Jpn. J. Pharmacol. **87**, 277 – 287 (2001)

Role of Dopaminergic System in Core Part of Nucleus Accumbens in Hyperlocomotion and Rearing Induced by MK-801 in Rats: A Behavioral and In Vivo Microdialysis Study

Izzettin Hatip-Al-Khatib[1,*], Funda Bölükbasi[2], Kenichi Mishima[3], Nobuaki Egashira[3], Katsunori Iwasaki[3] and Michihiro Fujiwara[3]

[1]*Department of Pharmacology, Faculty of Medicine, Pamukkale University, Denizli, 20027 Turkey*
[2]*J&J Janssen-Cilag, Istanbul, 81610 Turkey*
[3]*Department of Physiology and Pharmacology, Faculty of Pharmaceutical Sciences, Fukuoka University, Fukuoka 814-0180, Japan*

Received May 24, 2001 Accepted September 21, 2001

ABSTRACT—We investigated modification of the MK-801 effect on motor activity and extracellular amines concentration by 6-hydroxydopamine (6-OHDA)-induced lesion of core nucleus accumbens (cACC) of rats. In vivo microdialysis-HPLC showed that the concentrations (fmol/μl) of dopamine (DA), dihydroxyphenylacetic acid (DOPAC) and serotonin were 0.738 ± 0.135, 155.34 ± 41.01 and 0.334 ± 0.024, respectively, in the cACC of intact rats. The DOPAC/DA ratio was 264.24 ± 94.01. Unilateral lesion of the cACC with 6-OHDA (8 μg/μl) substantially reduced DA (–93%) and DOPAC (–97%) in desipramine (30 mg/kg, i.p.)-pretreated rats (6-OHDA+DMI rats) as compared to the 65% reduction rate of both amines in saline-pretreated rats (6-OHDA+saline rats). Moreover, DOPAC was reduced by 72% in 6-OHDA+DMI rats. MK-801 increased DOPAC (426 – 467%) and DOPAC/DA ratio (180 – 230%) in intact rats. On the other hand, MK-801 increased DA by 154% and 505% in 6-OHDA+saline and 6-OHDA+DMI rats, respectively. 6-OHDA reduced the effect of MK-801 on DOPAC and DOPAC/DA ratio. In the behavioral studies, MK-801 (0.01 – 0.3 mg/kg, i.p.) increased locomotor activity and rearing of intact rats. Bilateral 6-OHDA+DMI lesion of the cACC caused greater reduction in the effect of MK-801 (0.1 mg/kg) than that of the shell nucleus accumbens. These results suggest that increased extracellular DOPAC concentration (but not DA) and DOPAC/DA ratio in the cACC plays an important role in MK-801-hyperactivity.

Keywords: MK-801, Core nucleus accumbens (rat), Microdialysis, Motor activity

The nucleus accumbens (ACC) is a part of the mesocortical and mesolimbic dopaminergic system. The ACC receives dopaminergic inputs from the ventral tegmental area (VTA) and glutamatergic inputs that originate from cortical regions (including medial frontal), amygdala and midline thalamus (1). The ACC is involved in a variety of behavioral activities. The dopaminergic system in the ACC plays an important role in control of spontaneous, psychostimulants (2)- and MK-801 (3 – 6)-induced locomotor hyperactivity. On the other hand, the allocortical-originated glutamatergic afferents could modulate the psychomotor activation and drug reinforcement (7). Moreover, the glutamatergic and dopaminergic systems not only separately alter the behavioral effects but could also act by interacting and modulating the function of each other. A functional interaction has been reported between the glutamatergic system (via *N*-methyl-D-aspartate (NMDA) receptors) and the dopaminergic system at the striatal levels (8) with a negative modulatory effect of the glutamatergic system on the dopaminergic one (9). The consequence of glutamate block depends on which of glutamate receptors are blocked. In the ACC, it is suggested that antagonists that block only NMDA autoreceptors increase synaptic glutamate level and disinhibit dopaminergic terminals. On the other hand, NMDA and non-NMDA antagonists that block both the glutamate autoreceptors and postsynaptic receptors inactivate the dopaminergic terminals (10).

Cytoarchitectural and neurochemical investigations revealed that the ACC is composed of segregated subregions of different functional implications, structural characteristics and connectional properties. In the light of these studies, the ACC was found to be composed of core (cACC) located dorsal to the anterior commissure, shell (sACC)

*Corresponding author. FAX: +90-258-2132874
Email: izfunhatip2000@yahoo.com, ihatip@pamukkale.edu.tr

situated medially (11), and central part between the cACC and sACC (12). The sACC is in turn divided into dorsal (cone) and ventral parts (13). The cACC had been shown to contain greater dendrites and spines per unite volume (14) and higher percentage of neurons expressing mRNA for dopamine (DA) D_2, while sACC contains higher DA D_1 receptors (15). Moreover, the cACC and sACC are differentially modulated by respective projections from paranigral and parabrachial nuclei of VTA (16).

The cACC and sACC are involved in different behavioral activities. It has been reported that the cACC may be a key element in the neuropathology of impulsivity (17). Moreover, the cACC is connected with structures involved in regulation of motor activities (11) and stimulus-reward learning (18). The sACC, in contrast to cACC, stands out as a transmission area between the extrapyramidal and limbic system (19). It sends afferents to the hypothalamic area, a somewhat atypical connection pattern within the basal ganglia complex (20). The sACC is thought to "gate" the flow of information between excitatory amino acid afferents from limbic nuclei and motor systems (21). Moreover, the cACC and sACC exhibit different responses to various drugs. It has been found that serotonin (5-HT) 5-HT_2 receptor antagonists increase DA level to greater extent in the sACC, whereas DA D_2 antagonists increase DA to a greater extent in the cACC (22).

(+)-MK-801, (5*R*,10*S*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate, is a highly potent and selective non-competitive antagonist that acts as an open channel blocker at the NMDA receptors-operated ion channels. MK-801 produces dose-dependent behavioral effects such as coordinated and/or uncoordinated locomotor activities and stereotypy (3, 4, 23, 24) through actions involving glutamatergic, dopaminergic and possibly other systems. The MK-801 induced hyperlocomotion in monoamine depleted mice is proposed as a unique animal behavior for studying functions of the brain in vivo, as related to the NMDA-receptors ion channel complex (25). Moreover, the dysfunction of mesolimbic and mesocortical dopamine neurons induced by systemic administration of non competitive NMDA-receptor antagonists may have direct bearing on the neurobiology of psychotic states, in particular as regards to the generation of emotional and cognitive impairments (26). Although the ACC is reported to be involved in the effects of MK-801, no study is available regarding the role of the cACC in the behavioral effects of MK-801 combined with in vivo microdialysis. Such a study may also afford biochemical means to assess psychotomimetic liability of NMDA-receptor antagonists, and to determine the doses not associated with side effects that may reduce their usefulness as neuroprotective agents (27). Therefore, the present study was conducted to determine the effect of MK-801 on extracellular DA, dihydroxyphenylacetic acid (DOPAC) and 5-HT concentrations in the rats' cACC, and to evaluate the significance of this effect for MK-801-hyperactivity in intact and 6-OHDA-lesioned cACC, using in vivo microdialysis combined with high performance liquid chromatography (HPLC)-electrochemical detection (ECD).

MATERIALS AND METHODS

Animals

Male Wistar rats (Kyudo Co., Saga) weighing 250 – 280 g at the time of the experiments were used. The rats were housed in groups of five in Plexiglas cages (42 × 26 × 15 cm) with litter. The room temperature and humidity were kept at 22 ± 2°C and 55 ± 5%, respectively. A 12:12 light:dark cycle was used with the lights on at 07:00. The rats had free access to food and water except during the experiments. Animal housing and the following experiments were conducted according to guidelines and auspices of a protocol approved by Fukuoka University with commitment to the ethical regulations and the Guide for Care and Use of Laboratory Animal, NRC.

