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The Role of Dopamine and AMPA/Kainate Receptors in the Nucleus Accumbens in the Hypermotility Response to MK801

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WILLINS, D. L., S. NARAYANAN, L. J. WALLACE AND N. J. URETSKY. *The role of dopamine and AMPA/kainate receptors in the nucleus accumbens in the hypermotility response to MK801.* PHARMACOL BIOCHEM BEHAV 46(4) 881–887, 1993.—The purpose of this study was to evaluate the role of endogenous dopamine in the hypermotility response to MK801. The administration of MK801 (0.1 mg/kg, SC) to rats produced an intense stimulation of coordinated locomotor activity, which was not associated with stereotyped behavior. This stimulatory response was inhibited by pretreatment with either reserpine (5 mg/kg, IP) or α-methyl-p-tyrosine (2 doses of 250 mg/kg, IP). Similarly, pretreatment with the D_2 antagonist eticlopride (0.03 mg/kg, SC) or the D_1 antagonist SCH23390 (0.1 mg/kg, SC) produced a marked inhibition of MK801-stimulated hypermotility, and the combination of eticlopride (0.03 mg/kg, SC) and SCH23390 (0.03 mg/kg, SC) produced a greater inhibition of MK801-stimulated locomotion than either agent alone. The administration of SCH23390 or eticlopride directly into the nucleus accumbens inhibited the locomotor response to MK801, with the combination of both drugs producing a greater inhibition than either agent alone. The intra-accumbens administration of the α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA)/kainate receptor antagonists DNQX or GAMS also inhibited the locomotor response produced by MK801. These data suggest that the activation of D_1 and D_2 dopaminergic receptors and AMPA/kainate excitatory amino acid receptors in the nucleus accumbens is required for the stimulation of locomotor activity produced by MK801.

Nucleus accumbens MK801 Dopamine Hypermotility AMPA/kainate receptors

MK801 ((+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine maleate) is a noncompetitive antagonist of the NMDA receptor that binds to the cation channel associated with the NMDA-receptor complex (38). Recently there has been a great deal of interest in MK-801 as a potential anticonvulsant and neuroprotective agent (9,18,34). The administration of MK801 to rats produces a characteristic behavioral pattern which includes hyperlocomotion at lower doses and lateral head weaving and ataxia at higher doses (3,9, 10,11,20,36). It has been suggested that some of these behavioral effects may be mediated by an enhancement in central dopaminergic transmission. Thus, dopamine receptor antagonists have been shown to inhibit the hyperlocomotion induced by MK801 (10,12,27). Additionally, the motor activating effects of dopamine receptor agonists, such as L-DOPA and apomorphine, are potentiated by MK801 (7,24). These behavioral observations are consistent with the finding that MK801 produces an increase in dopamine turnover in various brain regions (25,32) and an increase in the firing rate of dopaminergic neurons originating in the ventral tegmental area (16). It therefore appears that the behavioral activation elicited by MK801 may be mediated, in part, by dopaminergic mechanisms in the brain.

The results of other studies do not support this hypothesis and suggest that the behavioral effects produced by MK801 are not mediated by endogenous dopamine. Thus, MK801 was able to stimulate locomotor activity after dopamine depletion by pretreatment with a combination of reserpine and α-methyl-p-tyrosine (6,8). MK801 did not change the levels of striatal dopamine or its metabolite, dihydroxyphenylacetic acid (17), and did not alter dopamine turnover in the nucleus accumbens (32). MK801 did not potentiate the behavioral stimulatory effects of methamphetamine and nomifensine, which enhance dopaminergic neurotransmission (17). The stimulation of locomotion by MK801 was not inhibited by either a D_1 or D_2 antagonist at doses that inhibited the stimulant response to amphetamine (2). Finally, while the direct administration of MK801 into the nucleus accumbens can

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stimulate a locomotor response, it is not antagonized by haloperidol (31). These studies suggest that the behavioral activation produced by MK801 is mediated by a mechanism which, at least in part, is independent of brain dopamine.

