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Inhibition by MK-801 of Morphine-Induced Conditioned Place Preference and Postsynaptic Dopamine Receptor Supersensitivity in Mice

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KIM, H.-S., C.-G. JANG AND W.-K. PARK. *Inhibition by MK-801 of morphine-induced conditioned place preference and postsynaptic dopamine receptor supersensitivity in mice.* PHARMACOL BIOCHEM BEHAV **55**(1) 11–17, 1996.—Intraperitoneal injection of morphine (5 mg/kg) in mice every other day for 8 days produced conditioned place preference (CPP). CPP effects were evaluated by assessing the difference in time spent in the drug-paired compartment and the saline-paired compartment of the place conditioning apparatus. The injection of a noncompetitive NMDA antagonist, MK-801 (0.05 and 0.1 mg/kg, IP), prior to and during morphine treatment in mice inhibited morphine-induced CPP. The development of postsynaptic dopamine (DA) receptor supersensitivity in mice displaying a morphine-induced CPP was evidenced by the enhanced response in ambulatory activity to the DA agonist, apomorphine (2 mg/kg). MK-801 inhibited that development of postsynaptic DA receptor supersensitivity. MK-801 also inhibited apomorphine-induced climbing behavior, suggesting that MK-801 inhibits dopaminergic activation mediated via the NMDA receptor. These results suggest that the development of morphine-induced CPP may be associated with the development of postsynaptic DA receptor supersensitivity. The development of morphine-induced CPP and DA receptor supersensitivity may be closely related to NMDA receptor-mediated dopaminergic activity, because morphine-induced changes in sensitivity to apomorphine, as well as apomorphine-induced climbing behavior in morphine treated mice, were both blocked by MK-801.

MK-801 Morphine CPP DA receptor supersensitivity

MORPHINE is an analgesic with significant abuse potential. This drug is primarily abused for its reinforcing or euphoric quality. Morphine's reinforcing effects are demonstrated in part by its ability to produce a conditioned place preference (CPP) (2,4), as well as by the fact that it is self-administered (52).

The CPP paradigm has been used as a model for studying the reinforcing effect of drug with dependence liability (7,50). Many such drugs are known to induce CPP, including morphine (2,4,38), heroin (8), cocaine (29), methamphetamine (47), and amphetamine (15). These drugs produce a reinforcing effect, which according to some hypotheses, may be due to their common property of facilitating dopaminergic transmission, either by stimulating the release of dopamine (DA) or inhibiting DA uptake.

Some neuropharmacological investigations have suggested that the mesolimbic and mesocortical dopaminergic systems are neuronal substrates mediating morphine-induced reinforcement (6,51). In support of this hypothesis, it has been shown that DA receptor antagonists such as haloperidol and SCH23390 antagonize morphine-induced CPP (26,40,41). 6-OHDA lesion of DA innervation of the nucleus accumbens is shown to decrease morphine-induced CPP (19). Also, it is known that opioid reinforcement may involve the activation of opiate μ receptors (22), and serotonergic receptors (9). However, the underlying mechanisms of CPP induced by morphine still remain unclear.

It has been demonstrated that behavioral sensitization after repeated administration of a reinforcing drug such as morphine can be attributed to dopaminergic hyperfunction in the central nervous system (37). This can be demonstrated by an

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increased response to a DA agonist, apomorphine (37). It is also reported that animals sensitized to morphine show an enhanced response to apomorphine, a direct DA receptor agonist, suggesting the development of DA receptor supersensitivity (3,20). These studies indicate that the development of DA receptor supersensitivity is one possible mechanism underlying behavioral sensitization induced by psychomotor stimulants or opioids.

According to some theories, CPP and behavioral sensitization induced by morphine may be modulated by the same mechanisms. Although CPP can be induced by treatment regimens that induce sensitization to other behaviors, it can also occur in the absence of sensitization. Morphine may derive its reinforcing quality by stimulating the same neurochemical system, which mediates psychomotor activity (54). Thus, it is hypothesized that the mechanisms underlying morphine-induced CPP may also involve postsynaptic DA receptor supersensitivity.