Experimental procedures

Stereotaxic procedure: The stereotaxic surgical manipulations were conducted under anesthesia with sodium pentobarbital (50 mg/kg, i.p.) using an angular Stellar rat stereotax instrument (Stoelting, Wood Dale, IL, USA). The angular approach was used in order to avoid damage to the structures close to the midsagittal line. The coordinates applied are relative to skull surface according to the Paxinos and Watson atlas (28).

In the behavioral studies, separate lesions of each of the cACC or sACC were performed bilaterally. The rats were pretreated with desipramine HCl (DMI, 30 mg/kg, i.p.) 30 min prior to infusion of 6-OHDA (6-OHDA+DMI rats). The rats were fixed in the stereotaxic frame with the upper incisor bar set at 3.3-mm below the interaural line. 6-OHDA was injected into the cACC or sACC using 10-μl microsyringes (Scientific Glass Pty, Ringwood, Australia) driven at a rate of 1 μl/2 min by a motor (B. Braun, Melsungen, Germany). The injection cannulae (9.5-mm-long, ID 0.55 mm, OD 0.7 mm; Eicom, Kyoto) were left in situ for a further 5 min after the end of each injection to ensure dispersal and to prevent back flow of the solution. The cACC was lesioned by single microinjection of 2 μl solution, containing 8 μg 6-OHDA, at 10° angle according to the following coordinates (mm): frontal from bregma, F = 1; lateral from midsagittal line, L = 3.2 (the point of the angular injection was 1.2 mm lateral to the target point in the cACC, which is 6.8-mm ventral to skull surface and 2.0-mm lateral to midsagittal line), dorsoventral, DV = 6.9. On the other hand, two separate

microinjections (each one was 1 μl containing 4 μg 6-OHDA) were carried out into the sACC at F = 1.6 to avoid diffusion into the diagonal band which may take place at more posterior coordinates. The first one was performed into the dorsal sACC at 19.5° angle from the vertical plane and according to the following coordinates (mm): F = 1.6, L = 3.2 (the point of the angular injection was 2.4 mm lateral to the target point in dorsal sACC, which is 6.8 mm ventral to skull surface and 0.8 mm lateral to the midsagittal line) and DV = 7.2. The second injection was done into the ventral sACC at 15° angle and according to the following coordinates (mm): F = 1.6, L = 3.2 (the point of the angular injection was 2.1 mm lateral to the target point in sACC, which is 7.8 mm ventral to skull surface and 1.1 mm lateral to the midsagittal line) and DV = 8.1. The angles were selected according to the tangent of lateral coordinates (from the point at the skull surface dorsal to each target point) to the DV from that point to each injection site. After each stereotaxic manipulation, the guide cannulae were secured with dummy cannulae, and the rat was housed singly in a cage until it recovered from anesthesia and then returned to group housing. Each rat received a prophylactic injection of penicillin in hindquarter muscle (100,000 U /day, i.m. for 3 days after operation). Two separate groups (n = 8 in each group) of sham-operated rats injected with the same volume of saline vehicle (containing 0.01% ascorbate) into either the cACC or sACC, but without 6-OHDA and served as control for the cACC and sACC rats, respectively.

In the microdialysis studies, guide cannulae (9-mm-long, ID 0.75 mm, OD 0.85 mm; Eicom) were implanted in the cACC of 6-OHDA+DMI rats and of those that received saline 30 min prior to infusion of 6-OHDA (6-OHDA+ saline rats). The coordinates for implantation of the guide cannulae were the same above-mentioned coordinates for injection into the cACC except the DV was 6.4 because the microdialysis probes protruded 1.0-mm from the guide cannulae.

Microdialysis of the cACC and HPLC: The microdialysis experiments were performed in freely moving and unanesthetized rats. The microdialysis probes (Eicom) consisted of a U-shaped dialysis membrane composed of cellulose hollow fiber (each arm was 1-mm-long, with an ID of 0.20 mm, OD of 0.22 mm and a surface area of 0.69 mm^2; molecular weight cut-off of 50 kD) were inserted into the distal end of the stainless steel tubing (9-mm-long, OD 0.70 mm, ID 0.55 mm). The dialysis probes were implanted 10 days after injection of 6-OHDA. Each rat with implanted probe was placed in a plexiglas chamber (50 cm × 35 cm × 35 cm). The inlet of the probe was connected to a microsyringe driven by a microinfusion pump (ESP-64, Eicom), whereas the outlet end was connected to an autoinjector (EAS-20 autoinjector, Eicom) coupled to HPLC-ECD (LC EP-300, Eicom) by a teflon tube (ID 0.1 mm, OD 0.4 mm, length 50 cm; the volume is 4 μl). The probes were perfused at rate of one μl/min with buffered Ringer's solution (147 mM NaCl, 4 mM KCl, 2.3 mM $CaCl_2$, pH 7.4). The experiments were started only after a stable output was obtained (180 min). Baseline samples (aliquots of 20 μl/20 min) were collected for 60 min by the autoinjector and analyzed with HPLC using a reverse-phase column (Eicom-pack MA-5ODS-octadecyl silane, 2.1ϕ × 150 mm; oven temperature, 25°C; Eicom). The mobile phase (flow rate 0.23 ml/min) was composed of a combination of buffer A (15.6 g/l $NaH_2PO_4 \cdot 2H_2O$) and buffer B (35.8 g/l $Na_2HPO_4 \cdot 12H_2O$). The final buffer (containing 20% v/v methanol, pH 6.0) was prepared by combining 1 liter buffer A with 160 ml buffer B, and adding $EDTANa_2$ (50 mg/l) and sodium-1-octane sulfate (500 mg/l); this buffer was vacuum filtered before use. The ECD was set at +0.45 V (oxidation potential) against an Ag/AgCl reference analytical electrode.

At the end of the experiments, coronal sections of the fore brain were cut at 25 μm to verify the probes and injection cannulae sites. Data from any rat with cannula or probe site located outside the intended target was excluded from the study (8/24 in sACC, and 4/20 in cACC in behavioral studies; 3/30 in microdialysis probe implantation). The sites of microinjection cannulae tips with extent of diffusion and location of microdialysis probes and area occupied by the active dialysis membrane in cACC are shown in Fig. 1.

Behavioral studies: The behavioral effects of various doses of MK-801 (0.01 – 0.3 mg/kg, i.p.) were investigated in intact rats. In the light of the results of these experiments, the behavioral effects of 0.1 mg/kg, i.p. MK-801 were studied 10 days after induction of 6-OHDA lesion. This dose was chosen because it increased the locomotor activity in this study, and it seemed to be a transitional dose from the one producing pure hyperlocomotion to that inducing ataxia/stereotypy with or without hyperlocomotion.

The coordinated locomotor activity (ambulation: movement with all four limbs, not accompanied by any ataxia or stereotypy, that alters the animal's position in the cage) was quantified using an activity cage (35 × 23 × 20 cm; Ugo Basile, Varse, Italy). Moreover, an experimenter unaware of the treatment quantified rearing (animal standing with its hind limbs extending to the floor and the forelimbs are mainly in the air). Each rat was individually adapted for 15 min to the activity cage and before the start of the recordings. MK-801 was injected i.p. at a single dose, and then the activity was measured after each injection for a period of 120 min.