In the present study we report additional experiments aimed at resolving the divergent views regarding the role of dopamine in the hypermotility response to MK801. We first reexamined the importance of endogenous dopamine in mediating the hypermotility response elicited by a dose of MK801 that does not produce ataxia by determining its effects in animals pretreated with reserpine, α-methyl-p-tyrosine, and dopamine receptor antagonists. Our results support the hypothesis that the locomotor stimulation produced by MK801 is mediated by endogenous dopamine. We extended these studies by determining the role of D_1 and D_2 dopamine receptors in the nucleus accumbens in this response. In addition, activation of AMPA/kainate receptors as well as dopamine receptors in the nucleus accumbens may be required for the expression of the hypermotility elicited by dopaminergic agonists (37). Therefore, we also determined the involvement of these receptors in the nucleus accumbens in the hypermotility response to MK801.

METHOD

Administration of Drugs Into the Brain

Male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis), weighing 200–300 g, were housed four animals per cage in a temperature-controlled environment (23 ± 1°C) with a 12-h on-off lighting cycle. For direct injection into the brain, the rats were lightly anesthetized with a halothane/oxygen mixture and placed in a stereotaxic frame (David Kopf Instruments, Tajunga, CA). A midline incision was made in the scalp, and holes were drilled bilaterally into the skull at the following coordinates: 10.2 mm anterior to the intraaural line and 1.2 mm lateral to the sagittal suture (29). A 10-μl Hamilton syringe (Hamilton Co., Reno, NV) was then inserted into the holes and lowered to a position 0.2 mm above the intraaural line. Drug solutions or vehicle were infused bilaterally in a volume of 0.5 μl/side at a rate of 0.5 μl/min. The needle was allowed to remain in position for an additional minute to allow for diffusion of the solution away from the needle tip. After removal of the needle, the incision was closed with wound clips and swabbed with 2% (w/v) lidocaine ointment.

Measurement of Locomotor Activity

Following direct injections into the nucleus accumbens, anesthesia was discontinued and the animals were removed from the stereotaxic frame. Following recovery from the anesthetic (5 min), animals were placed into motor activity cages (Opto-Varimex Minor, Columbus Instruments, Columbus, OH), and motor activity was monitored. The motor activity cages consisted of a 12 × 12 grid of infrared beams 3.5 cm apart and 5.0 cm from the bottom of the cage in a ventilated Plexiglas box measuring 42 cm square and 20 cm high. Ambulatory activity was measured as the number of times two consecutive beams were interrupted, and the data were recorded with a digital computer (Columbus Instruments). Experiments in which locomotor activity was monitored were performed between the hours of 0800 and 1600 in an isolated environmental room maintained at a temperature of 23 ± 1°C.

Histology

Following each experiment the animals were removed to a chamber containing halothane and anesthetized. Under anesthesia the animals were decapitated, and the brains were removed to a solution of 10% formalin where they were allowed to fix for 24 h. Frozen sections, 40 microns in thickness, were cut using a Cryo-Cut microtome (American Optical Corp., Buffalo) to verify the position of the injection cannula. Data points from animals in which needle tracks were found terminating outside of the nucleus accumbens were excluded from the study.

Drugs

d-Amphetamine sulfate, reserpine HCl, and α-methyl-p-tyrosine methyl ester were purchased from Sigma Chemical Co. (St. Louis). γ-D-Glutamylaminomethyl-sulphonate (GAMS) and 6,7-dinitroquinoxaline-2,3-dione (DNQX) were obtained from Tocris Neuramin (Essex, England). Eticlopride HCl and SCH23390 HCl were purchased from Research Biochemicals Inc. (Natick, MA). Halothane U.S.P. was obtained from Halocarbon Laboratories (N. Augusta, SC), and 2% lidocaine ointment was obtained from Astra Pharmaceuticals (Westborough, MA).

