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The Behavioral Effects of MK-801 Injected Into Nucleus Accumbens and Caudate-Putamen of Rats

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AL-KHATIB, I., H. C. KARADAG AND A. ULUGÖL. *The behavioral effects of MK-801 injected into nucleus accumbens and caudate-putamen of rats.* PHARMACOL BIOCHEM BEHAV **52**(4) 723-730, 1995.—In this study, we investigated the behavioral effects of MK-801 (1-20 μg) injected into the posterior parts of nucleus accumbens (ACC) and caudate-putamen (CP) in rats. Interactions of diazepam (DZP,10 μg), haloperidol (HPD, 2 μg), and scopolamine (SCOP, 10 μg) with 20 μg of MK-801 were also studied. All injections were done in 2 μl. In ACC, MK-801 increased locomotion, rearing, and head shakes. The effect of MK-801 especially at 20 μg was accompanied by a motor syndrome: head weaves, circling, body rolls, and ataxia. DZP nonsignificantly reduced the locomotion but it significantly ($p < 0.05$) reduced head shakes, weaves, circling, and body rolls produced by MK-801. HPD reduced grooming and head shakes. SCOP potentiated MK-801 hyperlocomotion, whereas it decreased body rolls, head shakes, and weaves. In CP, MK-801 increased locomotion, but less than in ACC ($p < 0.05$). The effect of MK-801 was significantly increased by SCOP. MK-801 also increased grooming (reduced by HPD and increased by SCOP) and at 5-20 μg induced oral movements that were decreased by HPD. These results indicate that the posterior part of ACC is involved in MK-801 hyperlocomotion and motor syndromes, whereas CP is involved in mediating grooming and oral movements. Blockade of the muscarinic cholinergic receptors seems to facilitate hyperlocomotion and decrease head shakes produced by MK-801. Mechanisms influenced by DZP and HPD appear to be involved in motor syndrome and oral movement, respectively, induced by MK-801, but not in hyperlocomotion.

MK-801 Nucleus accumbens Caudate-putamen Locomotion Motor syndrome

MK-801, DIZOCILPINE, [(5R, 10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo(a,d)-cyclohepten-5,10-imine hydrogen maleate] is a potent and selective noncompetitive antagonist of *N*-methyl-D-aspartate (NMDA) receptors. It acts directly at PCP recognition sites within the ion channels linked to NMDA-sensitive glutamate receptors (42). MK-801 exerts various pharmacologic effects such as anxiolytic (7), anticonvulsant (37), and neuroprotective effects against neural damage produced by several methods including NMDA (26). Because of its activities, MK-801 is a promising therapeutic agent. Moreover, the stereotypies produced by MK-801 may provide a more appropriate animal model than those produced by dopamine agonists to test the potential efficacy of the antipsychotic compounds, especially atypical ones (2,15).

In the rodents, MK-801 produces a variety of behavioral effects ranging from hyperactivity to stereotypies and motor syndromes such as lateral head weaving, circling, body rolls, and ataxia (18,19,21,37). These effects, although apparently similar to those obtained by increasing dopaminergic or serotonergic activity, are reportedly different from those induced by psychostimulants such as amphetamine. The exact mechanism(s) underlying the complex effects of MK-801 have not yet been identified. Different mechanisms are suggested to be involved in the effects of MK-801: glutamatergic (5), serotonergic (21), and α-adrenergic (5,22). Moreover, intact dopaminergic activity has been reported greatly to facilitate the stimulatory effects of MK-801 (19). MK-801 increases the dopaminergic tone in striatum and limbic forebrain (35). However, MK-801 is thought indirectly to modulate the dopaminergic system and subsequently to blockade of NMDA receptors (4,5,7,13,16,29,35,38). In the nucleus accumbens (ACC), on the other hand, it is suggested that the opiate (17)

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and glauatamatergic systems (28), respectively, exert inhibitory and facilitatory effects on MK-801.

Since its introduction, several experiments have been carried out using systemic injections of MK-801. However, few reports on the effect of direct microinjection of MK-801 into various brain regions are available in the literature. The site(s) where MK-801 exerts its activities has not been clarified yet. Accordingly, the present study aimed to determine the possible role of the posterior parts of two well-known dopaminergic regions in the brain—i.e., ACC and caudate-putamen (CP)—in the behavioral effects of MK-801.

METHOD

Animals

In this study we used Male Wistar rats (DETAM, Istanbul, Turkey) and reared in our laboratories) weighing 280–300 g. The animals were housed five per group in a Plexiglas cage (42 × 26 × 15 cm) under controlled temperature (22 ± 2°C), humidity (55 ± 5%), and 12 L : 12 D cycle (lights on from 0700–1900 h). The animals had free access to food and water except during the experiments.

