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Behavioural and Neurochemical Effects of Dizocilpine in the Olfactory Bulbectomized Rat Model of Depression

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REDMOND, A. M., J. P. KELLY AND B. E. LEONARD. *Behavioural and neurochemical effects of dizocilpine in the olfactory bulbectomized rat model of depression.* PHARMACOL BIOCHEM BEHAV **58**(2) 355–359, 1997.—The activity of dizocilpine (MK-801; 0.1 and 0.3 mg/kg) administered once daily intraperitoneally (IP) was assessed in the olfactory bulbectomized rat model of depression. Olfactory bulbectomy (OB) is associated with a variety of behavioural abnormalities, such as hyperactivity in the "open field" test. Previous studies have shown that chronic administration of antidepressants can reverse this behavioural deficit. In the present study, chronic treatment with 0.1 and 0.3 mg/kg of dizocilpine (IP) antagonized the lesion-induced hyperactivity in the "open field" test. Acute treatment with dizocilpine was associated with an increase in locomotor activity in both sham-operated and OB rats, with a greater response in the sham-operated group. Following chronic treatment, this hyperactivity was found to be greater in the OB-treated animals compared with the sham-treated animals. Olfactory bulbectomy reduced serotonin (5-HT), noradrenaline (NA), and dopamine (DA) concentrations in the frontal cortex. Chronic dizocilpine administration did not alter the 5-HT or NA response. In contrast, chronic administration of dizocilpine to OB animals did attenuate the OB-related deficit in DA. In the OB-operated control animals, there was an increase in DOPAC levels. In conclusion, chronic dizocilpine administration displays antidepressant-like activity in the OB rat model of depression. However, unlike conventional antidepressants, dizocilpine does not correct the 5-HT and NA neurotransmitter deficits that occur in this model. © 1997 Elsevier Science Inc.

Dizocilpine (MK-801) Bulbectomized rat Locomotor activity Brain amines

DIZOCILPINE (MK-801; (+)-5-methyl-10, 11-dihydro-5H-dibenzo [*a*,*d*] cyclohepten-5, 10-imine maleate) is a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist that blocks the neurophysiological effects of the NMDA receptor complex by binding to a site in the ion channel of the receptor, thereby blocking the channel for cations (36). Dizocilpine also inhibits the reuptake of dopamine and noradrenaline and, to a lesser extent, serotonin into brain slices in vitro (9,30).

Dizocilpine induces a complex behavioural syndrome in the rat including lateral head-weaving, body rolling, falling, hyperlocomotion, and ataxia (1,2,9,21,22). It has been shown to have anticonvulsive and neuroprotective properties (6,33). Like many noncompetitive and competitive NMDA receptor antagonists, dizocilpine has been found to be as effective as the tricyclic antidepressant imipramine in animal models used to detect antidepressant activity. Acute dizocilpine treatment has been found to be active in the forced swim test (29,34), which was devised as a rapid screening procedure for acutely administered antidepressants (24). Chronic dizocilpine administration has been found to display antidepressant-like effects in the chronic mild stress model of depression (19), and it diminishes the behavioural deficit produced by learned helplessness (15).

Chronic dizocilpine administration has also been found to downregulate β-adrenoceptors (20), an effect that is consistent with receptor adaptations for most antidepressant treatments (11,32). Chronic imipramine treatment reduced basal [^{3}H]MK-801 binding in the neocortex of both mice and rats (16). Taken together, these findings suggest that the NMDA receptor complex is involved in the mechanism of action of antidepressants.

Previous studies have concentrated on the effects of dizocilpine in naive rodents. Because antidepressant drugs do not

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show mood elevating effects in normal healthy human subjects, it is necessary to assess the activity of this compound in animal models that simulate certain aspects of depression. The olfactory bulbectomized (OB) rat is one such model (31,35).