DNQX was dissolved initially in 0.1 N NaOH and adjusted to the appropriate volume with phosphate buffer 0.5 M (pH 7.4). Reserpine was initially dissolved in a minimum amount of glacial acetic acid and adjusted to the appropriate volume with water. All other drugs were dissolved in saline or water and adjusted to pH 7.4 with 1 N NaOH. Doses shown for all intracranial injections refer to the amount injected on each side into the target brain structure. Control animals received injections of equal volumes (0.5 μl) of saline or vehicle.

Statistics

Data were expressed as the mean and standard error of the mean (SE). In experiments involving one control group and one treatment group, data were evaluated using Student's *t*

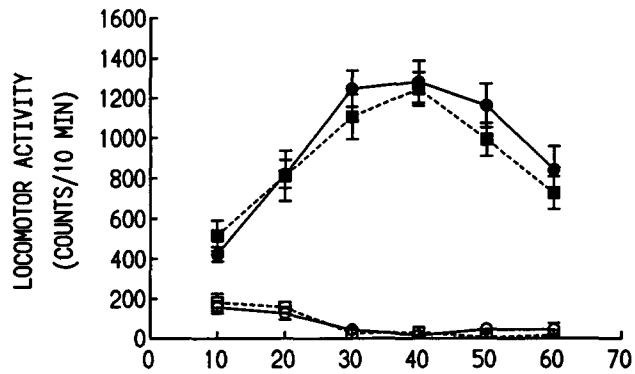

FIG. 1. The change in locomotor activity over time after the administration of MK801 (0.1 mg/kg, SC). The data for unanesthetized animals (---) that were injected with MK801 (■) were taken from the control groups of experiments described in Figs. 2, 3, and 4 (N = 23). The data for the halothane/O_2-anesthetized animals (—) that received MK801 (●) were taken from the control groups of experiments described in Figs. 5B, 6, and 7 (N = 43). Included in this figure are animals that were anesthetized with halothane/O_2 and injected with vehicle in the nucleus accumbens and saline SC (○; N = 8) and animals injected with saline SC (□; N = 4).

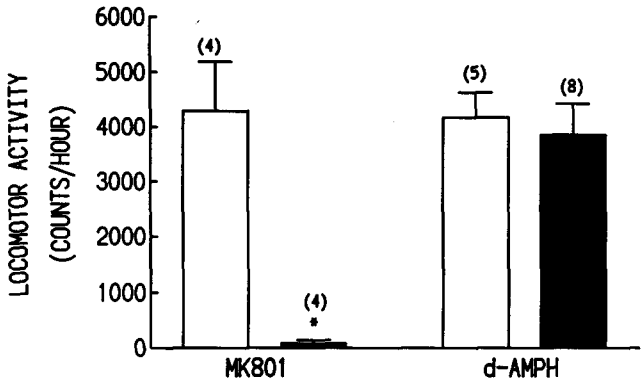

FIG. 2. The effect of reserpine on the locomotor stimulation induced by MK801 or amphetamine (d-AMPH). Rats were pretreated with reserpine (5 mg/kg, SC) or vehicle 18 h prior to the administration of MK801 (0.1 mg/kg, SC) or d-amphetamine (2 mg/kg, SC). Clear bars represent the vehicle-treated group, and solid bars represent the reserpine-treated group. Data are expressed as mean ± SE of counts recorded in a 1-h test period. Numbers in parentheses indicate the number of animals used in each experiment. *$p < 0.01$.

test, with a level of $p < 0.05$ considered significant. In experiments where multiple groups were compared to the same control group, significant differences were evaluated using the Dunnett's Test, with a level of $p < 0.05$ being considered significant.