Surgery

The rats were anesthetised by sodium pentobarbital (40 mg/kg, IP) and fixed in a Stellar rat stereotax instrument (Stoelting, IL). The guide cannulae (26 ga; Plastics One, VA) were implanted bilaterally according to Paxinos and Watson (27). The coordinates (mm) for implanting the guide cannulae were as follows: for ACC: frontal from bregma, F = +1.0; lateral from midsagittal line, L = 3; dorsoventral from the skull surface, DV = 6.2. The approach was by a 15° angle from the surface of the skull. For CP the coordinates (nonangular) were: F = −0.8, L = 3, DV = 5. The cannulae were then cemented by dental acrylate to stainless-steel mounting screws (0.13 × 3.2 mm length; Plastics One) fixed through holes in the skull. The cannulae were then sealed by dummy cannulae (Plastics One) except during the injections. The rats received penicillin (100,000 U/day, IM, for 3 days) after surgery. One week was allowed for the rats to recover after surgery and before any experiment.

Quantification of the Behavioral Effects of MK-801

The coordinated locomotor activity of the rats was measured by means of an activity cage (Ugo Basile, Varse, Italy). The apparatus was composed of a Perspex cage (inside dimensions 35 × 23 × 20 cm) with a translucent Plexiglas cover. The floor of the cage was made of 30 stainless-steel bars (3 mm in diameter) evenly spaced 11 mm apart and mounted in two external Perspex beams. The instrument was illuminated by an incandescent lamp mounted 55 cm above the activity cage. The rats could also be watched through a one-way mirror during the recordings. The locomotion was counted by an external timer-controlled printer connected to the equipment, which was sensitive only to the pure and coordinated locomotion but not to other activities (e.g., rolling, dragging, and swaying). Rearing and motor syndrome were each quantified by a separate experimenter unaware of the treatment during eight 10-min observation periods repeated at 5-min intervals for 120 min. This period was chosen because the maximum effect of systemic injection of MK-801 was obtained during 120 min (20). The duration of grooming and the number of head shakes and oral movements and each component of the motor syndrome (weaving: lateral head movements; circling: completing 360° by the whole body and/or rotation around the hind limbs; and rolling: side to side movements of the hind limbs) during 30 min were the nonlocomotor behavioral criteria observed and considered in this study. Moreover, the animals were considered to be ataxic if they showed swaying, abnormal gait, and delayed righting response at the end of each observation period. Ataxia was scored according to Tricklebank et al. (37). The scores were ranked on a scale of 0–3: absent = 0; equivocal = 1; moderate = 2; and intense = 3. The experiments were carried out in a soundproof room from 0900–1700 h. Each rat was adapted to the instrument for 15 min before the start of the recordings and then the behavioral effects were measured directly after completion of each injection. The Plexiglas box and floor were carefully cleaned by alcohol-soaked cotton before and after each measurement.

Drugs

The drugs used in this study were MK-801 (RBI, Natick, MA), diazepam (DZP; Deva, Istanbul, Turkey), haloperidol (HPD; Ali Raif, Istanbul, Turkey), and scopolamine (SCOP; Eczacıbaşı, Lüleburgaz, Turkey). The drugs were dissolved in sterile distilled water containing 0.9% NaCl, except HPD, which was dissolved in distilled water containing 0.8% lactic acid; the pH was adjusted to 7 by NaOH (30 mM). The injections into either ACC or CP were bilaterally made by microsyringes (Scientific Glass pty, Ringwood, Australia) driven at a rate of 1 μl/2 min by a motor (B. Braun, Melsungen, Germany), and connected via polyethylene connectors (Plastics One) to the injection cannulae (33 ga, Plastics One). The injection cannulae protruded one mm beyond the tips of the guide cannulae. The injection cannulae were left in situ for an additional 2 min after completing each injection and before remounting the dummy cannulae. The volume of each injection was kept constant at 2 μl. Five rats were included in each group. Each rat received no more than two injections. Five days were allowed to elapse between the two successive injections. The doses of DZP, HPD, and SCOP were selected according to the available literature on the basis of the specific effects produced by each one at the doses selected in this study. MK-801 was injected immediately after DZP, HPD, and SCOP.

At the end of each experiment, the sites of injections were verified by injecting 2 μl of cresyl violet into each region. Then, under deep ether anesthesia, the rats were decapitated and their brains were removed and frozen at −20°C. Sections of 50 μm were sliced starting 1 mm beyond each coordinate applied in the study to verify the site and extent of diffusion of the injections. The results are represented in Fig. 1 (ACC) and Fig. 2 (CP). The injection sites were found to be perfect in all rats in CP, whereas in only 15% of ACC rats were the injection sites aberrant and excluded from the study.