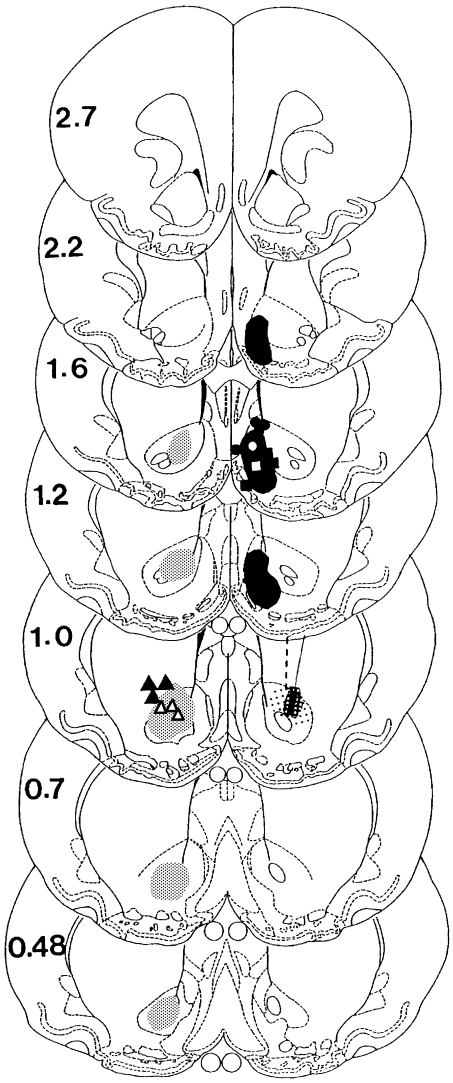

Fig. 1. Schematic representation of the parts of ACC sketched on sections from stereotaxic plates from Paxinos and Watson (28). The numbers indicate coordinates (mm) rostral to the bregma. The probe site, area occupied by the active dialysis membrane (dark-hatched) and extension of the site around the original location (light-dotted) in the cACC of rats considered in the study are shown in the right half at the coordinate 1.0. The location of the tips of microinjection cannulae in the cACC of rats considered (open triangle) or excluded (closed triangle) from the study are shown in the left half at coordinate 1.0. The extent of injection into the cACC (heavily dotted) of rats used in the study is also shown at five successive sections (coordinates 0.48 – 1.6) in the left half. The locations of the tips of microinjection cannulae into the dorsal sACC (included (open circle) or excluded (closed circle) from the study) and ventral sACC (included (open square) or excluded (closed square) from the study) are shown in the right half at coordinate 1.6. The extent of diffusion of the injections into the sACC of rats used in the study is shown as a shaded area at three successive sections (coordinates 1.2 – 2.2) in the right half.

Statistical analyses

The data were evaluated by multifactor analysis of variance (ANOVA) with repeated measure on one factor in the same animal (recording repeated at each time interval for either HPLC analysis or activity measurement) to evaluate the effect of dose, time and dose × time interaction followed by pairwise comparisons using the Newman-Keuls *post hoc* test if significance ($P<0.05$) was indicated. The independent factor is dose (subjects were injected once only) and the dependent factor is time (repeated measure). A check on the homogeneity was carried out using Bartlett's test. All data are presented as means ± standard error of means (n = 8 per each group for behavioral studies, and n = 6 for each group in the microdialysis-HPLC studies).

Drugs

The drugs used in this study were purchased from Research Biochemicals International (RBI, Natick, MA, USA). MK-801 and DMI were dissolved in sterile isotonic 0.9% saline. The i.p. administration was conducted at a volume of 1 ml/kg. The dosages are expressed as the weight of drug base. The solution of 6-OHDA was freshly prepared before each experiment by dissolving 6-OHDA in freshly prepared ice-cooled 0.01% ascorbic acid in sterile 0.9% isotonic saline solution. The solution was stored in a dark vial kept on ice in an insulated light-protected chest during the injection. The final concentration was 4 μg/μl for each injection into the sACC and 8 μg/μl for the injection into the cACC. The standards of DA, DOPAC and 5-HT were purchased from Sigma (St. Louis, MO, USA).

RESULTS

Microdialysis-HPLC analysis of the cACC

Effect on DA concentration

Figure 2A shows that the concentration of extracellular DA in the dialysates collected from the cACC of intact rats was 0.728 ± 0.04 fmol/μl. The concentration of DA showed a steady level throughout the 120 min analysis period (0.859 ± 0.2 fmol/μl). 6-OHDA induced a 65% depletion of DA ($F_{1,20} = 4.5$, $P<0.05$) in the 6-OHDA+ saline rats. However, 6-OHDA induced a 93% depletion of DA in 6-OHDA+DMI rats ($F_{1,20} = 14.56$, $P<0.01$). The depletion rate that was induced by 6-OHDA was significantly higher in 6-OHDA+DMI- than in 6-OHDA+saline rats ($F_{1,20} = 4.40$, $P<0.05$).

MK-801 did not significantly change DA in the dialysates collected from the cACC of intact rats, although a nonsignificant reduction (20% and 25%) was detected after 1 and 2 h, respectively ($F_{1,20} = 2.15$, n.s.). On the other hand, in 6-OHDA+saline rats, MK-801 increased DA by 146 – 163% ($F_{1,20} = 5.3$, $P<0.05$) to a level that was higher (by 8 – 24%) than that produced by MK-801 in intact rats, but no significant difference was detected between the two