RESULTS

The Effects of MK801 on Locomotor Activity in Normal and Dopamine-Depleted Rats

The administration of MK801 (0.1 mg/kg, SC) produced a marked stimulation of locomotor activity (Fig. 1). Locomotor activity steadily increased, reaching a peak level at 30 min after MK801 administration. The locomotion produced by this dose of MK801 appeared coordinated and controlled. Animals retained the ability to proceed around obstacles placed in their path and did not run into the cage walls. Halothane-oxygen anesthesia, which was used in some of the subsequent studies, did not appear to influence the intensity or the time course of the locomotor response to MK801 (Fig. 1). Doses of MK801 higher than 0.1 mg/kg produced a lower intensity stimulation of locomotor activity and were associated with stereotyped behavior that interfered with locomotion (data not shown). Higher doses of MK801 have been reported to produce stereotyped behavior and ataxia (2,9,26) and therefore were not used in the present study.

In order to investigate the role of vesicular dopamine in the locomotor stimulation produced by MK801, rats were pretreated with reserpine (5 mg/kg, IP) administered 18 h prior to MK801 to deplete dopamine stores. This pretreatment completely abolished the hypermotility response produced by MK801 (Fig. 2). For comparison, the effect of reserpine pretreatment on amphetamine-induced locomotor activity was evaluated. Reserpine did not inhibit the locomotor stimulatory response to amphetamine (2 mg/kg, SC) (Fig. 2).

In order to further investigate the specific role of catecholamines in MK801-stimulated locomotion, rats were pretreated with α-methyl-p-tyrosine (250 mg/kg, IP) 4 h and 1 h prior to systemic administration of MK801 (0.1 mg/kg, SC). α-Methyl-p-tyrosine pretreatment caused a 60% reduction in MK801-stimulated locomotor activity (Fig. 3).

The Effect of Dopamine Receptor Antagonists on Locomotor Activity Stimulated by MK801

In order to investigate the role of dopamine receptor subtypes in the locomotor stimulation induced by MK801, rats were pretreated with selective dopamine receptor antagonists 20 min prior to MK801 (0.1 mg/kg, SC). In agreement with a recent report, the D_1 dopaminergic antagonist SCH23390, at a dose of 0.03 mg/kg SC, did not inhibit the response to MK801. However, SCH23390 (0.1 mg/kg, SC) produced a

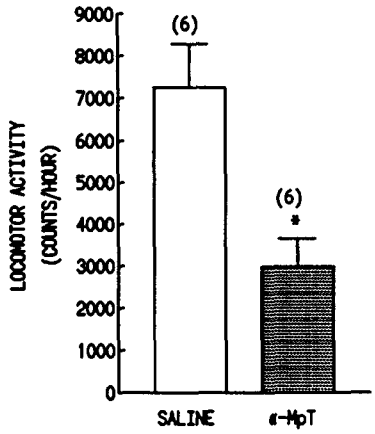

FIG. 3. The effect of α-methyl-p-tyrosine on the locomotor stimulation induced by MK801. Rats were pretreated with α-methyl-p-tyrosine methyl ester (α-MpT) (250 mg/kg, IP) or vehicle 4 h and 1 h prior to the treatment with MK801 (0.1 mg/kg, SC). Clear bars represent the vehicle-treated group, and dotted bars represent the α-MpT-treated group. Data are expressed as mean ± SE of counts recorded in a 1-h test period. Numbers in parentheses indicate the number of animals used in each experiment. *$p < 0.01$.