Removal of the olfactory bulbs in rats results in a series of neurochemical and behavioural changes that can be reversed selectively by chronic antidepressant treatment (35). The neurochemical mechanisms underlying the behavioural deficits in bulbectomized rats are far from clear. Bulbectomy is thought to cause the behavioural deficits partly through alterations in the serotonergic system. Destruction of serotonergic terminals in the olfactory bulbs by intrabulbar injection of 5, 7-dihydroxytryptamine produced behavioural deficits similar to those caused by olfactory bulbectomy (14). Alterations in the excitatory amino acid receptor system are also possible. Excitatory amino acid (glutamate) neurotransmitter concentrations have been found to be decreased (4,27), whereas that of glycine is slightly increased in the olfactory cortex following olfactory bulbectomy (8). NMDA receptor binding sites labelled with dizocilpine have been found to be decreased in discrete regions of the brain following olfactory bulbectomy (5). The hyperactivity induced in rats by challenge injections of dizocilpine and phencyclidine has been found to be drastically attenuated in OB rats compared with sham-operated controls (5,26).

The aims of the present study were to examine a possible involvement of the NMDA receptor in the mechanism of action of antidepressants in the OB rat model of depression by: a) looking at the effects of dizocilpine in the "open field" test following chronic administration in the olfactory bulbectomized rat; b) recording home cage locomotor activity changes following dizocilpine administration on days 1, 7, 15, and 21 of treatment; and c) examining indoleamine concentrations in the frontal cortex of OB- and dizocilpine-treated rats following chronic administration.

METHODS

Animals

Male Sprague–Dawley rats weighing 230–250 g were obtained from Harlan Olac (Bicester, Oxon, UK). The animals were housed four per cage (two shams and two OBs) and maintained in a room with controlled temperature (20–22°C) and light (light period 0800–2000 h) conditions. Food and water were given ad lib, apart from the periods of behavioural measurements.

Olfactory Bulbectomy

After a 1-week acclimation period, bilateral OB was performed in rats anaesthetised with 2.5% (w/v) 2-2-2-tribromoethanol (10 ml/kg IP) essentially as described by Cairncross et al. (3). Following exposure of the skull, two drill holes of 2 mm diameter were made 5 mm rostral to the bregma and 2 mm lateral to the midline at a point corresponding to the posterior margin of the orbit of the eye. In the case of OB rats, the olfactory bulbs were aspirated using a water suction pump. Care was taken not to damage the frontal cortex. After the operation, bleeding was controlled by plugging the holes with haemostatic sponge (Haemofibrine®, Specialites Septodont, France). Oxytetracycline dusting powder was sprinkled on the wound prior to closure. Sham-operated animals were treated in the same way but, although the dura above the bulbs was pierced, the bulbs were left intact. The animals were allowed to recover for 14 days following surgery; they were handled daily throughout the recovery period to eliminate any aggressiveness that would otherwise arise (12).

Drug Administration

The following compounds were used in the study: dizocilpine (Research Biochemical Incorporation, Natwick, MA, USA) and 2-2-2-tribromoethanol (Aldrich Chemical Co., Gillingham, UK).

Two weeks after surgery, drug treatment began. Dizocilpine was dissolved in saline and administered at doses of 0.1 and 0.3 mg/kg IP once daily for 22 days, in an injection volume of 1 ml/kg. Control animals received saline.

"Open Field" Test

On day 15 of dizocilpine treatment, and before MK-801 administration on that day, each rat was placed singly into the centre of the "open field" apparatus, as described by Gray and Lalljee (7). The "open field" consisted of a circular base 90 cm in diameter, which was divided into 10-cm squares by faint yellow lines. The wall surrounding the base consisted of a 75-cm-high aluminium sheet. Illumination in the room was provided by a 60-W bulb positioned 90 cm above the floor of the apparatus. Ambulation (number of squares crossed) was recorded over a 3-min observation period for each animal between 0700 and 0900 h.

Home Cage Activity

Home cage locomotor activity was measured on days 1, 7, 15, and 22 of treatment. On the day prior to monitoring locomotor activity, animals were singly housed. Locomotor activity was measured by placing the cage, which was similar to the home cage, into a compartment on top of which a passive infrared sensor was attached. This sensor was fitted with a frensel lens that split the infrared beam into 16 zones that radiated across the floor of the cage. Each sensor was then connected to an IBM computer and the data stored (as counts per minute) (17). The monitoring of home cage locomotor activity commenced 30 min before the IP injection of dizocilpine for that day. Activity was monitored continuously over a period of 6 h.