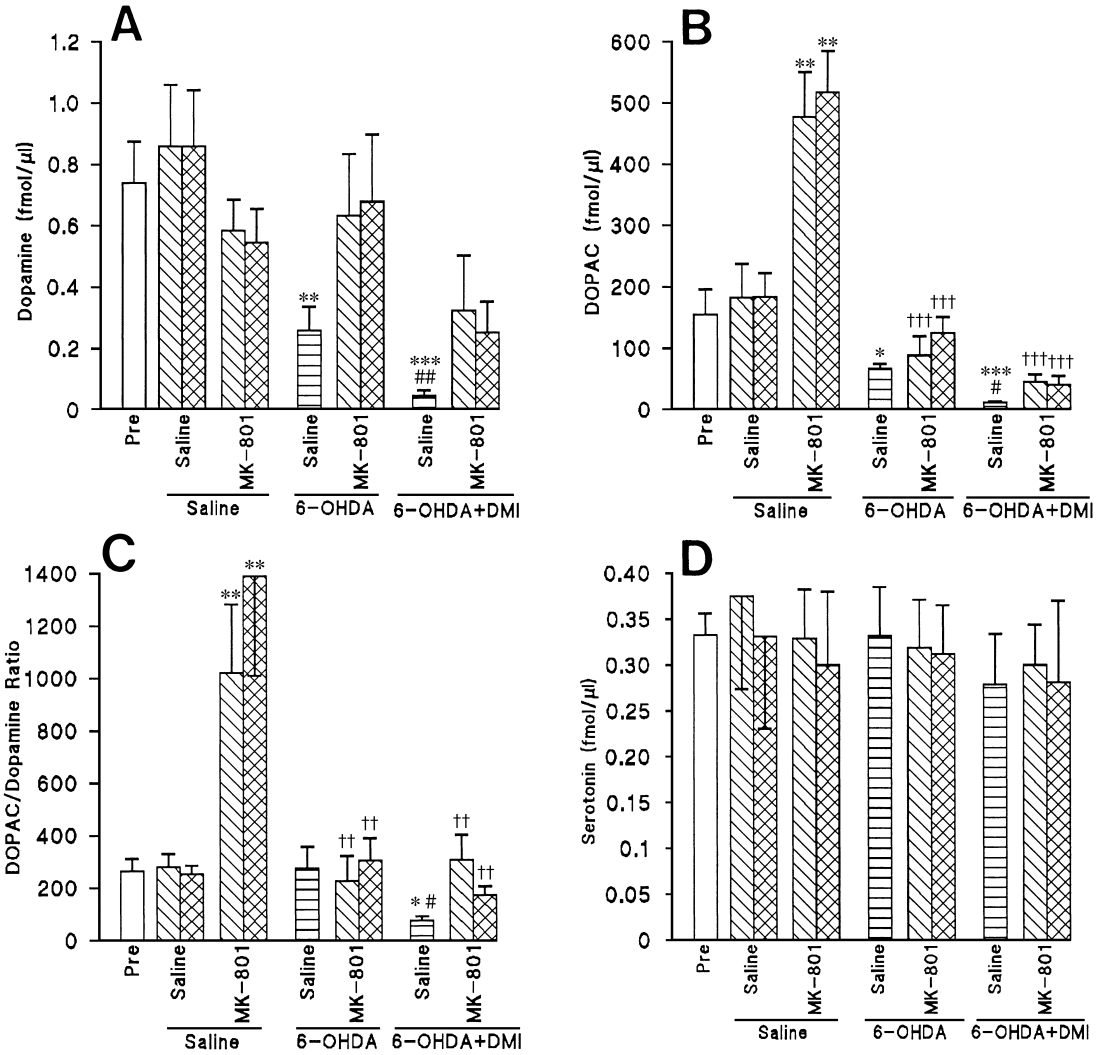

Fig. 2. Effect of MK-801 (0.1 mg/kg, i.p.) on extracellular concentration of dopamine (A), DOPAC (B), DOPAC/DA ratio (C) and serotonin (D) in dialysates collected from the cACC of intact and 6-OHDA-lesioned rats. Pre: baseline 60-min samples obtained before saline or MK-801 injection in intact rats. In 6-OHDA-lesioned rats, the cACC was dialyzed 10 days after induction of lesion. The effect of MK-801 in intact or lesioned rats was determined in dialysate aliquots (20 μl/20 min) collected for 2 h and presented as the mean of the first (60 min, striped column) and second h (120 min, crossed column). Each column and bar represent the mean ± S.E.M. of each group (n = 6). Statistical significances: *P<0.05, **P<0.01, ***P<0.001, compared to saline+saline; $^{\#}P$<0.05, $^{\#\#}P$<0.01, compared to 6-OHDA+saline; $^{\dagger\dagger}P$<0.01, $^{\dagger\dagger\dagger}P$<0.001, compared to saline+MK-801.

groups ($F_{1,20}$ = 0.28, n.s.). Moreover, MK-801 produced a 570 – 590% increase of DA in 6-OHDA+DMI rats ($F_{1,20}$ = 6.51, P<0.025), but the effect of MK-801 was nonsignificantly lower (by 40%) than that produced by MK-801 in intact rats ($F_{1,20}$ = 4.21, P<0.1, n.s.). The results also showed that the reduction in the effect of MK-801 was greater in 6-OHDA+DMI- than in 6-OHDA+saline rats ($F_{1,20}$ = 4.3, P<0.05).

Effect on DOPAC concentration

Figure 2B shows that the concentration of DOPAC in dialysates collected from the intact cACC was 189.32 ± 37.4 fmol/μl. The level of DOPAC continued steadily throughout the analysis after 60 min (182.8 ± 55.5 fmol /μl) and 120 min (183.9 ± 85.3 fmol/μl). 6-OHDA lesion substantially reduced DOPAC. The concentration of DOPAC was reduced in dialysates collected from the cACC of 6-OHDA+saline (–65%; $F_{1,20}$ = 12.82, P<0.01) and 6-OHDA+DMI rats (–97%; $F_{1,20}$ = 19.94, P<0.001). The depletion rate was significantly higher in 6-OHDA+DMI- than in 6-OHDA+saline rats ($F_{1,20}$ = 6.88, P<0.025).

MK-801 increased the concentration of DOPAC in the cACC of intact rats to 447 ± 121.1 fmol/μl ($F_{1,20}$ = 8.88, P<0.01). The effect of MK-801 was decreased by 73 – 79% in 6-OHDA+saline- ($F_{1,20}$ = 15.02, P<0.001) and by 90% in 6-OHDA+DMI rats ($F_{1,20}$ = 20.86, P<0.001). The re-

duction of MK-801 effect was greater in 6-OHDA+DMI- than in the 6-OHDA+saline rats ($F_{1,20} = 8.33$, $P<0.01$).

Effect on DOPAC/DA ratio

Figure 2C shows DOPAC/DA ratio in dialysates collected from the cACC of intact and 6-OHDA-lesioned rats and the effect of MK-801 in each group. In the intact rats, the DOPAC/DA ratio was 260 ± 43 after the stabilization period. The ratio was between 212 ± 39 and 214 ± 28, at 60 min and 120 min following saline administration. The results showed that 6-OHDA alone did not significantly decrease DOPAC/DA ratio (−12%; $F_{1,20} = 0.004$, n.s.). However, 6-OHDA+DMI significantly decreased (by 72%) DOPAC/DA ratio ($F_{1,20} = 9.03$, $P<0.01$). Moreover, the results showed that reduction of the DOPAC/DA ratio was greater in 6-OHDA+DMI- than in 6-OHDA+saline rats ($F_{1,20} = 8.17$, $P<0.01$).

MK-801 increased (180 – 230%) DOPAC/DA ratio in the intact rats ($F_{1,20} = 12.81$, $P<0.01$). The effect of MK-801 was reduced by 78% (compared to the effect in intact rats) in 6-OHDA-lesioned rats ($F_{1,20} = 11.68$, $P<0.01$), and MK-801 did not increase DOPAC/DA ratio as compared to the pre value in the same group. On the other hand, MK-801 increased (by 80 – 83%) DOPAC/DA ratio in OHDA+DMI-lesioned rats ($F_{1,20} = 5.62$, $P<0.05$), but the effect of MK-801 was lower (by 70 – 88%) than that in intact rats ($F_{1,20} = 12.66$, $P<0.01$).

The statistical analyses revealed that the treatment × time interactions with repeated analysis for DA, DOPAC and DOPC/DA ratio were statistically not significant, indicating their steadiness during the 120-min microdialysis period.

The HPLC analysis of dialysates showed that the cACC contained 0.334 ± 0.024 fmol/μl 5-HT after the stabilization period. The concentration was lowered by further dialysis for 60 min (0.241 ± 0.09 fmol/μl) and 120 min (0.219 ± 0.09 fmol/μl), but the difference was not significant. Moreover, none of the treatments significantly altered 5-HT concentration (Fig. 2D).

Behavioral studies

Effects of MK-801 in intact rats

Effects on locomotor activity: Figure 3A shows that MK-801 (0.01 – 0.3 mg/kg) increased locomotor activity ($F_{4,35} = 13.06$, $P<0.001$ compared to the control). The effect decreased with time ($F_{8,280} = 15.76$, $P<0.001$). A significant time × dose interaction was obtained ($F_{32,280} = 2.18$, $P<0.001$) indicating differences among various doses of MK-801 (and with regard to control) at different time intervals. The effect of MK-801 increased at doses of 0.01 – 0.1 mg/kg. The significant effect reached the maximum level 60 min after 0.01 mg/kg. At 0.05 and 0.1 mg /kg, the effect of MK-801 commenced rapidly: a significant effect was obtained within the first 15 min, reaching the maximum level after 45 min and then decreased, but the significant effect persisted throughout the study. On the other hand, the effect of MK-801 at 0.3 mg/kg was observed rapidly, 3 – 4 min after injection. A significant effect was obtained during the first 15 min, reaching the maximum level after 30 min. The effect decreased thereafter gradually for 75 min. After 75 min, it decreased rapidly, but still remained significantly higher than the control for 105 min. The results also showed that the magnitude of the effect induced by MK-801 at 0.3 mg/kg was smaller than that produced by the doses of 0.05 and 0.1 mg/kg.