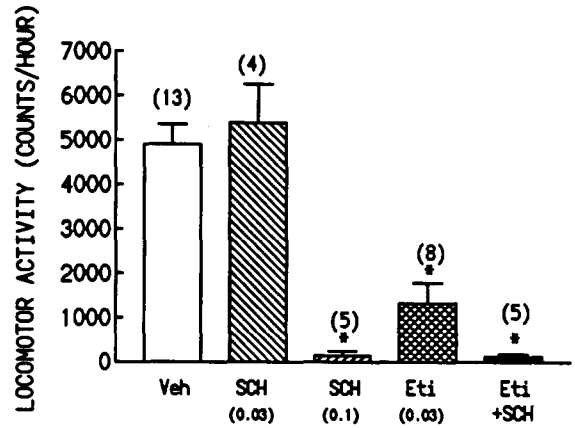

FIG. 4. The effects of systemic administration of dopamine receptor antagonists on MK801-stimulated locomotor activity. MK801 was administered SC at a dose of 0.1 mg/kg. SCH23390 (hatched bars) (0.03 mg/kg or 0.1 mg/kg, SC), eticlopride (cross-hatched bars) (0.03 mg/kg, SC), or a combination of the two drugs (solid bars) both at 0.03 mg/kg SC was administered 20 min prior to MK801. Data are expressed as the mean ± SE of the counts recorded in a 1-h test period, and numbers of animals are presented in parentheses. *$p < 0.01$.

marked inhibition of the response to MK801 (Fig. 4), and this dose of SCH23390 is in the range that has previously been shown to inhibit functional dopaminergic effects (1). Similarly, pretreatment with the D_2 selective antagonist eticlopride (0.03 mg/kg, SC) inhibited MK801-stimulated locomotor activity by approximately 70% (Fig. 4). The combination of the SCH23390 and eticlopride (both at a dose of 0.03 mg/kg, SC) produced a greater inhibition (97% decrease) than that produced by either compound alone (Fig. 4). Rats that received SCH23390, eticlopride, or the drugs in combination maintained the ability to respond to external stimulation, indicating that the dopamine receptor antagonists did not produce catalepsy at the doses studied.

To determine if the activation of dopamine receptors in the nucleus accumbens is required for the behavioral activation by MK801, the dopamine receptor antagonists were administered bilaterally into the nucleus accumbens of rats 2 min prior to the systemic administration of MK801 (0.1 mg/kg, SC). For comparison, a group of rats were injected with amphetamine (0.5 mg/kg, SC) after the intra-accumbens administration of the dopaminergic antagonists. Locomotor activity was recorded for one hour. The direct administration of either SCH23390 or eticlopride into the nucleus accumbens inhibited the locomotor stimulation induced by either d-amphetamine (Fig. 5A) or MK801 (Fig. 5B). The amphetamine-stimulated locomotion appeared to be more sensitive to eticlopride pretreatment, since the intra-accumbens administration of eticlopride (0.03 μg) inhibited the response to d-amphetamine but did not significantly change that to MK801. However, the 1.0-μg dose of eticlopride inhibited the locomotor response to MK801, and the combination of 0.3 μg SCH23390 and 0.03 μg eticlopride produced a much greater inhibition of locomotion than that produced by either antagonist alone (an 89% reduction) (Fig. 5B).