Statistical Analysis

Data for the behavioral effects (except ataxia) were analysed by the parametric analysis of variance (ANOVA) followed by Duncan's post hoc multiple comparison test. $p < 0.05$ was regarded as significant. The data for the effect in each region at each time interval were evaluated by multiple one-way ANOVA. Moreover, the data in each region were pooled and analyzed for determining the significance of differences resulting from the doses and brain region (i.e., between ACC and CP) by two-way ANOVA. The effect on ataxia was analysed by the nonparametric Kruskal–Wallis method followed by Mann–Whitney *U*-test. These methods

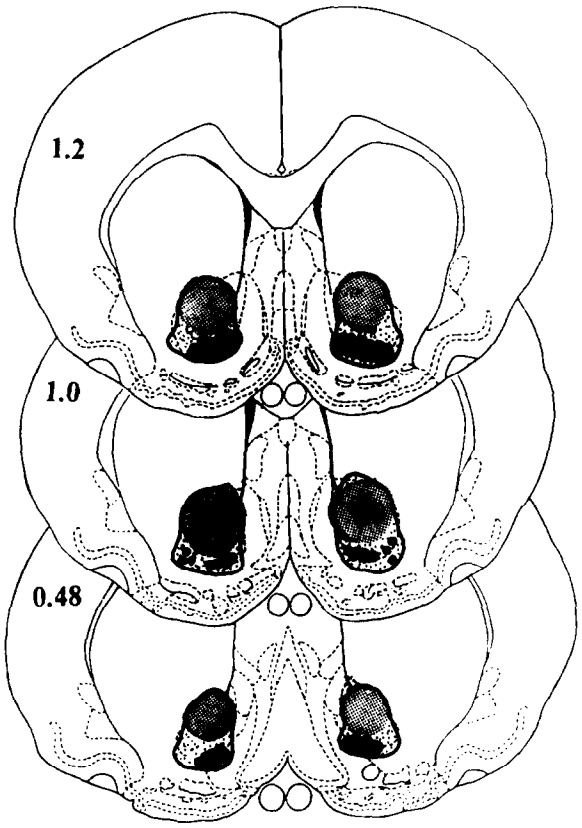

FIG. 1. Histologic composites of the sites for microinjection into the nucleus accumbens transferred visually on the corresponding coronal sections of the Paxinos and Watson atlas (27) at three different coordinates. Circles show correct injection sites in this study; dark and/or overlapped circles show aberrant injection sites not presented in the study. The extent of diffusion of the correct and aberrant injection sites are also delineated and shown as dark and light stippled areas, respectively. The values shown in each section indicate the coordinates (mm) anterior to the bregma.

were applied because the data for ataxia were expressed ordinally as scores that were replaced by ranks, and their variances were heterogenous. Moreover, these statistical methods are the reliable methods for the ordinal level of measurement with a power efficiency of around 95%, when compared with the parametric ANOVA test (33).

RESULTS

Effects on Locomotion and Rearing

Although MK-801 significantly increased locomotion, following injection into both ACC and CP, the increase was greater ($p < 0.05$) after injection into ACC than into CP.

In ACC (Fig. 3A), MK-801 (1-20 μg) increased locomotor activity. The effect was dose-dependently increased at 1 and 5 μg, then decreased at 10 μg and again increased at 20 μg. The dose-related effect of MK-801 at 1-10 μg started after injection and continued during the experiment. However, the effect of MK-801 at 20 μg increased after 15 min and reached a peak after 60 min. Analysis of data at each time interval showed that the significant effect of MK-801 persisted for 90 min at 1 and 5 μg, and for 75 min at 10 μg. However, the effect at 20 μg remained significant for 120 min. Interaction studies with MK-801 (20 μg) showed that HPD (2 μg) and DZP (10 μg) did not modify the effect of MK-801. However, SCOP (10 μg), significantly increased the effect of MK-801 15-30 min after injection.

In CP (Fig. 3B), MK-801 at 5-10 μg significantly increased locomotion. The effect commenced after injection and persisted for 60 min. The effect of MK-801 decreased at 20 μg, when the effect was not different from that at 1 μg. Interaction studies with MK-801 (20 μg) showed that DZP (10 μg) and HPD (2 μg) decreased the effect of MK-801 for 30 and 60 min, respectively. On the other hand, SCOP (10 μg) significantly increased the effect of MK-801 on locomotion at 15-45 min after injection. The peak effect was obtained after 15 min.

MK-801 significantly increased rearing. The effect of injection into ACC was greater than that into CP ($p < 0.05$).

In ACC, MK-801 at 1-20 μg increased rearing (Fig. 4A). The effect was increased by increasing the dose from 1 to 5 μg, then decreased at 10 and 20 μg, at which the effect of the latter dose was not significantly different from that of saline.