Determination of Brain Biogenic Amine Concentrations

On day 23 of the study, rats were killed by decapitation, the brains removed, and the frontal cortex dissected (23). Concentrations of serotonin, noradrenaline, dopamine, and DOPAC were measured by high-performance liquid chromatography with electrochemical detection (28). The brain region was homogenized by sonication in 1.0 ml elution buffer (pH 2.8) containing 0.1 M citric acid, 0.1 M sodium dihydrogen phosphate, 1.4 mM octane-1-sulphonic acid, and 0.1 mM EDTA. This differed from the mobile phase in that it was "spiked" with 20 ng/50 μl *N*-methyl dopamine as an internal standard. Homogenates were centrifuged at 15,000 rpm in a Hettich Mikro/K refrigerated centrifuge for 15 min. A 50-μl sample of the supernatant was injected directly into a reverse-phase column (RP 18, 25 cm × 4 mm internal diameter, particle size 5 μm) for separation of indoles and catecholamines (flow rate 1 ml/min). The neurotransmitters were quantified using a Merck-Hitachi D-2000 integrator.

Statistical Analysis of Data

The data from the behavioural tests were examined with the Kruskal–Wallis test followed by the Mann–Whitney

TABLE 1

EFFECT OF CHRONIC DIZOCILPINE ADMINISTRATION ON AMBULATION SCORES IN THE OPEN FIELD TEST FOLLOWING OLFACTORY BULBECTOMY

Treatment	*n*	Ambulation
Sham + vehicle	8	61 (55–68)
Sham + dizocilpine (0.1 mg/kg)	7	52 (37–65)
Sham + dizocilpine (0.3 mg/kg)	8	52 (37–66)
OB + vehicle	9	90 (84–116)***
OB + dizocilpine (0.1 mg/kg)	7	59 (51–90)†
OB + dizocilpine (0.3 mg/kg)	7	55 (51–92)†

Data are expressed as median values, with interquartile ranges shown in parentheses. n = number of animals in group. ***$p < 0.001$ vs. sham + vehicle. †$p < 0.05$ vs. OB + vehicle.

U-test. Physiological data were analyzed by two-way analysis of variance followed by Student's *t*-test. Probabilities less than 0.05 were considered statistically significant.

RESULTS

Mean body weight in the sham-operated and bulbectomized control groups increased by 7% and 4%, respectively, during the period of drug administration [$F(5, 42) = 2.67, p < 0.05$]. Body weight gain in the OB controls was significantly reduced compared with sham-operated controls ($p < 0.05$) during the period of drug treatment. Chronic dizocilpine administration at either dose had no effect on body weight gain of either the sham-operated or OB rats compared with controls.

In the "open field" test, a typical increase in ambulation scores was found in the OB group compared with the sham-operated group [$H = 18.46$, df = 5, $p < 0.05$] (Table 1). This hyperactivity was significantly attenuated in the groups treated with 0.1 and 0.3 mg/kg dizocilpine ($p < 0.05$).

On day 1 of drug treatment, there was an increase in activity scores of sham and OB animals after administration of 0.3 mg/kg dizocilpine, with a significant elevation in the sham-treated group ($p < 0.05$ vs. sham + vehicle) (Table 2). The hyperactivity induced by dizocilpine was slightly lower in the OB-treated animals compared with the sham-operated animals, but this difference did not reach significance [$H = 13.96$, df = 5, $p < 0.05$].

On day 7 [$H = 3.05$, df = 5, $p = 0.692$], day 15 [$H = 7.77$, df = 5, $p = 0.170$], and day 21[$H = 9.95$, df = 5, $p = 0.078$], the 0.3-mg/kg dose of dizocilpine elevated locomotor activity; this response was found to be slightly higher in the OB-operated groups compared with the sham-operated group. Activity in the OB control group was also higher than in sham controls on days 15 and 21 of treatment.