For over a decade, neuronal interactions between the excitatory amino acids (EAA), particularly glutamate, and DA have attracted much interest. A considerable amount of attention has been focused on glutamate–DA interactions within the striatum. The striatum contains high concentrations of glutamate and has dopaminergic terminals, arising from the midbrain. The corticostriatal pathway is thought to be one source of striatal glutamate (58). In vivo, release of DA from nigrostriatal neurons can be stimulated by low concentrations of glutamate, suggesting that DA release is controlled by glutamatergic mechanisms (11). It has been demonstrated that MK-801 preferentially antagonizes the L-glutamate-induced release of [^{3}H] DA from rat mesencephalic cultured cells (30).

Recently, it has been reported that an intraaccumbens microinjection of an NMDA antagonist inhibits the locomotor activity stimulated by heroin, cocaine, or DA treatment (36). Repeated treatment with an NMDA receptor antagonist, MK-801, prevents the development of opiate tolerance and dependence (48) and interferes with the development of behavioral sensitization to psychostimulants (56). These studies suggest that NMDA receptors might play a crucial role in morphine-induced CPP.

Based on the evidence outlined above, it is hypothesized that the NMDA antagonist, MK-801, can modulate morphine-induced CPP. The primary purpose of this study was to examine the effect of MK-801 on the CPP induced by morphine in mice. To determine the neuropharmacological mechanisms underlying the CPP induced by morphine, DA receptor supersensitivity was also examined. The effect of MK-801 on apomorphine-induced climbing behavior was also measured to investigate the antidopaminergic activity of MK-801.

METHOD

Animals and Drugs

ICR male mice weighing 20–26 g, in groups of 10–15 were used in all experiments. They were housed 10 mice in a cage with water and food available ad lib under an artificial 12 L:12 D cycle (light at 0700 h) and constant temperature (22 ± 2°C).

The drugs used were morphine hydrochloride (Je-il Pharm. Co., Korea), MK-801 hydrogen maleate [(+)-5-methyl-10, 11-dihydroxy-5H-dibenzo-(a,d)cyclo-hepten-5,10-imine, RBI., USA] and apomorphine hydrochloride (Sigma, St. Louis, MO). Except for apomorphine, all drugs were dissolved in physiological saline. Apomorphine was dissolved in saline containing 0.1% ascorbic acid, just prior to the experiment.

Measurement of CPP Induced by Morphine

Apparatus. The CPP apparatus and procedure used were the same as described in our previous report (21), and by others (15,40). The CPP apparatus was a modification of the apparatus used by Mucha et al. (31). It consisted of two square-base Plexiglas compartments (15 × 15 × 15 cm), one with a white box and the other with a black box jointed by a gray tunnel (3 × 3 × 7.5 cm), which could be closed by guillotine doors. To provide tactile difference between the floors of two compartments, the white compartment had a wire mesh floor and the black compartment had a metal grid floor. Removal of the guillotine doors during the pretesting and the final testing phases allowed animals free access to both compartments, and the time spent by the mice in each of the two compartments was recorded for 15 min using infrared detectors interfaced with a computer. The tunnel was designed to be just small enough for the passage and place choice of a mouse. The time spent by the mice in the tunnel was ignored, because the time spent in the tunnel comprised less than 5% or so of the total time measured. All conditioning or test sessions were conducted under ambient light (20–30 lx).

Procedures. Preliminary data from our laboratory indicated that naive mice spend more time in the black compartment than in the white compartment when given free-choice access to the entire apparatus for 15 min. Thus, to establish conditioning, we paired morphine with the initially nonpreferred white compartment. The control mice received an intraperitoneal injection of saline immediately before exposure to the white or black compartment. Morphine dissolved in saline (0.1 ml/10 g) was given immediately before the mice were placed in the white compartment. To test the effect of MK-801 (0.05 and 0.1 mg/kg, IP) alone or in combination with morphine, MK-801 was administered 30 min prior to the morphine or saline injection, respectively.