Effects on rearing: Figure 3B shows that MK-801 increased rearing of intact rats ($F_{4,35} = 6.22$, $P<0.001$). The significant effect was obtained at 0.05 and 0.1 mg/kg, observed during the first 15-min interval and continued for 60 and 45 min, respectively. The effect decreased by time ($F_{8,280} = 8.20$, $P<0.001$, for time factor) and there

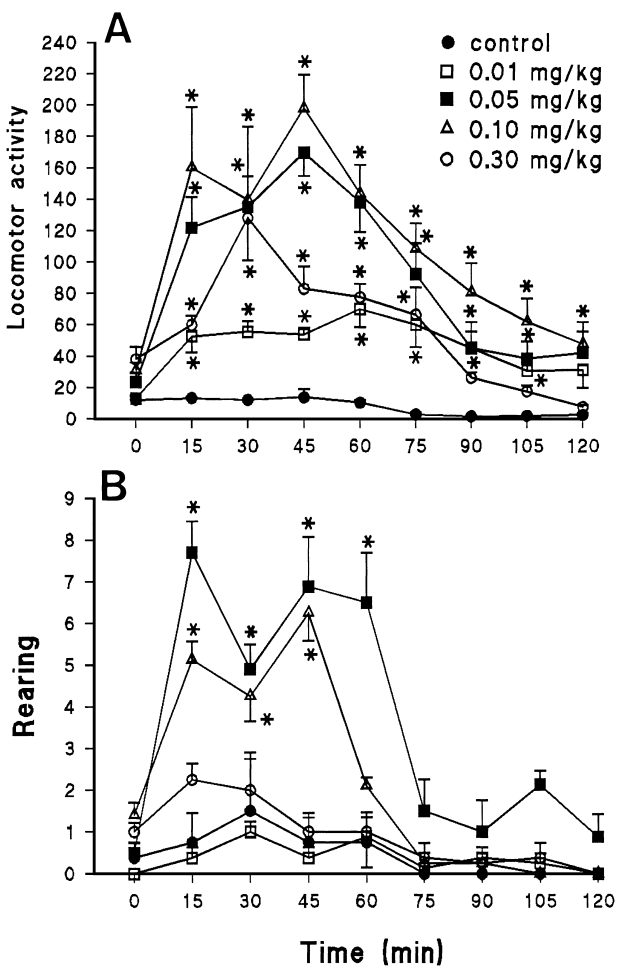

Fig. 3. Effect of MK-801 (0.01 – 0.30 mg/kg, i.p.) on the locomotor (A) and rearing (B) activity of intact rats. Each point represents the mean ± S.E.M. of each group (n = 8). The control group received 0.9% saline, i.p. at rate of 1 ml/kg. *$P<0.05$, compared to control.

was a significant dose × time interaction ($F_{32,280} = 2.66$, $P<0.001$) indicating differences in the effect of various doses of MK-801 (and with regard to the control) at different time intervals.

Effect of MK-801 in 6-OHDA+DMI rats

Figure 4A shows that lesion of the cACC and sACC decreased the effect of MK-801 (0.1 mg/kg) on locomotor activity ($F_{2,21} = 22.93$, $P<0.001$). Moreover, a different time effect for each lesion (compared to the effect of MK-801 in intact rats) was obtained ($F_{8,168} = 4.8$, $P<0.001$). A significant lesion × time interaction was obtained ($F_{16,168} = 4.76$, $P<0.001$), indicating that cACC and sACC lesions have different profiles. The lesion of the cACC induced a greater reduction in the effect of MK-801 as compared to lesion of the sACC ($F_{1,14} = 13.47$, $P<0.01$). Moreover, the significant effect of the cACC lesion on MK-801 was observed throughout the experiment, whereas that of the sACC lesion was observed only for 45 min. After 60 min, the effect of MK-801 on locomotor activity was slightly (not significantly) higher in the sACC- than in the cACC-lesioned rats. Figure 4B shows that lesions of the cACC reduced the effect of MK-801 on rearing ($P<0.05$ compared to intact, and $P<0.01$ compared to sACC-lesioned rats). However, MK-801 produced higher rearing in sACC-lesioned rats than in intact rats ($P<0.05$). It is note worthy that MK-801-induced rearing in sACC-lesioned rats or reduction of the MK-801 effect in the cACC-lesioned rats was observed during the first 30 and 45 min, respectively. Moreover, MK-801 increased rearing of the cACC- and sACC-lesioned rats after 90 min, but the effect did not reach a significant level ($F_{2,21} = 0.86$, $P<0.44$) except at 120 min ($P<0.05$).

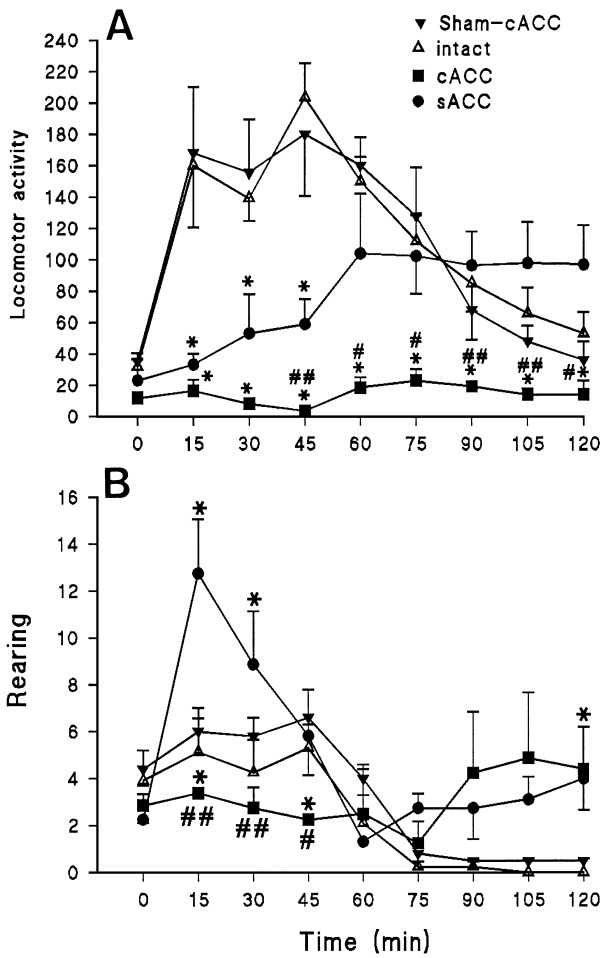

Fig. 4. Effect of 6-OHDA-induced lesion of the cACC and sACC on hyperlocomotor (A) and rearing (B) activity of rats induced by MK-801 (0.1 mg/kg, i.p.). The effect of MK-801 was evaluated 10 days after induction of lesion. Each point represents the mean ± S.E.M. of each group (n = 8). Statistically significant differences: *$P<0.05$, compared to intact; $^{\#}P<0.05$ and $^{\#\#}P<0.01$, compared to sACC lesion.

DISCUSSION

Microdialysis-HPLC revealed that the cACC contains a high basal extracellular level of DA and DOPAC compared to that of 5-HT. It has been reported that the basal DA output in the cACC is not significantly different from that in the sACC (29). The concentrations of DA and DOPAC that were detected in this study are similar to those reported in the striatum (30). Moreover, the steady DA level reported in this study is close to that reported in the sACC (31), but higher than that reported in the whole ACC (32). This discrepancy may be due to differences in the subregion of the ACC, the coordinates or the analytical procedures used. Moreover, the high DOPAC/DA ratio that was also detected in the present study is consistent with the greater DA utilization reported in the cACC, as compared to the sACC (19), indicating a high DA metabolic rate in addition to the high concentration of DA in the cACC.