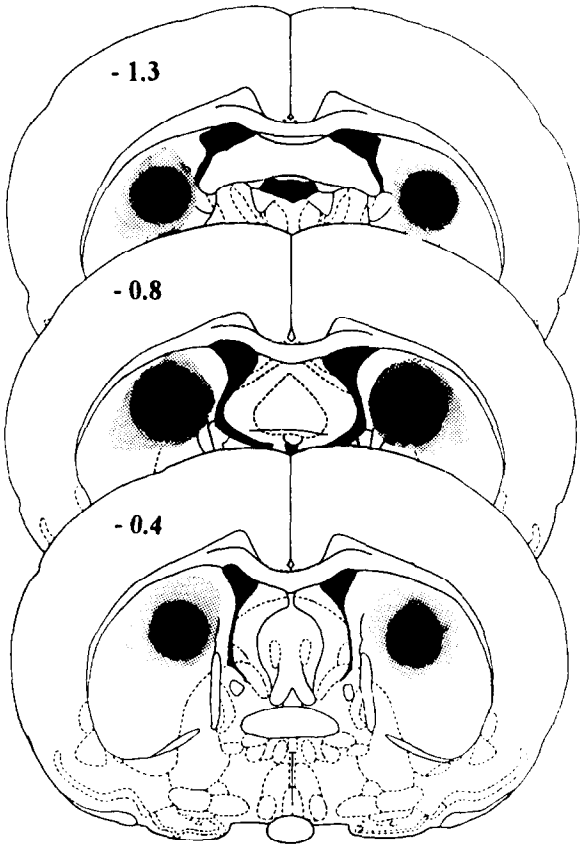

FIG. 2. Histologic composites of the sites for microinjection into caudate-putamen transferred visually on the corresponding coronal sections of the Paxinos and Watson atlas (27) at three different coordinates. Shown are the sites (circles) of the injections that were all correct and considered in the study. The extent of diffusion that are commonly observed around the injection sites are shown as darker stippled areas that fade at the periphery (lighter stippled areas) according to the extent of diffusion. The values indicated in each section are for the coordinates (mm) posterior to bregma.

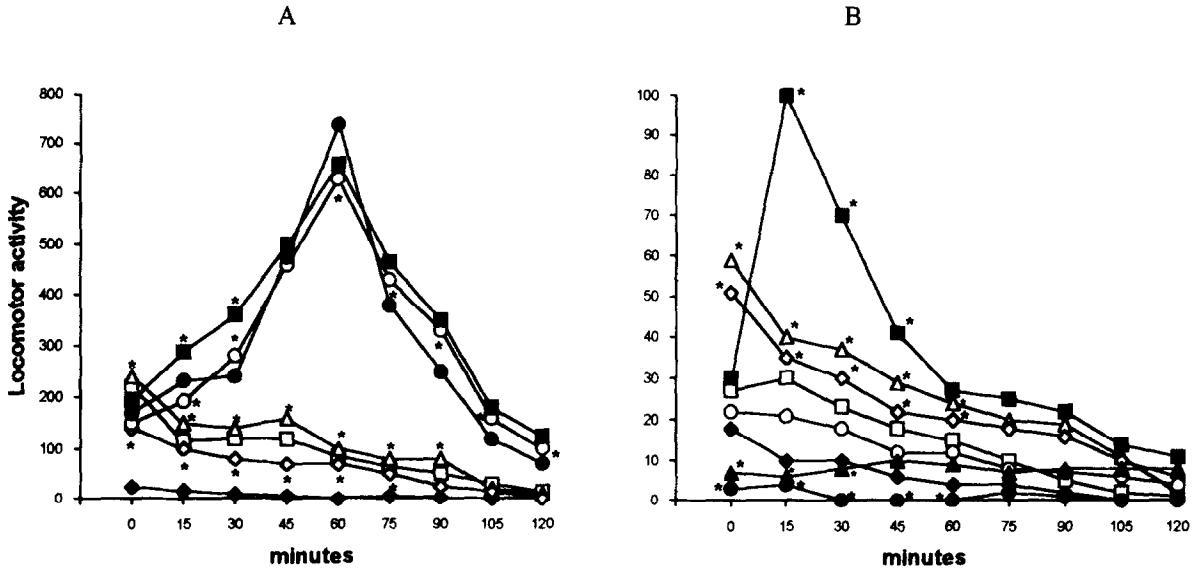

FIG. 3. Effect of MK-801 on the locomotor activity of rats following direct injection into the nucleus accumbens (A) and caudate-putamen (B). The values at each time point are the means of 10 measurements obtained from five rats per group injected twice and represent data recorded for 10 min following each point. Standard errors, varied not more than 20% of each mean, are omitted for clarity. *$p < 0.05$: MK-801 alone compared with saline; MK-801 combined with diazepam (10 μg) or halperidol (2 μg) or scopolamine (10 μg) compared with MK-801 (20 μg) alone. ♦, Saline; □, 1 μg; △, 5 μg; ◇, 10 μg; ○, 20 μg MK-801. Combinations of MK-801 (20 μg) with ▲, diazepam; ●, haloperidol; and ■, scopolamine and also shown. All doses were given in a constant volume of 2 μl. The data for the interaction of DZP with MK-801 in (A) were omitted for clarity. The locomotor activity in the case of injection into the nucleus accumbens (A) was greater than that obtained by injection into the caudate putamen (B). The scale in (A) is 8-10-fold that of (B).

The significant effect of 5 μg continued for 45 min, whereas the effects of 1 and 10 μg remained significant only for the first 10-min observation period. The effect of MK-801 was decreased by DZP and HPD 15 min after injection. On the other hand, SCOP did not modify the effect of MK-801 on rearing.