Pretesting phase: on day 1, the mice were preexposed to the test apparatus for 15 min. The guillotine doors were raised and each animal was allowed to move freely between the two compartments. On day 2, baseline preference was determined for the nonpreferred side vs. the preferred side for 15 min.

Conditioning phase: on days 3, 5, 7, and 9, the mice were injected with morphine before confinement in the white compartment, the nonpreferred side, for 60 min. On days 4, 6, 8, and 10, the mice were injected with saline before being confined in the black compartment, the preferred side, for 60 min.

Testing phase: on day 11, the guillotine doors were raised. The mice were placed in the tunnel in the central part of the apparatus, and the time spent by the mice in the two compartments was recorded for 15 min.

Place preference data were expressed as the difference in seconds between time spent in the drug-paired compartment [conditioned stimulus (CS+); least preferred initially], and the time spent in the saline-paired compartment (CS−). Values from both pretest baseline and test conditions were shown. Animals that acquire a place preference shift their preference to the drug-paired compartment (27). An increase in time in the drug-paired compartment shows that the animal spent more time in the originally less preferred compartment, presumably due to the reinforcing effects of the morphine that were conditioned to this environment (27).

Measurement of Postsynaptic DA Receptor Supersensitivity in CPP Mice

The apparatus and procedure used were the same as described in previous reports (3,21). This method produces a

consistent and reliable measure of the development of DA receptor supersensitivity in morphine-treated animals. The enhanced response to apomorphine was not observed in mice treated with morphine only once. Additional groups of mice that had received the same conditioning regimen, as well as repeated injections of morphine or MK-801 according to the schedule of the CPP experiment, were used to determine whether the enhanced response to apomorphine resulted from the repeated administration of morphine. Development of DA receptor supersensitivity was evidenced by enhanced responses in ambulatory activity to the DA agonist, apomorphine, 24 h after the final CPP confinement. The ambulation-increasing activity of apomorphine was measured by a modification of Bhargava's method (3). The ambulatory activity of mice was measured by a tilting-type ambulometer (AMB-10, O'hara Co., Ltd., Japan). Each mouse was placed in the ambulometer (20 cm in diameter; 18 cm in height). After an adaptation period of 10 min, mice were given apomorphine 2 mg/kg (SC), a dose that produced a significant increase in ambulatory activity. Ambulatory activity following apomorphine treatment was measured for 20 min.

Measurement of Apomorphine-Induced Climbing Behavior

The apparatus and procedure used were the same as described in previous reports (12,21,34). Climbing behavior has been used as a simple method to assess striatal DA activity and to screen DA agonists or antagonists, because apomorphine-induced climbing is reduced after destruction of the striatum, and is enhanced by 6-OHDA–induced lesions of DA input into the striatum, which presumably induce receptor supersensitivity (34). In the previous experiment, chronic treatment with MK-801 inhibited the development of the CPP and DA receptor supersensitivity induced by morphine. However, 24 h after the final CPP confinement, reduced apomorphine-induced climbing behavior was not observed in other groups of mice that had received the same treatment with MK-801 alone, as in the CPP experiment. Thus, the apomorphine-induced climbing behavior in mice treated acutely with a single dose of MK-801 was determined to investigate the antidopaminergic activity of MK-801 on the postsynaptic DA receptor.

The climbing behavior in mice was measured by a modification of the method of Protais and coworkers (34). MK-801 (0.05, 0.1, and 0.2 mg/kg) was administered intraperitoneally to mice 30 min prior to injection of apomorphine. Immediately after a SC injection of apomorphine 2 mg/kg, the mice were put into cylindrical individual cages (12 cm in diameter; 14 cm in height) with walls of vertical metal bars (2 mm in diameter; 1 cm apart). After a 5-min period of exploratory activity, climbing behavior was measured by all-or-none scores at 10, 20, and 30 min after the administration of apomorphine, and the three scores were averaged. The scores of this behavior were evaluated as follows: four paws on the floor, 0 point; forefeet holding the wall, 1 point; four paws holding the wall, 2 points.