It has been suggested that the primary effects of systemic MK-801 injection resemble those displayed in the ACC and VTA (33). In addition to a direct effect, MK-801 could affect the ACC indirectly by modulating dopaminergic activity in the VTA and prefrontal cortex (4). It has been reported that MK-801 at the dose used in the microdialysis-HPLC analyses in this study (0.1 mg/kg, i.p.) causes moderate activation of DA neurons in the VTA. It enhances release of excitatory amino acids that act on AMPA/kainate receptors in paranigral subdivision of the VTA, which in turn increases neuronal activity of the mesoaccumbens pathway, and consequently increases dopaminergic activity in the cACC. On the other hand, MK-801 has been reported to reduce the activity of neurons in the parabrachial subdivision of the VTA (by blocking NMDA receptors), inactivates the mesocortical pathway that projects to prefrontal cortex, and subsequently disinhibits the frontal

cortical projection to the sACC (34, 35).

The neurochemical effects of MK-801 vary according to the brain-region under investigation. It has been reported that MK-801 increases DA release in the locus coeruleus, but decreases uptake of norepinephrine in the locus coeruleus and that of 5-HT in the dorsal raphe nucleus. However, different results had been reported for effect of MK-801 on DA release in the ACC: no effect (36, 37), increase (26, 32, 38, 39) and even decrease (40). Our results indicate that MK-801at 0.1 mg/kg did not increase DA level in the cACC. However, the same dose of MK-801 has been reported to increase DA level in the sACC, but not in the cACC, due to the relative degree of NMDA-receptor antagonism in the sACC (27). Accordingly, it could be suggested that MK-801 at a low dose does not increase DA level in the cACC due to a regional selectivity, failure in inhibiting the intrinsic GABA neurons and disinhibiting DA release (38) or to lack of effect on sigma 1 and 2 receptors subtypes (41) in the cACC.

The dose of MK-801 is another determinant of its effects. The present results showed that MK-801 did not increase the basal extracellular DA, but increased only DOPAC and DOPAC/DA ratio in the cACC of intact rats. This result indicates the possible increase of DA turnover in this area (42). Our results are consistent with those showing an increased DA metabolism, rather than DA concentration, induced by MK-801 in the ACC (43, 44). However, our results are different from those reporting increased DA level by MK-801. One possible explanation for this discrepancy is the dose of MK-801. In our study, we used 0.1 mg/kg, whereas in other studies, higher doses of MK-801 (0.3 mg/kg) were used. At such high doses MK-801 increases extracellular level of DA, 5-HT and norepinephrine (45) and may affect other transmitters and receptors in the brain.

The behavioral effects of MK-801 also depend on brain region, dose and time after injection. A subthreshold i.p. dose of MK-801 produces locomotor stimulation after alpha-methyl-noradrenaline injection into the ACC but not into the dorsal striatum, prefrontal cortex or thalamus (38). MK-801-hyperlocomotion is accompanied by increased DA release in the cACC, but not in the ventral pallidum (46). The present results showed that MK-801 produced a hyperlocomotor activity with the maximum effect obtained at 0.1 mg/kg. Our results are consistent with the behavioral studies showing either hyperlocomotion at the beginning (shortly after injection of MK-801) or stereotypy at higher doses of MK-801 (23). Moreover, these results are also in line with previous investigations showing that MK-801 at 0.01 – 0.1 mg/kg, i.p. produces hyperactivity that is not associated with stereotypy during the first two-hour after injection (24, 47) and prevents habituation to the test monitor during activity measurement (48).

The activity of MK-801 depends on the availability of free DA D_1 receptors (33, 49, 50), functional state and integrity of dopaminergic system (6), and the association between DA and excitatory amino acids that occurs postsynaptically in the ACC (5). An intact dopaminergic activity facilitates the stimulatory effects of MK-801 (51, 52). Disruption of the dopaminergic transmission in the ACC possibly removes an important part of the functional circuitry consisting of VTA-ACC-pallidal pathways and decreases both the spontaneous locomotor activity and MK-801-induced hyperlocomotion. The present results showed that 6-OHDA reduced DA and DOPAC levels and DOPAC/DA ratio in the cACC. 6-OHDA also decreased the effect of MK-801 on DOPAC and DOPAC/DA ratio in the cACC. However, MK-801 increased DA, DOPAC and DOPAC/DA in the 6-OHDA-lesioned rats, but the effect was less than that induced by MK-801 in the intact cACC. This result could be due to the increased metabolic rate of the remaining dopaminergic cells in the cACC. However, these cells are scarce and upregulated with lesser potential for increased dopamine release and synthesis (ceiling effect) than intact neurons (9). Accordingly, MK-801 increased but did not revert 6-OHDA-depleted DA to the normal level.

The behavioral consequences of 6-OHDA lesion of the ACC depend on the extent of DA depletion. A depletion rate of 90% produces hypoactivity, whereas 67% depletion produces hyperactivity (53). The extent and selectivity of 6-OHDA-induced depletion of DA obtained in this study is consistent with that reported in the ACC (54). The present study showed that MK-801-hyperlocomotion was substantially reduced in 6-OHDA+DMI rats, a result in accordance with that reported by other investigators (55). This effect could be due to the selective effect of MK-801 on DOPAC and DOPAC/DA (as reported in this study) and the extensive depletion of DOPAC in addition to DA and DOPAC/DA ratio in the cACC (9). However, the present results are different from those in which it was reported that 6-OHDA-induced lesion of the ACC did not attenuate the effect of higher doses (0.15 or 0.3 mg/kg) of MK-801 on locomotor activity (56). This discrepancy could be attributed to the higher doses of MK-801 or to the extent of lesion, which may have included not only the cACC but also the sACC in the latter study.

The present results revealed that although lesion of the cACC and sACC extensively reduced MK-801-hyperlocomotion, the reduction induced by lesion of the cACC was greater than that induced by the sACC. This difference between the cACC and sACC could be attributed to different activities displayed by MK-801 in either substructure, reflecting and/or emanating from their different functional importance, structural characters and connections with other cortical and subcortical areas. The sACC is a target

for inhibitory prefrontal dopaminergic cortical input (57). It could be suggested that disruption of this inhibitory pathway, or its' inhibition by MK-801, could result in an enhanced biochemical responsiveness of the dopaminergic innervation of the ACC. The latter effect could also be responsible for the slight (nonsignificant) increase of the locomotor activity that was observed 60 min after injection of MK-801 into rats with lesion of the sACC. Moreover, in these rats, MK-801 significantly increased rearing for 30 min. The sACC exhibits greater chemical-neuroanatomical diversity than the cACC. Since the dopaminergic neurons in the sACC are less labile to 6-OHDA, those which could survive 6-OHDA lesion are expected to be of greater activity with increased DA synthesizing and releasing capacity. It could be suggested that these hyperactive dopaminergic neurons may be responsible for MK-801-rearing, because increased dopaminergic activity elicit greater increases in rearing and feeding behavior in the shell than in the core (58). On the other hand, lesion of the sACC induces behavioral changes by modifying the activity displayed in the cACC or in the mesocortical pathway. The sACC is directly connected to the cACC by a robust feed-forward pathway (59). Lesion of the sACC could directly induce a mechanism of behavioral switching in the cACC and transition to states of heightened psychomotor arousal (60) which was observed as increased rearing following MK-801 in the sACC rats. Moreover, lesion of the sACC disrupts the interaction between mesocortical and other dopamine neurons projecting to the sACC and generates an imbalance in the function of the accumbal output pathways. It could be suggested that these changes contribute to MK-801-induced rearing via: i) producing generalized locomotor hyperactivity which was observed as significant rearing for 30 min and then continued as nonsignificant hyperlocomotion observed 60 min after MK-801 in the sACC rats; ii) changing (increase) of basal dopamine turnover in the amygdaloid complex to which the sACC is connected and iii) decreasing basal dopamine turnover in the medial prefrontal cortex. These mechanisms are proposed for isolation-rearing (61) and could also be involved in MK-801-rearing as the above mentioned effects are also produced by both MK-801 and the sACC lesion.