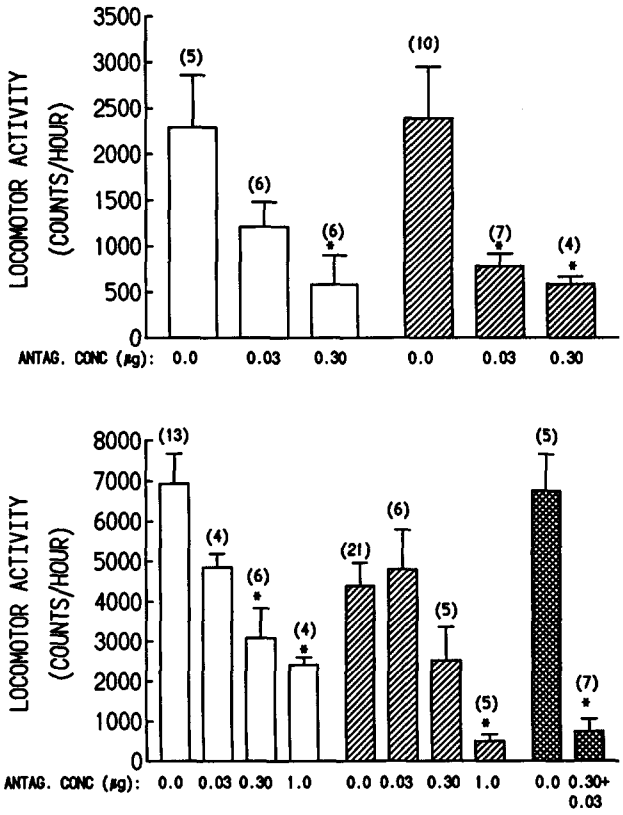

FIG. 5. The effect of intra-accumbens administration of dopamine receptor antagonists on (top) d-amphetamine- (0.5 mg/kg, SC) and (bottom) MK801 (0.1 mg/kg, SC)-stimulated locomotor activity. Clear bars represent the effects of the D_1 antagonist SCH23390, hatched bars represent the effects of the D_2 antagonist eticlopride, and the cross-hatched bars represent the effects of a combination of these antagonists (SCH23390, 0.3 μg, and eticlopride, 0.03 μg). Data are expressed as mean ± SE of counts recorded in a 1-h test period. The numbers in parentheses indicate the number of animals used in each experiment. *$p < 0.01$.

The Effect of the Bilateral Administration of AMPA/Kainate Receptor Antagonists Into the Nucleus Accumbens on the Hypermotility Produced by Systemic MK801

In order to investigate whether AMPA/kainate glutamate receptors in the nucleus accumbens are involved in the locomotor response to systemic MK801, rats were injected bilaterally in the nucleus accumbens with either DNQX (1 μg/0.5 μl) or vehicle or GAMS (5 μg/0.5 μl) or vehicle and then injected 2 min later with MK801 (0.1 mg/kg, SC). These doses of DNQX and GAMS were chosen because they have been shown previously to markedly inhibit the locomotor stimulation produced by the intra-accumbens administration of the excitatory amino acid AMPA (4) or by the systemic administration of d-amphetamine or cocaine (22,37). DNQX and GAMS inhibited MK801-stimulated locomotion by 68% and 56%, respectively (Figs. 6 and 7). At these doses, neither of the AMPA/kainate receptor antagonists reduce the locomotor activity of rats treated with saline (37).

DISCUSSION

The results of the present study suggest that the stimulation of locomotor activity produced by the noncompetitive NMDA receptor antagonist MK801 is dependent upon central dopaminergic neurotransmission. Disruption of the dopaminergic

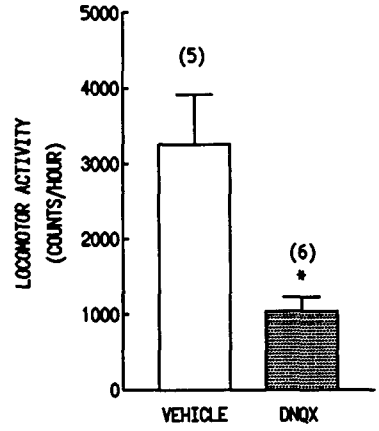

FIG. 6. The effect of intra-accumbens administration of DNQX (1 μg) on MK801 (0.1 mg/kg, SC)-stimulated locomotor activity. Clear bars represent the vehicle-treated group, and dotted bars represent the DNQX-treated group. Data are expressed as mean ± SE of counts recorded in a 1-h test period. The numbers in parentheses indicate the number of animals used in each experiment. *$p < 0.01$.

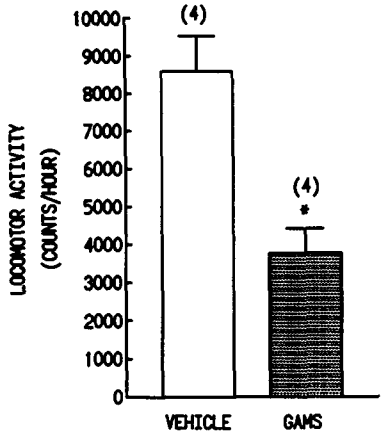

FIG. 7. The effect of intra-accumbens administration of GAMS (5 μg) on MK801 (0.1 mg/kg, SC)-stimulated locomotor activity. Clear bars represent the vehicle-treated group, and dotted bars represent the GAMS-treated group. Data are expressed as mean ± SE of counts recorded in a 1-h test period. The numbers in parentheses indicate the number of animals used in each experiment. *$p < 0.01$.