Statistics

The data were expressed as a mean ± SE. The statistical significance of drug effects was assessed by an analysis of variance (ANOVA), and the significance between individual dose conditions and the corresponding control group was determined by a Dunnett's test in all experiments except for climbing results, which were analyzed by a Mann–Whitney *U*-test from a pharmacological calculations program (46).

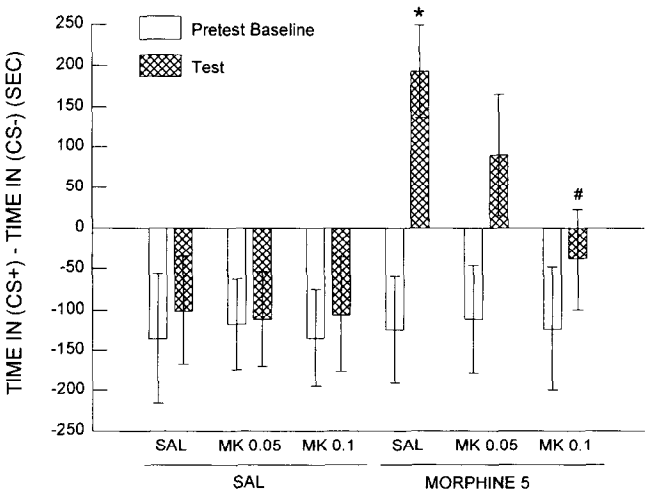

FIG. 1. Inhibitory effect of MK-801 on morphine-induced CPP. MK-801 [0.05 or 0.1 mg/kg (IP)] was administered 30 min prior to the injection of morphine (5 mg/kg) or saline (IP). In the conditioning phase, mice were injected with saline or morphine just before confinement in the black or white compartment for 60 min every day for 8 days. The data were expressed as the mean ± SE of the differences in the time spent in the drug-paired side [conditioned stimulus (CS+)] and the saline-paired side (CS−) for both pretest and test sessions (15 min). *$p < 0.05$, compared with that of the saline control group. #$p < 0.05$, compared with the morphine control group. Abbreviations: SAL, saline; MK, MK-801.

RESULTS

Inhibitory Effect of MK-801 on Morphine-Induced CPP

In a preliminary study, 2.5 mg/kg of morphine yielded a CPP score of 99 s, 5 mg/kg of morphine yielded a score of 181 s, and 10 mg/kg of morphine yielded a score of 120 s. Therefore, 5 mg/kg of morphine was used in this experiment, because that dose produced the maximum CPP score. The groups treated with 0.05 mg/kg and 0.1 mg/kg of MK-801 alone did not show any CPP compared with that of the saline control group (Fig. 1). The group pretreated with 0.05 mg/kg of MK-801 did not show any significant inhibition of morphine-induced CPP, compared with the 193 s score of the morphine control group. However, the group pretreated with 0.1 mg/kg of MK-801 showed a marked inhibition of morphine-induced CPP. Thus, that group yielded a score of −38 s, which was 231 s less than that of the morphine control group, $F(2, 30) = 3.46$, $p < 0.05$.

Inhibitory Effect of MK-801 on the Development of Postsynaptic DA Receptor Supersensitivity in Morphine-Treated Mice

Ambulatory activity produced by apomorphine was enhanced in mice treated with morphine, compared with mice treated with saline. The groups treated with 0.05 mg/kg and 0.1 mg/kg of MK-801 alone did not show any changes in ambulatory activity compared with the group treated with saline. The group treated with morphine showed a significant increase in ambulatory activity in response to 2 mg/kg of apomorphine, yielding 249 counts, 78 counts more than the 171 counts of the saline control group. Meanwhile, the group pretreated with 0.05 mg/kg of MK-801 did not show any significant inhibition in its enhanced ambulatory response to apomorphine, compared