In the frontal cortex, there was a significant decrease in the concentration of noradrenaline [$F(5, 45) = 3.79, p < 0.05$] and serotonin [$F(5, 45) = 3.16, p < 0.01$] in the OB group compared with sham controls (Table 3). Dizocilpine administration significantly elevated the dopamine concentration in both sham and OB-operated animals compared with their respective controls [$F(5, 45) = 0.85, p < 0.05$]. There was a decrease in the concentration of dopamine in the OB group compared with sham controls, an effect that was reversed by chronic dizocilpine (0.3 mg/kg) treatment ($p < 0.05$). DOPAC levels were slightly increased in the OB control group compared with sham controls, but this did not reach statistical significance. The DOPAC concentration was increased by dizocilpine (0.3 mg/kg) in the sham group compared with controls [$F(5, 45) = 3.79, p < 0.05$].

DISCUSSION

Surgical removal of the olfactory bulbs in the rat was associated with increased locomotor activity in the open field test. These results are consistent with the findings in previous studies (25,35). In the "open field" test, chronic administration of dizocilpine did not result in any behavioural changes in the sham-operated groups. However, it was found to attenuate the hyperactive response found in the OB control group compared with sham controls. The attenuation of this behavioural response is a property shared by a variety of typical and atypical antidepressants (34).

In a study carried out by Panconi et al. (18), it was suggested that the apparent antidepressant effects of dizocilpine in the tail suspension test and forced swim test did not result from the activity of the compound at the NMDA receptor complex but may be due to dopamine-related motor stimulant effects of dizocilpine. In contrast, in our study, dizocilpine did not affect ambulation scores in the sham-treated groups but decreased ambulation scores in the OB group. The fact that chronic dizocilpine did not alter the ambulation scores in sham-treated animals indicates that the effect of dizocilpine in the OB rat is not due to a stimulant or a sedative effect of the drug.

Previously it was found that OB animals showed a blunted hyperactive response following a dizocilpine challenge and a phencyclidine (PCP) challenge (5,25). The results of the present study indicate that acute dizocilpine (0.3 mg/kg) (day 1) increased home cage locomotor activity in both sham and OB-operated treated animals, this response being greater in

TABLE 2

TOTAL HOME CAGE LOCOMOTOR ACTIVITY COUNTS OVER A 5-h PERIOD FOLLOWING DIZOCILPINE ADMINISTRATION

Treatment	*n*	Day 1	Day 7	Day 15	Day 21
Sham + vehicle	8	125 (46–355)	223 (151–405)	135 (83–251)	100 (61–160)
Sham + dizocilpine (0.1 mg/kg)	8	187 (71–224)	294 (177–635)	115 (41–296)	132 (67–204)
Sham + dizocilpine (0.3 mg/kg)	8	693 (191–1,051)*	226 (100–520)	209 (141–274)	142 (113–322)
OB + vehicle	8	198 (104–315)	189 (104–389)	213 (130–332)	178 (90–206)
OB + dizocilpine (0.1 mg/kg)	8	123 (65–233)	205 (100–330)	175 (126–217)	104 (81–121)
OB + dizocilpine (0.3 mg/kg)	8	437 (190–578)	312 (195–635)	327 (198–579)	226 (148–351)

Data are expressed as median values, with interquartile ranges shown in parentheses. n = number of animals in group. *$p < 0.05$ vs. sham + vehicle.

TABLE 3

NEUROTRANSMITTER CONCENTRATIONS IN THE FRONTAL CORTEX OF OB AND SHAM-OPERATED ANIMALS FOLLOWING CHRONIC DIZOCILPINE ADMINISTRATION

Treatment	NA	DA	DOPAC	5-HT
Sham + vehicle	5,518 ± 578	4,491 ± 549	961 ± 69	10,999 ± 471
Sham + dizocilpine (0.1 mg/kg)	4,938 ± 344	6,465 ± 1,720	1,340 ± 255	10,588 ± 580
Sham + dizocilpine (0.3 mg/kg)	4,631 ± 141	6,916 ± 991	1,457 ± 163*	10,037 ± 367
OB + vehicle	4,038 ± 144*	3,162 ± 785	1,327 ± 245	8,984 ± 446**
OB + dizocilpine (0.1 mg/kg)	3,771 ± 392	7,154 ± 1,034†	1,263 ± 176	9,300 ± 646
OB + dizocilpine (0.3 mg/kg)	3,273 ± 504	6,554 ± 1,685	1,186 ± 217	8,077 ± 967

Data are expressed as means ± SEM, in units of ng/g. *$p < 0.05$. **$p < 0.01$ vs. sham + vehicle. †$p < 0.05$ vs. OB + vehicle.

the sham than in the OB group, thus showing a response similar to previous findings. The blunted hyperactive effect seen in OB rats following acute dizocilpine administration may be due to alterations in the NMDA receptor complex following bulbectomy.