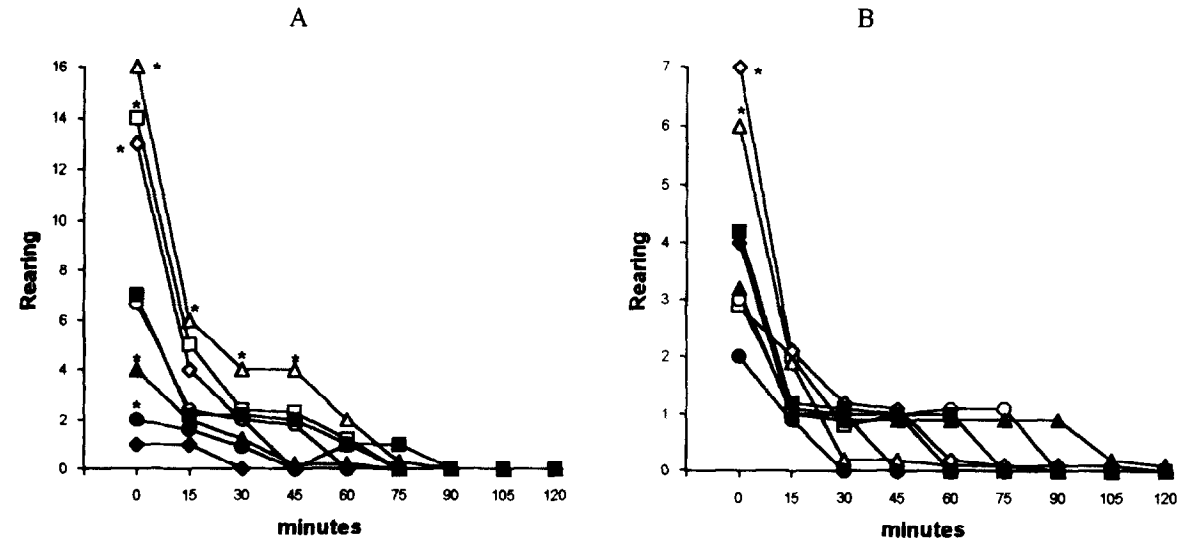

FIG. 4. Effect of MK-801 on the rearing of rats following direct injection into the nucleus accumbens (A) and caudate-putamen (B). The values at each time point are the means of 10 measurements obtained from five rats per group injected twice and represent data recorded for 10 min following that point. Standard errors ranged between 20 and 40% of the means and were omitted for clarity. *$p < 0.05$: MK-801 alone compared with saline; MK-801 combined with diazepam (10 μg), haloperidol (2 μg), or scopolamine (10 μg) compared with MK-801 (20 μg) alone. ♦, Saline; □, 1 μg; △, 5 μg; ◇, 10 μg; ○, 20 μg MK-801. Combinations of MK-801 (20 μg) with ▲, diazepam; ●, haloperidol; and ■, scopolamine and also shown.

In CP, MK-801 significantly increased rearing at 5 and 10 μg but only for the first 10-min observation period after injection. DZP and SCOP did not modify the effect of MK-801 (20 μg). HPD slightly (nonsignificantly) decreased the effect of MK-801 (Fig 4B).

Effects on Grooming

The rats that received saline into either ACC or CP displayed some grooming activities. Injection of MK-801 into ACC did not produce a significant change in grooming (data not shown). On the other hand, MK-801 injected into CP significantly increased grooming for 30 min (Fig. 5). The maximum effect was obtained at 1-5 μg. The effect decreased at 10 μg, then slightly (nonsignificantly) increased at 20 μg. Interaction studies showed that DZP did not modify the effect of MK-801 (20 μg). However, HPD antagonized the effect of MK-801, whereas SCOP significantly potentiated the effect of MK-801 on grooming.

Effects on Head Shakes

We found that injections of saline into ACC or CP produced slight head shakes in the rats for a brief period (15 min after injection). MK-801 at 5-20 μg significantly increased head shakes for 15 min after injection into ACC (Fig. 6). The effect of MK-801 was increased by increasing the doses up to 10 μg, then decreased at 20 μg. The effect of MK-801 (20 μg) was decreased by DZP, HPD, and SCOP.

In CP, head shakes were not significantly changed in the groups that received only MK-801, whereas they decreased significantly in the groups that received a combination of MK-801 (20 μg) with DZP, HPD, or SCOP (data not shown).

MK-801-Induced Motor Syndrome

We found that injections of MK-801 (10-20 μg) into ACC produced a motor syndrome characterized by head weaves,

