrne, P.P., Pages, K.P., Russo, J.E., Jaffe, C., Blume, A.W., Kingsley, E., Cowley, D.S. and Ries, R.K. Nefazodone treatment of major depression in alcohol-dependent patients: a double-blind, placebo-controlled trial. *J. Clin. Psychopharmacol.* 20: 129-136, 2000.
32. Shibata, S., Nakanishi, H., Watanabe, S. and Ueki, S. Effects of chronic administration of antidepressants on mouse-killing behavior (muricide) in olfactory bulbectomized rats. *Pharmacol. Biochem. Behav.* 21: 225-230, 1984.
33. Song, C. and Leonard, B.E. The effects of olfactory bulbectomy in rat, alone or in combination with antidepressants and endogenous factors, on immune function. *Hum. Psychopharmacol.* 10: 7-18, 1995.
34. Song, C. and Leonard, B.E. The olfactory bulbectomised rat as a model of depression. *Neurosci. Biobehav. Rev.* 29: 627-647, 2005.
35. Takaoka, N., Yoshimura, H. and Ogawa, N. Comparison of the effects of benzodiazepine and nonbenzodiazepine anxiolytics on mouse-killing behavior in rats. *Jpn. J. Pharmacol.* 46: 315-318, 1988.
36. Ueki, S. Mouse-killing behavior (muricide) in the rat and the effect of antidepressants. In: *New Vistas in Depression*, edited by Langer, S.Z., Takahashi, R., Segawa, T. and Briley, M., Oxford: Pergamon, 1982, pp. 187-194.
37. Vaillant, G.E. Is alcoholism more often the cause or the result of depression? *Harv. Rev. Psychiatry* 1: 94-99, 1993.
38. Yamamoto, T., Yatsugi, S., Ohno, M. and Ueki, S. Inhibition of mouse-killing behavior by S-adenosyl-L-methionine in midbrain raphe-lesioned and olfactory-bulbectomized rats. *Pharmacol. Biochem. Behav.* 34: 395-398, 1989.