In the present study, dizocilpine administration resulted in a hyperactive response that was enhanced in the OB-treated animals on days 15 and 21 compared with sham-treated animals. Repeated treatment with dizocilpine has been found to cause a reduction in the density of glutamate binding sites on NMDA receptors, but dizocilpine binding sites are not affected (13). In support of this hypothesis, cortical slices removed from rats repeatedly treated with MK-801 show a reduced response to NMDA, suggesting a downregulation of NMDA receptors. Thus, it is possible that readaptation in the functioning of the NMDA receptor complex in the OB rat occurs following chronic dizocilpine treatment.

It is thought that the dizocilpine-induced locomotor hyperactivity may be mediated by indirect facilitation of dopaminergic transmission caused by inhibition of the NMDA receptor and subsequent release of dopamine neurons from the inhibitory control of the glutamatergic system (9). In addition, it has been found that there is an increase in dopamine metabolism 30 min after dizocilpine administration in the medial prefrontal cortex (10). In the present study, we found a decrease in dopamine in the OB rats compared with the sham controls after chronic dizocilpine administration. The DOPAC/DA ratio was found to be constant in sham-control and MK-801-treated animals. OB resulted in an increase in the DOPAC/DA ratio compared with sham controls. The increase in the OB control group was attenuated by chronic MK-801 treatment. This indicates that the behavioural response in OB rats maybe a result of alterations in dopamine and indirectly possibly glutamatergic transmission in the OB rat.

It is interesting that chronic MK-801 administration in the OB rat does not decrease locomotion in the nonstressful environment of the home cage but does in the stressful "open field" apparatus. Chronic MK-801 decreases "open field" behaviour parallel to the decrease in dopamine turnover (DOPAC/DA ratio).

In the present study, there were decreases in the concentrations of noradrenaline and serotonin in the frontal cortex in the OB groups. These findings are similar to those of previous studies [for a review, see (30)]. However, chronic dizocilpine administration, unlike antidepressant treatment, did not reverse these neurotransmitter changes in the OB rat.

It may be concluded that chronic dizocilpine treatment reduced the OB deficits in the "open field" test. The deficit in DA seen in the OB rat was reversed by chronic dizocilpine administration. This indicates that the reversal of the OB-related hyperactivity in the "open field" test by MK-801 may be as a result of adaptations in the dopaminergic system in this model of depression. It was found that the hyperactive response induced by dizocilpine is reduced following bulbectomy. However, this response is enhanced in OB animals compared with sham animals following chronic dizocilpine exposure, thus suggesting that abnormalities in the glutamatergic system that may indirectly result in changes in the dopaminergic system may underlie some of the behavioural changes that occur in the OB rat. It would therefore appear that dizocilpine, a noncompetitive antagonist at the NMDA receptor complex, exhibits antidepressant activity in the preclinical behavioural test examined here.