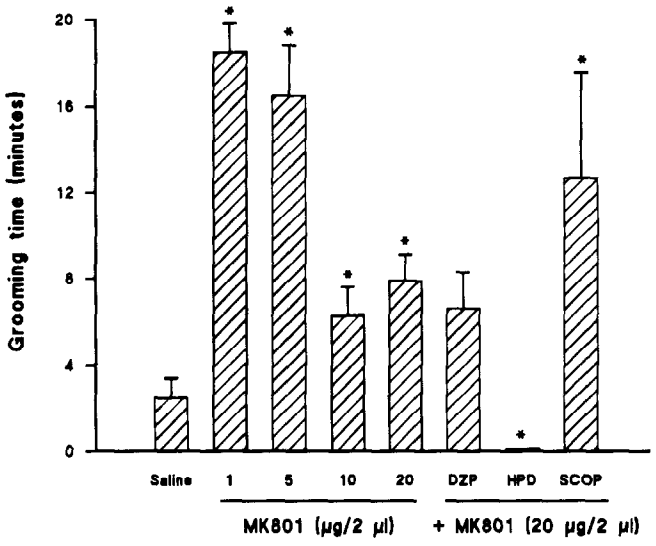

FIG. 5. Effect of MK-801 on the grooming of rats following direct injection into the caudate-putamen. Values are the mean grooming time (min) ± SE during a 30-min observation priod. n = 10 measurements of five rats per group injectecd twice. *$p < 0.05$: MK-801 alone compared with saline; combinations of diazepam (DZP, 10 μg), haloperidol (HPD 2 μg), or scopolamine (SCOP, 10 μg) with MK-801 compared with MK-801 (20 μg) alone.

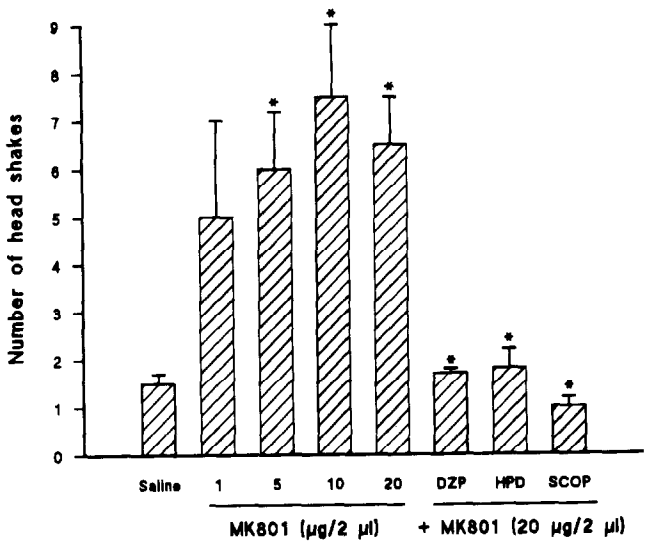

FIG. 6. Effect of MK-801 on head shakes of rats following its direct injection into nucleus accumbens. Values are mean head shakes counted ± SE 15 min after injection. n = 10 measurements of five rats per group injected twice. *$p < 0.05$: MK-801 alone compared with saline; combinations of diazepam (DZP), haloperidol (HPD), and scopolamine (SCOP) with MK-801 compared with MK-801 (20 μg) alone.

circling, and body rolls. The effect was prominent at 20 μg (significant compared with 10 μg), commenced after injection, and became prominent after 15-45 min. DZP reduced MK-801 (20 μg) -induced head weaves, body roles, and circling. HPD displayed no significant interactory effect with MK-801. SCOP reduced head weaves and body rolls (Fig. 7).

MK-801 injected into ACC also induced ataxia at 10 and 20 μg (Fig. 8). The ataxic effect (particularly in the hindlegs) became apparent after 15 min and continued for 30 min. Interestingly, the rats showed increased locomotor activity despite the accompanying ataxia. This ataxic effect of MK-801 was not significantly modified by DZP, HPD, or SCOP.

MK-801-Induced Oral Movements

We found that MK-801 (5-20 μg) injected into CP produced, in a dose-dependent manner, oral movements (dyskinesia) for 30 min after injection. These effects were accompanied by biting and licking in 20% of the group that received 20 μg MK-801. Only HPD significantly reduced MK-801-induced oral movements (Fig. 9).

Other behavioral effects were also produced by injections of MK-801 (20 μg) into ACC (sniffing, backpeddling, and forepaw treading) and CP (sniffing), but their frequency and intensity were to an extent that did not deserve quantification.

DISCUSSION

The present study revealed both qualitative and quantitative differences in the extent of involvement of ACC or CP in mediating the complex behavioral effects of MK-801.

Biphasic and time-dependent effects had been reported for the systemic injection of MK-801. The effect was increased by increasing the dose up to 0.5 mg/kg, then decreased at 3 mg/kg (15,18,19,37). This effect was thought to be due to a reduction in the muscle tone caused by MK-801. Interestingly, the

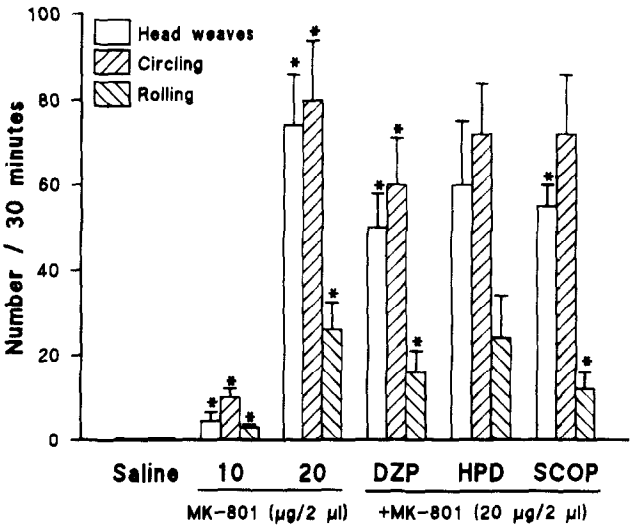

FIG. 7. MK-801-induced head weaves, circling, and body rolls of rats following direct injection into the nucleus accumbens. Values are means ± SE 15-45 min after injections. MK-801 at 1 and 5 μg produced no effect, and their data are not shown. $n = 10$ measurements of five rats per group injected twice. *$p < 0.05$: MK-801 alone compared with saline; combinations of diazepam (DZP), haloperidol (HPD), and scopolamine (SCOP) with MK-801 compared with MK-801 (20 μg) alone.