system by the administration of drugs which interfere with the synthesis and storage of dopamine or block dopamine receptors markedly inhibited the hypermotility elicited by MK801. The dopamine receptors that mediate this response appear to be located in the nucleus accumbens, since the direct administration of dopamine receptor antagonists into this region inhibited the MK801-induced locomotor stimulation. Previous studies have shown that the locomotor stimulant responses to amphetamine and cocaine, which are dependent upon enhanced dopaminergic neurotransmission in the nucleus accumbens, are also inhibited by the intra-accumbens administration of antagonists of the AMPA/kainate receptor in this brain region (15,22,37). These antagonists also inhibited the stimulant response to MK801. These observations suggest that the locomotor stimulation elicited by MK801 is dependent upon the activation of both dopamine receptors and AMPA/kainate receptors in the nucleus accumbens.

The results observed with dopamine-depleting drugs strongly suggest that vesicular dopamine is involved in the hypermotility elicited by MK801. Reserpine, which inhibits the storage and release of monoamines by impairing synaptic vesicle function, did not inhibit the locomotor stimulation produced by amphetamine [Fig. 2; see also (21,35)]. This observation indicates that animals that received reserpine were capable of responding to locomotor stimulation and is consistent with the hypothesis that the effects of amphetamine are produced by the release of dopamine from a cytoplasmic pool, rather than from a vesicular storage pool, in dopamine nerve terminals. Reserpine, however, almost completely inhibited the stimulation of locomotor activity produced by MK801, suggesting the involvement of stored monoamines in this effect. Pretreatment of rats with the selective tyrosine hydroxylase inhibitor α-methyl-p-tyrosine also reduced the stimulation of locomotor activity elicited by MK801 (Fig. 3), supporting a role for catecholamines in the MK801-induced locomotor response. This hypothesis is consistent with the results of other studies showing that the ipsilateral circling (in unilateral 6-hydroxydopamine-lesioned rats) and locomotor activation in naive mice produced by MK801 are inhibited by pretreatment with dopaminergic antagonists (10,12,27). While the locomotor stimulation elicited by MK801 was reduced by α-methyl-p-tyrosine, it was not entirely eliminated. This observation may indicate that sufficient endogenous catecholamine stores remain available after α-methyl-p-tyrosine pretreatment to mediate some degree of locomotor stimulation.

The systemic administration of SCH23390 and eticlopride inhibited the MK801-stimulated locomotor response, and the concurrent administration of both drugs produced a greater inhibition than either drug alone. This suggests that the MK801-induced stimulation is mediated by the activation of both D_1 and D_2 dopamine receptors.

The dopamine receptors that are necessary for the locomotor stimulation produced by MK801 appear to be located in the nucleus accumbens. Thus, the administration of either SCH23390 or eticlopride into the nucleus accumbens produced an inhibition of the locomotor response to MK801 as well as to amphetamine, which stimulates locomotor activity by enhancing dopamine neurotransmission in the nucleus accumbens (23,30). The D_2 antagonist was able to block amphetamine-stimulated locomotion at doses which were ineffective in inhibiting the locomotor response to MK801. One possible explanation for this arises from the finding that reserpine completely inhibited the locomotor response to MK801. This suggests that the locomotor activity produced by MK801 is dependent upon the depolarization-induced release of dopamine. The blockade of presynaptic D_2 receptors may therefore facilitate transmission by reducing the effects of autoinhibition in the accumbens. This would result in an increase in the synaptic concentration of dopamine in response to MK801, which in turn may decrease the effect of a competitive antagonist of postsynaptic D_2 receptors. Alternatively, the greater effectiveness of eticlopride in inhibiting amphetamine-stimulated locomotion could be related to the lower activity of the amphetamine-treated animals compared to those receiving MK801, which would be reflected in a decreased concentration of dopamine in the vicinity of the dopamine receptor. The inhibition of the MK801-stimulated locomotor response produced by the combination of a D_1 and D_2 antagonist was greater than that produced by either antagonist alone (Fig. 5B). These studies suggest that MK801-stimulated locomotor activity may be mediated by the activation of both D_1 and D_2 dopamine receptors in the nucleus accumbens.