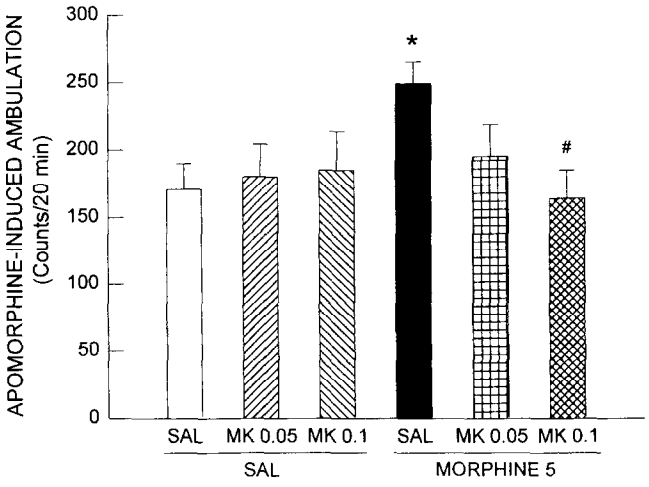

FIG. 2. Inhibitory effect of MK-801 on the development of postsynaptic DA receptor supersensitivity in morphine-treated mice. The development of DA receptor supersensitivity was determined by the enhancement of ambulatory activity to apomorphine 24 h after the final CPP confinement. Mice were injected with apomorphine [2 mg/kg (SC)] and first allowed to ambulate for 10 min and then tested for 20 min. *$p < 0.05$, compared with the saline control group. #$p < 0.05$, compared with the morphine control group. Abbreviations: SAL, saline; MK, MK-801.

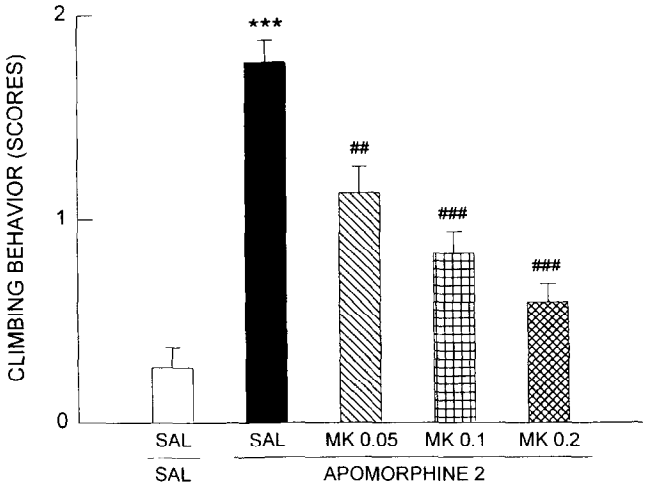

FIG. 3. Inhibitory effect of MK-801 on apomorphine-induced climbing behavior. MK-801 [0.05, 0.1 and 0.2 mg/kg (IP)] were administered to mice 1 h prior to the injection of apomorphine [2 mg/kg (SC)]. Immediately after the injection of apomorphine, the mice were put into individual cylindrical cages. After a 5-min period of exploratory activity, climbing behavior was measured by all-or-none score at 10, 20, and 30 min after the administration of apomorphine, and the three scores were averaged. ***$p < 0.001$, compared with the saline control group. ##$p < 0.01$, ###$p < 0.001$, compared with the apomorphine control group. Abbreviations: SAL, saline; MK, MK-801.

with that of morphine control group. However, pretreatment with 0.1 mg/kg of MK-801 produced a significant inhibition of apomorphine-enhanced ambulatory activity, resulting in 164 counts, 85 counts less than that of morphine control group, $F(2, 28) = 4.86$, $p < 0.05$ (Fig. 2). These results suggest that DA receptor supersensitivity develops in morphine-treated mice, and that MK-801 blocks the development of DA receptor supersensitivity in morphine-treated mice.