metabolism of MK-801 (39) and its effect on metabolism in the cerebral cortex also show biphasic behavior (8). In this study, the effect of MK-801 on locomotion, rearing, and grooming (especially within the the first 30 min) was also biphasic: The effects increased at doses of 1-5 μg, then declined at 10 μg. At 20 μg, the effect of MK-801 on locomotion lasted for 120 min despite the concomitant motor syndrome. This result could be attributed to the absence of any muscle relaxation suggested for the systemic injection of MK-801.

The behavioral effects produced by injection of MK-801 into ACC were similar (except for salivation) to those reported for its systemic injection at doses above 0.5 mg/kg (i.e., hyperlocomotion and motor syndrome) (19,21,37). Moreover, the circling produced by MK-801 in this study was characterized by both rotation of the rats about either end of the chamber and circling around the horizontal axis with their hindlegs at the same location. These types of circling were similar to those reported elsewhere (17,18).

ACC has been reported to be a site of activity of NMDA and other excitatory amino acids (3,10,32). MK-801 has also been reported to increase locomotion after being injected into ACC (28). The activity of MK-801 in ACC could involve dopamine and AMPA/kainate receptors (41) and elevate DOPA and HVA levels (20). Moreover, MK-801 increases the metabolic activity in the limbic region (8). In this study, MK-801 injected into ACC produced a significant increase in locomotion aside from the motor syndrome at 10 and 20 μg. ACC receives excitatory amino acid inputs from the frontal cortical regions and possibly other subcortical regions (11). It has been reported that dopamine receptors display inhibitory activity on the descending cortico-accumbal glutaminergic pathways. The receptors involved in this activity were dopamine D_2 receptors, which may not be identical to D_2 receptors in other brain regions (31). MK-801 produces downregulation of the inhibitory cortical dopaminergic receptors. This activity eliminates the inhibitory effect of dopamine D_2 receptors and may in turn lead to disinhibition of the glutaminergic neurones and, finally, enhancement of the dopaminergic neurotransmission in ACC (14,24,34,40). Accordingly, it could be suggested that antagonism of the inhibitory function(s) and release of the stimulatory one(s) by MK-801 could also be involved in hyperlocomotion and possibly other effects produced by MK-801 in ACC.

Although CP contains NMDA receptors (9) and is a part of the corticostriatal pathway in which glutamate serves as a transmitter, it is excluded as a site for the locomotor-stimulating effect of CPP, an NMDA antagonist (16). Our results also showed that injection of MK-801 into the posterodorsal part of CP produced lesser hyperlocomotion than its injection into ACC but increased grooming and caused oral movements. The latter effect is similar to the lingopharyngeal events reported for the systemic injection of MK-801 (23). It seems that the posterodorsal part of CP is involved in MK-801 stereotypies more than in hyperlocomotion. However, MK-801 could also produce some effects in other parts of CP, such as the anterodorsal one, which is involved in the behavioral effects of NMDA and its antagonist DL-2 amino-5-phosphonovaleric acid (AP5) (30). The variation in the role of different parts of CP in the effects of MK-801 and related drugs could be attributed to either the heterogeneity of CP or differences in the activities displayed by each drug in various parts of the heterogenous structure of CP. Moreover, the difference in the effect of MK-801 in ACC and CP could also be due to differences in the feedback mechanisms between the two brain regions, or to the fact that MK-801 itself may exert differential effects on the feedback system in ACC and CP (19).

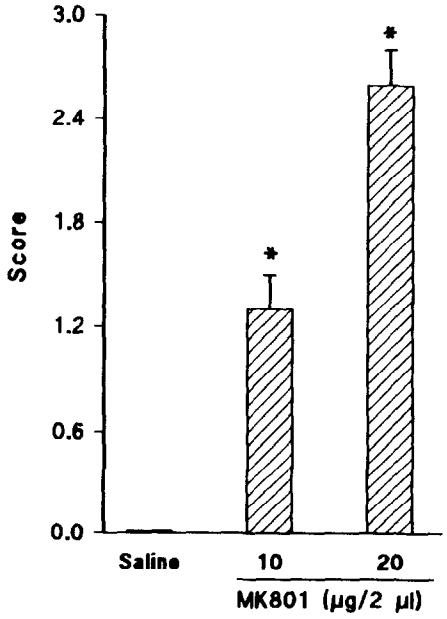

FIG. 8. Ataxia induced by injections of MK-801 into the nucleus accumbens. Values are mean ataxia scores ± SE 15-30 min after injections. MK-801 at 1 and 5 μg produced no significant effect and their data are not shown. $n = 10$ measurements of five rats per group injected twice. *$p < 0.05$ compared with saline.