In conclusion, the present results revealed that MK-801 at 0.1 mg/kg, i.p. produced maximum hyperlocomotion and increased the concentration of DOPAC (but not that of DA) and DOPAC/DA ratio in the intact cACC. 6-OHDA-induced lesion of the cACC induced greater reduction in MK-801-hyperlocomotion than lesion of the sACC, and decreased the effect of MK-801 on DOPAC concentration and DOPAC/DA ratio in the cACC.

Acknowledgments

The authors thank Fukuoka University, Eicom and Pamukkale University, Turkey for supporting this study.

REFERENCES

1 Fuller TA, Russchen FT and Price JL: Sources of presumptive glutamatergic/ aspartergic afferents to the rat ventral striatopallidal region. J Comp Neurol **258**, 317 – 338 (1987)
2 Koob GF: Drugs of abuse: anatomy, pharmacology, and function of reward pathways. Trends Pharmacol Sci **13**, 177 – 184 (1992)
3 Al-Khatib I, Karadag HC and Ulugöl A: The behavioral effects of MK-801 injected into nucleus accumbens and caudate-putamen of rats. Pharmacol Biochem Behav **52**, 723 – 730 (1995)
4 Dai H, Gebhardt K and Carey RJ: Time course effects of MK-801: the relationship between brain neurochemistry and behavior. Brain Res Bull **36**, 175 – 180 (1995)
5 Ouagazzal A, Nieoullon A and Amalric M: Effects of D1 and D2 receptor blockade on MK-801- induced hyperlocomotion in rats. Psychopharmacology (Berl) **111**, 427 – 434 (1993)
6 Svensson A, Carlsson ML and Carlsson A: Glutamatergic neurons projecting to the nucleus accumbens can affect motor function in opposite directions depending on the dopaminergic tone. Prog Neuropsychopharmacol Biol Psychiatry **18**, 1203 – 1218 (1994)
7 Pulvirenti L, Berrier R, Kreifeidt M and Koob GF: Modulation of locomotor activity by NMDA receptors in the nucleus accumbens core and shell regions of the rat. Brain Res **664**, 231 – 236 (1994)
8 Amalric M, Ouagazzal A, Baunez C and Nieoullon A: Functional interaction between glutamate and dopamine in the rat striatum. Neurochem Int **25**, 123 – 131 (1994)
9 Richard MG and Bennett JP Jr: NMDA receptor blockade increases in vivo striatal dopamine synthesis and release in rats and mice with incomplete dopamine-depleting nigrostriatal lesion. J Neurochem **64**, 2080 – 2086 (1995)
10 Youngren KD, Daly DA and Moghaddam B: Distinct actions of endogenous excitatory amino acids on the outflow of dopamine in the nucleus accumbens. J Pharmacol Exp Ther **264**, 289 – 293 (1993)
11 Zahm DS and Heimer L: Two transpallidal pathways originating in the rat nucleus accumbens. J Comp Neurol **302**, 437 – 446 (1990)
12 Kodsi MH and Swerdlow NR: Reduced prepulse inhibition after electrolytic lesions of nucleus accumbens subregions in the rat. Brain Res **773**, 45 – 52 (1997)
13 Zahm DS: Compartments in the rat dorsal and ventral striatum revealed following injection of 6-hydroxydopamine into the ventral mesencephalon. Brain Res **552**, 164 – 169 (1991)
14 Pickel VM, Beck-Sickinger AG, Chan J and Weiland HA: Y1 receptors in the nucleus accumbens: ultrastructural localization and association with neuropeptide Y. J Neurosci Res **52**, 54 – 68 (1998)
15 Lu XY, Ghasemzadeh MB and Kalivas PW: Expression of D1 receptor, D2 receptor, substance P and enkephalin messenger RNAs in the neurons projecting from the nucleus accumbens. Neuroscience **82**, 767 – 780 (1998)
16 Kalivas PW, Duffy P and Barrow J: Regulation of the mesocorticolimbic dopamine system by glutamic acid receptor