In contrast to the present findings, it has been reported that MK801 was able to stimulate locomotor activity in mice pretreated with a combination of reserpine and α-methyl-p-tyrosine (5,6,7,8). There are many differences between the present study and those by Carlsson and Carlsson (6). First, the species used were different in the two studies. Second, the conditions under which locomotor activity was evaluated were different. While in the present study each rat was tested in an individual activity monitoring cage, in the study by Carlsson and Carlsson (6) the activity of three animals was evaluated in a single cage. Thus it is possible that social interaction may have had a significant effect on locomotor activity. Third, the type of locomotor stimulation produced by MK801 in animals pretreated with reserpine and α-methyl-p-tyrosine appears to be qualitatively different from that of the animals used in the present study. Mice that were given MK801 following reserpine and α-methyl-p-tyrosine were reported to exhibit locomotion in a forward direction only, and to stop moving completely if presented with an obstacle, such as the cage wall (5). In the present study, rats receiving MK801 ran around the perimeter of the cages and turned to avoid running into the

walls of the activity cages and obstacles in their path. Finally, the dose of MK801 used in the studies of Carlsson and Carlsson (6,7) was 10 to 40 times higher than the doses used in the present studies. While such high doses of MK801 may stimulate locomotor activity in mice by mechanisms that are independent of dopamine, the administration of MK801 at doses greater than 0.1 mg/kg to rats produced stereotypy and varying degrees of ataxia, which interfered with locomotor stimulation.

It has been reported that the stimulation of locomotor activity produced by the intra-accumbens administration of MK801 was not reversed by the co-administration of haloperidol (31), suggesting that the effects produced by MK801 at this site are independent of dopaminergic neurotransmission. However, blockade of dopamine receptors in the nucleus accumbens inhibited the stimulation of locomotion produced by the systemic administration of MK801 (Fig. 5B). Therefore, the site where MK801 is acting, following systemic administration, may be outside the nucleus accumbens. It has been shown that systemic administration of NMDA antagonists PCP and MK801 markedly increased the firing rate of dopaminergic neurons in the ventral tegmental area (16), the site of the dopaminergic perikarya that project to the nucleus accumbens. This is consistent with the finding that NMDA antagonists administered into the ventral tegmental area produce a hypermotility response (13). These observations suggest that the locomotor stimulation produced by the systemic administration of MK801 may be due to an action of this drug in the ventral tegmental area, leading to an increased firing of dopaminergic neurons and an enhanced dopaminergic neurotransmission in the nucleus accumbens.

In addition to dopaminergic afferents from the ventral tegmental area, the nucleus accumbens receives afferent glutamatergic projections from the hippocampus, the amygdala, and the medial prefrontal cortex. It has been suggested that these projections play a role in the regulation of locomotor activity (28). In support of this concept is the observation that infusion of excitatory amino acid agonists into the nucleus accumbens produced a hypermotility response, which can be inhibited by specific excitatory amino acid antagonists (14,19,33). In addition, antagonists of AMPA/kainate receptors infused into the nucleus accumbens inhibit the stimulation of locomotor activity produced by the indirectly acting dopaminergic agonists amphetamine and cocaine and directly acting dopaminergic agonists (22,37). The finding that the locomotor stimulation produced by MK801 is inhibited by antagonists of AMPA/kainate receptors and dopaminergic receptors supports the hypothesis that the stimulation of locomotion produced by drugs that enhance dopaminergic neurotransmission in the nucleus accumbens requires the activation of both AMPA/kainate receptors and dopaminergic receptors at this site.

ACKNOWLEDGEMENTS

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