Inhibitory Effect of MK-801 on Apomorphine-Induced Climbing Behavior

Apomorphine (2 mg/kg) was used in this experiment, because the maximum response was observed with this dose in a preliminary experiment using 0.5, 1.0, 2.0, and 4.0 mg/kg of apomorphine (data not shown). The groups treated only with saline and MK-801 (0.05, 0.1, and 0.2 mg/kg) did not by themselves show any climbing behavior. Pretreatment with MK-801 (0.05 mg/kg) produced a significant inhibition of apomorphine-induced climbing behavior resulting in a score of 1.13, 0.64 less than the score of 1.77 of the apomorphine control group. In addition, the pretreatment with MK-801 (0.1 and 0.2 mg/kg) resulted in significant inhibition of apomorphine-induced climbing behavior, yielding scores of 0.83 and 0.59, both of which were less than that of the apomorphine control group, $F(3, 36) = 19.14$, $p < 0.01$)] (Fig. 3). These results show that a single administration of MK-801 inhibits apomorphine-induced climbing behavior, demonstrating the antidopaminergic action of MK-801.

DISCUSSION

In this experiment, chronic treatment with morphine produced CPP. This result is consistent with the results from other studies (2,4,38).

Morphine indirectly stimulates dopaminergic systems through an agonistic action on the opioid system; in particular, the mu-receptor site may be critical for the effects of opioids on the DA system (28,39). Furthermore, morphine increases the release of DA from presynaptic terminals in the striatum, thereby facilitating dopaminergic activity (1,24). Chronic administration of morphine leads to postsynaptic changes such as increased sensitivity to DA receptor stimulation. In other words, both postsynaptic DA receptor supersensitivity and behavioral sensitization, result from chronic administration of morphine (37).

Generally, it has been postulated that drugs that reduce the availability of catecholamines in the presynaptic neuron, or which block the action of catecholamines on postsynaptic receptors, attenuate the behavioral effects and reinforcing effects of stimulants in the monkey and rat (33,53). The initial support for DA involvement in opiate-mediated reward-related effects is exhibited by finding that DA receptor antagonists attenuate the reinforcing effect of morphine (41–43). In addition, direct DA receptor agonists such as apomorphine (32,49) and bromocriptine (17) produce reinforcing effects. Moreover, a microinjection of morphine into the nucleus accumbens establishes the CPP (51). Morphine-induced CPP is impaired by the lesion of the nucleus accumbens (19). Therefore, the reinforcing effect of opioids is due to the enhanced mesolimbic DA release resulting in an activation of the mesolimbic DA pathway (55). Meanwhile, there is a report that opioids may be rewarding independent of DA (22).

In the present study, the CPP induced by morphine was inhibited by MK-801. It has been demonstrated that striatal dopaminergic nerve terminals possess the NMDA receptor (5,23), and that these presynaptic receptors are involved in the control of DA release (11,23), suggesting that the regulation of central DA release may be partially mediated via the NMDA receptor. These results indicate that MK-801 could also modulate DA activity mediated through the NMDA receptor. In support of our results, it has been reported that MK-801 inhib-

its the development of reverse tolerance to cocaine and amphetamine (18,35). MK-801 preferentially antagonizes the release of [^{3}H] DA from rat mesencephalic cultured cells induced by L-glutamate (30) and completely blocks the NMDA-evoked release of [^{3}H] DA from striatal synaptosomes (23). These studies suggest that not only the opiate μ receptor (22), but also the NMDA receptor participates in behavioral responses mediated by the dopaminergic system (18,35).

In contrast to the present results, there are reports that MK-801 by itself produces a significant place preference in rats (16,25) and fails to block amphetamine-induced CPP in rats (16). In addition, Carlezon and Wise (10) have reported that MK-801 enhances the rewarding effect of morphine as determined by brain stimulation reward. The discrepant results obtained in those studies could be due to the following procedural differences: different species as subjects (rats vs. mice), different number of conditioning trials, discrepant conditioning duration, as well as different drug doses and routes of administration. Meanwhile, the unbalanced CPP method was used in this study as a matter of convenience to allow the testing of a large number of animals. In addition, an unbalanced paradigm was used to maximize the potential shift in place preference following conditioning with appetitive rewards (7). However, this procedure has been criticized as a measure of drug reward, because other factors may be involved in increasing the time spent in the nonpreferred side (50). The optimal procedure would be to counterbalance the drug-paired and vehicle-paired compartments. With morphine, however, similar results are obtained with the balanced and unbalanced paradigms (4).