REFERENCES

1. Bejanian, M.; Pechnick, R. N.; George, R.: Effects of acute and chronic administration of (+)-SKF 10,047 on body temperature in the rat: Cross-sensitization with phencyclidine. J. Pharmacol. Exp. Ther. 253:1253–1259; 1990.
2. Bubster, M.; Keseberg, U.; Notz, P. K.; Schmidt, W. J.: Differential behavioural and neurochemical effects of competitive and non-competitive NMDA receptor antagonists in rats. Eur. J. Pharmacol. 229:75–82; 1992.
3. Cairncross, K. D.; Wren, A. F.; Cox, B.; Schnieden, H.: Effects of olfactory bulbectomy and domicile on stress induced corticosterone release in the rat. Physiol. Behav. 19:485–487; 1977.
4. Collins, G. G. S.: Amino acid transmitter candidates in various regions of the primary olfactory cortex following bulbectomy. Brain Res. 296:145–147; 1984.
5. Dennis, T.; Beauchemin, V.; Lavoie, N.: *N*-methyl-D-aspartate receptors in the rat brain following olfactory bulbectomy: Autoradiographic and behavioural studies. Abstracts, Society for Neurosciences Meeting, Miami Beach, FL, 13–18 November, 1994:934.
6. Gill, R.; Foster, A. C.; Woodruff, G. N.: Systemic administration of MK-801 protects against ischemia induced hippocampal neurodegeneration in the gerbil. J. Neurosci. 7:3343–3349; 1987.
7. Gray, J. A.; Lalljee, B.: Sex differences in emotional behaviour in the rat: Correlation between the "open field" defecation and active avoidance. Anim. Behav. 22:856–861; 1974.
8. Harvey, J. A.; Scholfield, C. N.; Graham, L. T.; Aprison, M. H.: Putative neurotransmitters in denervated olfactory cortex. J. Neurochem. 24:445–449; 1975.
9. Hiramatsu, M.; Cho, A. K.; Nabeshima, T.: Comparsions of the behavioural and biochemical effects of the NMDA receptor antagonists, MK-801 and phencyclidine. Eur. J. Pharmacol. 166: 359–366; 1989.