subtypes. J Pharmacol Exp Ther **251**, 378 – 387 (1989)
17 Cardinal RN, Pennicott DR, Sugathapala CL, Robbins TW and Everitt BJ: Impulsive choice induced in rats by lesions of the nucleus accumbens core. Science **292**, 2499 – 2501 (2001)
18 Parkinson JA, Willoughby PJ, Robbins TW and Everitt BJ: Disconnection of anterior cingulate cortex and nucleus accumbens core impairs pavlovian approach behavior: further evidence for limbic cortical-ventral striatopallidal systems. Behav Neurosci **114**, 42 – 63 (2000)
19 Deutch AY and Cameron DS: Pharmacological characterization of dopamine systems in the nucleus accumbens core and shell. Neuroscience **46**, 49 – 56 (1992)
20 Heimer L, Zahm DS, Churchill L, Kalivas PW and Wohltmann C: Specificity in the projection patterns of accumbal core and shell in the rat. Neuroscience **41**, 89 – 125 (1991)
21 Pennartz CM, Delleman-Ven Der Weel MJ, Kitai ST and Lopes Da Silva FH: Presynaptic dopamine D1 receptors attenuate excitatory and inhibitory limbic inputs to the shell region of the rat nucleus accumbens studied in vitro. J Neurophysiol **67**, 1325 – 1335 (1992)
22 Marcus MM, Nomikos GG and Svensson TH: Differential actions of typical and atypical antipsychotic drugs on dopamine release in the core and shell of the nucleus accumbens. Eur Neuropsychopharmacol **6**, 29 – 38 (1996)
23 Danysz W, Essmann U, Breink I and Wilke R: Glutamate antagonists have different effects on spontaneous locomotor activity in rats. Pharmacol Biochem Behav **48**, 111 – 118 (1994)
24 Willins DL, Narayanan S, Wallace LJ and Uretsky NJ: The role of dopamine and AMPA/kainate receptors in the nucleus accumbens in the hypermotility response to MK-801. Pharmacol Biochem Behav **46**, 881 – 887 (1993)
25 Okuyama S, Imagawa Y and Tomisawa K: Behavioral evidence for modulation by sigma ligands of (+)MK-801-induced hyperlocomotion in monoamine-depleted mice. Neuropharmacology **35**, 467 – 474 (1996)
26 Mathe JM, Nomikos GG, Blakeman KH and Svensson TH: Differential action of dizocilpine (MK-801) on the mesolimbic and mesocortical dopamine systems: role of neuronal activity. Neuropharmacology **38**, 121 – 128 (1999)
27 Marcus MM, Mathe JM, Nomikos GG and Svensson TH: Effects of competitive and non-competitive NMDA receptor antagonists on dopamine output in the shell and core subdivisions of the nucleus accumbens. Neuropharmacology **40**, 482 – 490 (2001)
28 Paxinos G and Watson C: The Rat Brain in Stereotaxic Coordinates, Second edition, Academic Press, San Diego (1986)
29 Wu YL, Yoshida M, Emoto H and Tanaka M: Psychological stress selectively increases extracellular dopamine in the 'shell', but not in the 'core' of the rat nucleus accumbens: a novel dual-needle probe simultaneous microdialysis study. Neurosci Lett **275**, 69 – 72 (1999)
30 Ishida Y, Hashiguchi H, Todaka K, Kuwahara I, Ishizuka Y, Nakane H, Uchimura D, Nishimori T and Mitsuyama Y: Serotonergic activity in the rat striatum after intrastriatal transplantation of fetal nigra as measured by microdialysis. Brain Res **788**, 207 – 214 (1998)
31 Giorgetti M, Javaid JI, Davis JM, Costa E, Guidotti A, Appel SB and Brodie MS: Imidazenil, a positive allosteric $GABA_A$ receptor modulator, inhibits the effects of cocaine on locomotor activity and extracellular dopamine in the nucleus accumbens shell without tolerance liability. J Pharmacol Exp Ther **287**, 58 – 66 (1998)
32 Yoshida M, Yokoo H, Mizoguchi K, Tanaka T, Emoto H and Tanaka M: NMDA- and MK801-induced changes in dopamine release are attenuated in kainic acid-lesioned nucleus accumbens of conscious rats: an in vivo microdialysis study. Brain Res **786**, 226 – 229 (1998)
33 Narayanan S, Willins D, Dalia A, Wallace L and Uretsky N: Role of dopaminergic mechanisms in the stimulatory effects of MK-801 injected into the ventral tegmental area and the nucleus accumbens. Pharmacol Biochem Behav **54**, 565 – 573 (1996)
34 Svensson TH: Dysfunctional brain dopamine systems induced by psychotomimetic NMDA-receptor antagonists and the effects of antipsychotic drugs. Brain Res Rev **31**, 320 – 329 (2000)
35 Svensson TH, Mathé JM, Nomikos GG, Schilström B, Marcus M and Fagerquist M: Interactions between catecholamines and serotonin: Relevance to the pharmacology of schizophrenia. Adv Pharmacol **42**, 814 – 818 (1998)
36 Callado LF, Hopwood SE, Hancock PJ and Stamford JA: Effects of dizocilpine (MK-801) on noradrenaline, serotonin and dopamine release and uptake. Neuroreport **11**, 173 – 176 (2000)
37 Weihmuller FB, O'dell SJ, Cole BN and Marshall JF: MK-801 attenuates the dopamine-releasing but not the behavioral effects of methamphetamine: an in vivo microdialysis study. Brain Res **549**, 230 – 235 (1990)
38 Svensson A, Carlsson ML and Carlsson A: Crucial role of the accumbens nucleus in the neurotransmitter interactions regulating motor control in mice. J Neural Transm (Gen Sect) **101**, 127 – 148 (1995)
39 Tran-Nguyen LT, Castaneda E and MacBeth T: Changes in behavior and monoamine levels in microdialysate from dorsal striatum after 6-OHDA infusions into ventral striatum. Pharmacol Biochem Behav **55**, 141 – 150 (1996)
40 Kashihara K, Hamamura T, Okuma K and Otsuki S: Effect of MK-801 on endogenous dopamine release in vivo. Brain Res **528**, 80 – 82 (1990)
41 Ault DT and Werling LL: Phencyclidine and dizocilpine modulate dopamine release from rat nucleus accumbens via sigma receptors. Eur J Pharmacol **386**, 145 – 153 (1999)
42 Hatip-Al-Khatib I, Mishima K, Iwasaki K and Fujiwara M: Microdialysates of amines and metabolites from core nucleus accumbens of freely moving rats altered by dizocilpine. Brain Res **902**, 108 – 118 (2001)
43 Busber M, Tzschentke T and Hauber W: Behavioural and neurochemical interactions of the AMPA antagonist GYKI 52466 and the non-competitive NMDA antagonist dizocilpine in rats. J Neural Transm (Gen Sect) **101**, 115 – 126 (1995)
44 Loscher W, Annies R and Honack D: Comparison of competitive and uncompetitive NMDA receptor antagonists with regard to monoaminergic neuronal activity and behavioural effects in rats. Eur J Pharmacol **242**, 263 – 274 (1993)
45 Yan QS, Reith ME, Jobe PC and Dailey JW: Dizocilpine (MK-801) increases not only dopamine but also serotonin and norepinephrine transmission in the nucleus accumbens as measured by microdialysis in freely moving rats. Brain Res **765**, 149 – 158 (1997)
46 Kretschmer BD: NMDA receptor antagonist-induced dopamine release in the ventral pallidum does not correlate with motor

activation. Brain Res **859**, 147 – 156 (2000)
47 Starr MS and Starr BS: Comparison of the effect of NMDA and AMPA antagonists on the locomotor activity induced by selective D1 and D2 dopamine agonists in reserpine-treated mice. Psychopharmacology (Berl) **114**, 469 – 476 (1994)
48 Frantz K and Van Hartesveldt C: The locomotor effects of MK801 in the nucleus accumbens of developing and adult rats. Eur J Pharmacol **368**, 125 – 135 (1999)
49 Czyrak A, Mackowiak M, Fijal K, Chocyk A and Wedzony K: Impact of metyrapone on MK-801-induced alterations in the rat dopamine D1 receptors. Pol J Pharmacol **49**, 305 – 316 (1997)
50 Martin P, Svensson A, Carlsson A and Carlsson ML: On the roles of dopamine D-1 vs. D-2 receptors for the hyperactivity response elicited by MK-801. J Neural Transm (Gen Sec) **95**, 113 – 121 (1994)
51 Churchill L, Austin MC and Kalivas PW: Dopamine and endogenous opioid regulation of picrotoxin-induced locomotion in the ventral pallidum after dopamine depletion in the nucleus accumbens. Psychopharmacology (Berl) **108**, 141 – 146 (1992)
52 Liljequist S, Ossowska K, Grabowska-Anden M and Anden NE: Effect of the NMDA receptor antagonist, MK-801, on locomotor activity and on the metabolism of dopamine in various brain areas of mice. Eur J Pharmacol **195**, 55 – 61 (1991)
53 Jones GH and Robbins TW: Differential effects of mesocortical, mesolimbic, and mesostriatal dopamine depletion on spontaneous conditioned and drug-induced locomotor activity. Pharmacol Biochem Behav **43**, 887 – 895 (1992)
54 Emerich DF and Walsh TJ: Hyperactivity following intradentate injection of colchicine: a role for dopamine systems in the nucleus accumbens. Pharmacol Biochem Behav **37**, 149 – 154 (1990)
55 Andrés ME, Gysling K and Bustos G: Differential regulation of dopamine release by *N*-methyl-D-aspartate receptors in rat striatum after partial and extreme lesion of the nigrostriatal pathway. Brain Res **797**, 255 – 266 (1998)
56 Ouagazzal A, Nieoullon A and Amalric M: Locomotor activation induced by MK-801 in the rat: postsynaptic interaction with dopamine receptors in the ventral striatum. Eur J Pharmacol **251**, 229 – 236 (1994)
57 Deutch AY: Prefrontal cortical dopamine systems and the elaboration of functional cortico-striatal circuits: implications for schizophrenia and Parkinson's disease. J Neural Transm (Gen Sec) **91**, 197 – 221 (1993)
58 Swanson CJ, Heath S, Stratford TR and Kelley AE: Differential behavioral responses to dopaminergic stimulation of nucleus accumbens subregions in the rat. Pharmacol Biochem Behav **58**, 933 – 945 (1997)
59 Zahm DS: Functional-anatomical implications of the nucleus accumbens core and shell subterritories. Ann NY Acad Sci **877**, 113 – 128 (1999)
60 Canales JJ and Iversen SD: Dynamic dopamine receptor interactions in the core and shell of nucleus accumbens differentially coordinate the expression of unconditioned motor behaviors. Synapse **36**, 297 – 306 (2000)
61 Heidbreder CA, Weiss IC, Domeney AM, Pryce C, Homberg J, Hedou G, Feldon J, Moran MC and Nelson P: Behavioral, neurochemical and endocrinological characterization of the early social isolation syndrome. Neuroscience **100**, 749 – 768 (2000)