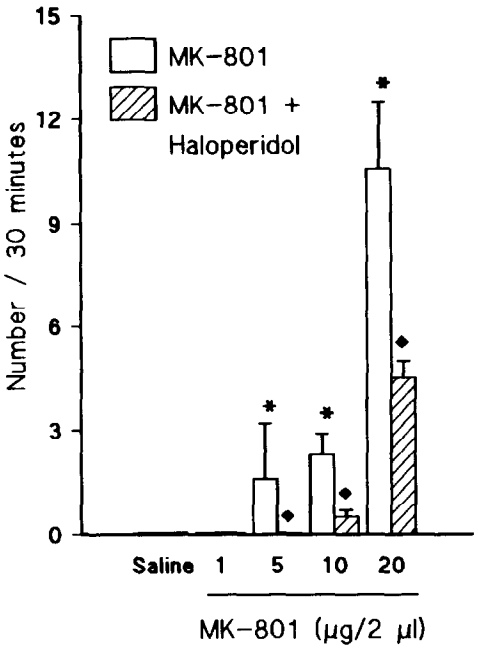

FIG. 9. Oral movements induced by the injection of MK-801 into the caudate-putamen. Values are mean oral movements ± SE observed during 30 min after injection. n = 10 measurements of five rats per group injected twice. *$p < 0.05$: MK-801 compared with saline; ♦$p < 0.05$; MK-801 + haloperidol compared with the corresponding dose of MK-801.

The behavioral effects of MK-801 in this study are reminiscent of the effects produced by dopaminergic and/or serotonergic drugs. Some reports cast doubt on the hypothesis of a functional interaction between the dopaminergic and glutamatergic system in rat CNS (12); others had failed to detect an effect of MK-801 on the level of DA or DOPAC in CP (13). However, MK-801 seems indirectly to modulate the dopaminergic function. Some studies suggest that the intact dopaminergic system is involved in the stimulatory action of MK-801 (19), but most probably indirectly and independently of the presynaptic mechanisms (5,13,16,29). In line with the latter findings, we also found that dopamine (10 and 20 μg/2 μl) did not potentiate MK-801 hyperlocomotion (data not shown).

One of the characteristics of MK-801 hyperlocomotion is its specific inhibition by the atypical antipsychotic clozapine (15). Moreover, it had been found that HPD decreased MK-801-induced stereotypy and hyperactivity after systemic (IP) injection (2,7,36,38). In this study, HPD also decreased locomotion, grooming, and oral movements in CP, but it did not decrease MK-801 hyperlocomotion or motor syndrome in ACC. This result agrees with other results in which direct injection into ACC and systemic injection showed that HPD did not block the locomotor-stimulating effect of MK-801 (18,28). It seems that the locomotor-stimulating effect of MK-801 in ACC is insensitive to HPD. This finding could also explain the reason for the failure of systemic injections of HPD to block the effects of MK-801. Moreover, the present results also show that any blockade by HPD of MK-801 stereotypy, which was observed on their systemic injection, was exerted in posterior CP but not in ACC. It is worth mentioning that our results also showed that HPD, instead of decreasing or antagonizing, nonsignificantly increased the effect of MK-801 on locomotion after injection into ACC (especially during the 1st h). This result could be due to the additive blockade of the inhibitory pathway in ACC.

In rodents, MK-801 produces behavioral effects similar to those caused by benzodiazepine (25). Also, some of the stimulant effects of MK-801 such as wall contacts and turn-rounds are increased by DZP (2). It is suggested that this result could be due to a shift between the positive and negative feedback loops in favor of the former (1). However, our results did not suggest any potentiation of MK-801 by DZP, because DZP did not potentiate the effect of MK-801. Instead, DZP decreased the effect of MK-801 in ACC (head shakes and weaves, circling, body rolls, and rearing) and CP (locomotion).

MK-801 potentiates the locomotor stimulatory effect of a combination of muscarinic receptor antagonists (atropine and biperidine) and α-adrenergic agents such as clonidine and α-methyl-dopa (6). Moreover, a forceful synergism with regard to locomotor activity was observed when a subthreshold dose of MK-801 was combined with atropine (5). Our results showed that SCOP potentiated MK-801 hyperlocomotion and decreased head shakes, weaves, and body rolls in ACC but increased grooming in CP. These results suggest a potential for muscarinic blockade to demonstrate hyperlocomotion (in ACC) and grooming (in CP), and to decrease the motor syndrome caused by MK-801 in ACC.

In conclusion, the results of the present study revealed a greater role of the posterior part of ACC than CP in mediating MK-801 hyperlocomotion (potentiated by SCOP) and MK-801 motor syndrome (decreased by DZP and SCOP). CP is involved in MK-801-induced oral movements and grooming (decreased by HPD).

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