10. Huiliang, D.; Gebhardt, K.; Carey, J.: Time course effects of MK-801: The relationship between brain neurochemistry and behaviour. Brain Res. Bull. 36:175–180; 1995.
11. Koe, B. K.; Vinich, F. J.: Adaptive changes in central nervous system receptor systems. Annu. Rep. Med. Chem. 19:41–50; 1984.
12. Leonard, B. E.; Tuite, M.: Anatomical, physiological and behavioural aspects of olfactory bulbectomy in the rat. Int. Rev. Neurobiol. 22:251–286; 1981.
13. Manallack, D. T.; Lodge, D.; Beart, P. M.: Subchronic administration of MK-801 in the rat decreases cortical binding of [^{3}H]D-AP5, suggesting down-regulation of the cortical N-methyl-D-aspartate receptors. Neuroscience 30:87–97; 1989.
14. Martin, C. A.: Neurotoxin induced olfactory bulbectomy: Biochemical and behavioural correlates [M.Sc. thesis]. Dublin: National University of Ireland; 1992.
15. Meloni, D.; Gambarana, C.; Graziella, M.; de Montis, G.; Pra, P. D.; Taddei, I.; Tagliamonte, A.: Dizocilpine antagonizes the effect of chronic imipramine on learned helplessness in rats. Pharmacol. Biochem. Behav. 46:423–426; 1993.
16. Nowak, G.; Trullas, R.; Layer, T.; Skolnick, P.; Paul, I. A.: Adaptive changes in the *N*-methyl-D-aspartate receptor complex after chronic treatment with imipramine and 1-aminocyclopropanecarboxylic acid. J. Pharmacol. Exp. Ther. 265:1380–1386; 1993.
17. Nsimba, S. E. D.; Kelly, J. P.; Leonard, B. E.: Dose-dependent behavioural effect of phencyclidine (PCP). Med. Sci. Res. 22:207–209; 1994.
18. Panconi, E.; Roux, J.; Attenbaumer, M.; Hamper, S.; Porsolt, R. D.: MK-801 and enantiomers: Potential antidepressants or false positives in classical screening model? Pharmacol. Biochem. Behav. 46:15–20; 1993.
19. Papp, M.; Moryl, E.: Antidepressant activity of non-competitive and competitive NMDA receptor antagonists in a chronic mild stress model of depression. Eur. J. Pharmcol. 263:1–7; 1994.
20. Paul, I. A.; Trullas, R.; Skolnick, P.; Nowak, G.: Down regulation of cortical β-adrenoceptors by chronic treatment with functional NMDA antagonists. Psychopharmacology 106:285–287; 1992.
21. Pechnick, R. N.; Hiramatsu, M.: The effects of MK-801 on body temperature and behaviour in the rat: Cross-sensitization and cross-tolerance with phencyclidine. Eur. J. Pharmcol. 252:35–42; 1994.
22. Pechnick, O. W.; Wong, C. A.; George, R.; Thurkauf, A.; Jacobson, A. E.; Rice, K. C.: Comparsion of the effects of the acute administration of dexoxadrol, levoxadrol, MK-801 and phencyclidine on body temperature in the rat. Neuropharmacology 28:829–835; 1989.
23. Popov, N.; Pohle, W.; Rosler, V.; Matthies, H.: Regionale Verteilung von gamma-Aminobuttersaure, Glutaminsaure, Asparaginsaure, Dopamin, Noradrenalin and Serotonin im Rattenhirn. Acta Med. Biol. Germ. 18:695–702; 1967.
24. Porsolt, R. D.; LePichon, M.; Jalfre, M.: Depression: A new animal model sensitive to antidepressant treatment. Nature 266:730–732; 1977.
25. Redmond, A. M.; Kelly, J. P.; Leonard, B. E.: Effects of paroxetine and fluvoxamine on behavioural changes in a number of paradigms in the olfactory bulbectomized rat model of depression. J. Serotonin Res. 3:199–205; 1994.
26. Redmond, A. M.; Kelly, J. P.; Leonard, B. E.: Effects of olfactory bulbectomy and chronic amitriptyline treatment on phencyclidine (PCP)-induced hyperactivity. Med. Sci. Res. 23:351–352; 1995.
27. Scholfield, C. N.; Moroni, F.; Corradetti, R.; Pepeu, G.: Levels of synthesis of glutamate and aspartate in the olfactory cortex following bulbectomy. J. Neurochem. 41:135–138; 1983.
28. Seyfried, C. A.; Adams, G.; Greve, T.: An automated direct-injection HPLC-method for the electrochemical/fluorimeter quantitation of monoamines and related compounds optimized for screening of large numbers of animals. Biomed. Chromatogr. 1:78–88; 1986.
29. Skolnick, P.; Muller, R.; Young, A.; Boje, K.; Trullas, R.: Chronic treatment with 1-aminocyclopropanecarboxylic acid desensitizes behavioural responses to compounds acting at the *N*-methyl-D-aspartate receptor complex. Psychopharmacology 107:489–496; 1992.
30. Snell, L. D.; Yi, S. J.; Johnson, K. M.: Comparison of the effects of MK-801 and phencyclidine on catecholamine uptake and NMDA-induced norepinephrine release. Eur. J. Pharmacol. 145: 223–226; 1988.
31. Song, C.; Leonard, B. E.: The effect of olfactory bulbectomy in the rat, alone or in combination with antidepressants and endogenous factors, on immune function [review]. Hum. Psychopharmacol. 10:7–18; 1995.
32. Sulser, F.; Janowsky, A. J.; Okada, F.; Manier, D. H.; Mobley, P. L.: Regulation of recognition and action function of norepinephrine (NE) receptor-coupled adenylate cyclase system in brain: Implications for the therapy of depression. Neuropharmacology 22:425–431; 1983.
33. Tricklebank, M. D.; Singh, L.; Oles, R. J.; Preston, C.; Iversen, S. D.: The behavioural effects of MK-801: A comparsion with antagonists acting non-competitively and competitively at the NMDA receptor. Eur. J. Pharmacol. 167:127–135; 1989.
34. Trullas, R.; Skolnick, P.: Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. Eur. J. Pharmacol. 185:1–10; 1990.
35. Van Riezen, H.; Leonard, B. E.: Effects of psychotropic drugs on the behavior and neurochemistry of olfactory bulbectomized rats. In: File, S.E., ed. Psychopharmacology of anxiolytics and antidepressants. New York: Pergamon Press; 1991:231–250.
36. Wong, E. H. F.; Knight, A. R.; Woodruff, G. N.: [^{3}H]MK-801 labels a site on the *N*-methyl-D-aspartate receptor channel complex in rat brain membranes. J. Neurochem. 50:274–281; 1988.