The present results demonstrated that doses of MK-801, which are well below those that produce untoward side effects such as ataxia, depression, or stereotypy, markedly blocked the apomorphine-induced climbing behavior. The climbing behavior induced by apomorphine in mice is likely due to stimulation of postsynaptic DA receptors (12,34). The results of the apomorphine/MK-801 interaction study suggest that the postsynaptic dopaminergic effects of apomorphine may be modulated by NMDA receptors interacting with DA receptors. In addition, in separate additional experiments, it appeared that apomorphine-induced climbing behavior in mice was also inhibited by low doses of two different noncompetitive NMDA receptor antagonists [2.5, 5.0, and 10 mg/kg of ketamine (IP), reduced the apomorphine-induced climbing behavior by 38, 43, and 50%, and 40 mg/kg of dextrorphan (IP) reduced the apomorphine-induced climbing behavior by 63%, compared with that of the apomorphine (2 mg/kg) control group]. Smith and Bolam (45) proposed that both dopaminergic and corticostriatal terminals make contact with the dendrites of the striatal output cells, and hypothesized that this arrangement forms the basis of dopaminergic modulation of incoming cortical signals and subsequent influence on outgoing signals. Furthermore, it has been reported that NMDA receptor activation is required for the expression of D_1 DA receptor-mediated function (44). Therefore, it is suggested that apomorphine induces local dopaminergic activation and, thus, selectively amplifies information from corticolimbic areas. But blockade of NMDA receptors attenuates activation of the output pathway and, thus, lowers the general level of DA-induced activation at the postsynaptic DA receptor. It is, therefore, likely that the blockade of NMDA receptors results in behavioral effects such as the inhibition of apomorphine-induced climbing behavior as opposed to general inhibition of ambulatory behavior. The present results indicate that MK-801 has antidopaminergic activity, and the inhibition by MK-801 of apomorphine-induced climbing behavior may result from the blockade of the NMDA receptor, which converges with DA receptor into the same postsynaptic neuron within the striatum, rather than from an untoward side effect of a particular drug as Yang and Mogenson suggested (57). In support of this explanation, there is a report that apomorphine-induced climbing behavior is partially decreased by low doses of GDEE, but is almost completely blocked by the highest doses of GDEE (14). These results, therefore, imply that MK-801 can inhibit the dopaminergic activation mediated via the NMDA receptor.

Also, DA receptor supersensitivity developed in morphine-treated mice. It has been demonstrated that postsynaptic D_1 receptor sensitivity is increased following chronic administration of morphine (41). Repeated treatment with MK-801 inhibited the development of the postsynaptic DA receptor supersensitivity in morphine-treated mice. In support of these results, MK-801 was shown to block imipramine-induced DA receptor supersensitivity to quinpirole, a DA receptor agonist (13). MK-801 prevents the development of opiate tolerance and dependence (48) and interferes with the development of sensitization to psychostimulants (56).

Accordingly, it is presumed that the inhibitory effect of MK-801 on the CPP induced by morphine is closely related to the modulation of DA activation at both presynaptic and postsynaptic sites. The action of morphine on the DA receptor is indirect (28,39), and this indirect action results in the activation of the postsynaptic DA receptor. The enhanced behavioral sensitivity of postsynaptic DA receptor is blocked by MK-801.

From the results of this study, it is concluded that the development of morphine-induced CPP may be associated with enhanced DA receptor sensitivity, and the development of morphine-induced CPP and DA receptor supersensitivity may be partially related to the dopaminergic activation modulated by NMDA receptors, because the morphine-influenced dopaminergic phenomena tested and apomorphine-induced climbing behaviors were both blocked by MK-801.

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