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Effects of Morphine in the Nucleus Accumbens on Stimulant-Induced Locomotion

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LAYER, R. T., N. J. URETSKY AND L. J. WALLACE. *Effects of morphine in the nucleus accumbens on stimulant-induced locomotion.* PHARMACOL BIOCHEM BEHAV **40**(1) 21–26, 1991.—This study assessed the effects of morphine in the nucleus accumbens on motility elicited by dopaminergic and other classes of drugs, using locomotor activity as the measured response. Dopaminergic stimulants, d-amphetamine (10 μg) or dopamine (20 μg, 2 hours after nialamide, 200 mg/kg, IP) induced large increases in locomotor activity when injected into the nucleus accumbens. This response was blocked by coadministration of morphine (5 μg). The hypermotility response elicited by α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA; 0.5 μg), an excitatory amino acid agonist, was also abolished by coadministration of morphine. Increasing the dose of AMPA to 1.5 μg partially overcame the morphine block, while increasing the dose of amphetamine to 50 μg did not. In other experiments, morphine (5 μg) injected into the nucleus accumbens blocked the hypermotility elicited by systemic caffeine (10 mg/kg, SC) or scopolamine (0.5 mg/kg, SC) or intra-accumbal MK-801 (5 μg). However, picrotoxin (0.15 or 0.5 μg) injected into the nucleus accumbens elicited a hypermotility that was not attenuated by coinjection of morphine (5 or 10 μg). These data demonstrate that opiate and dopaminergic pathways have competing actions on the regulation of locomotion in the nucleus accumbens. Furthermore, the results with combinations of picrotoxin and morphine suggest the presence of two distinct locomotor pathways or a GABA receptor site "downstream" from the morphine site in a single pathway.

Morphine Amphetamine AMPA Dopamine Locomotor activity Nucleus accumbens Picrotoxin
MK-801 Scopolamine Caffeine

THE nucleus accumbens is a brain region which has been described as a functional interface between limbic and motor systems (22). One of the procedures used to study the role of the nucleus accumbens in the regulation of motility has been to measure locomotor activity after microinjection of compounds directly into the region. The results of such studies indicate that several different neurotransmitter systems in the nucleus accumbens are involved in the regulation of motor responses. The most extensively studied is the dopaminergic system. Activation of dopaminergic receptors either indirectly via amphetamine-induced release of dopamine or directly with injected dopamine or apomorphine produces a marked increase in locomotor activity (18, 19, 25). Agonists for glutamatergic excitatory amino acid receptors also stimulate locomotor activity (1, 3, 12). Among these, activation of the quisqualic acid or α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor elicits the largest and most consistent response (12). There appears to be an interaction between the glutamatergic and dopaminergic systems as intact dopaminergic neurotransmission in the nucleus accumbens is required for the locomotor-stimulating effects of the quisqualate receptor agonist AMPA (3,12). Picrotoxin, which blocks the chloride channel associated with the GABA-A receptor, also stimulates a marked increase in locomotor activity (23). However, this response appears to be independent of the dopaminergic system, as it is not inhibited by dopaminergic receptor blockers (23).

In contrast to the stimulation of locomotor acitivity by dopaminergic and glutamatergic agonists, activation of some other neurotransmitter receptors in the nucleus accumbens results in a decreased level of motor activity. Thus injection of morphine into this region results in akinesia and catalepsy (8,34). This effect appears to be the result of the activation of μ-receptors, as the response is achieved by selective μ-agonists (10). The specificity of this effect is further evidenced by observations that specific δ-agonists increase locomotor activity (10,14) and that specific kappa-agonists have little effect (14).

The fact that both μ-opiate receptor agonists and direct and indirect acting dopaminergic agonists act within the nucleus accumbens to produce opposite effects on motility suggests that dopaminergic and opioid systems have an antagonistic interaction in the nucleus accumbens. The specific anatomy and biochemistry that contribute to this interaction have not been conclusively determined. Some studies suggest that morphine-induced akinesia may be the result of a decrease in dopaminergic transmission in the striatum and nucleus accumbens (4, 5, 20, 26, 27, 29, 30, 35). This hypothesis is supported by several observations. First, both morphine and drugs which impair dopaminergic transmission such as haloperidol can produce catalepsy and akinesia after systemic administration (2,20); second, opiate receptors are localized on both nucleus accumbens (26) and nigrostriatal dopaminergic neurons (27); third, an opiate degrading enzyme, enkephalinase, has been localized to nigrostriatal dopaminergic neurons (21); fourth, opiates can decrease dopamine release from striatal slices (4, 27, 35); and fifth, opiates can inhibit d-amphetamine-induced turning behavior of rats with unilateral 6-hydroxydopamine-induced lesions of nigrostria-

tal dopaminergic neurons (30). One direct test of dopaminergic-opiate interactions in the nucleus accumbens has been reported. Morphine coinjected into the nucleus accumbens with dopamine blocks the locomotor stimulating effect of the catecholamine (9). Thus morphine may inhibit dopaminergic synapses in the nucleus accumbens both by acting presynaptically at the dopaminergic nerve terminal and by acting postsynaptically.

The observations reported above argue strongly for dopaminergic-opiate interactions within striatum and nucleus accumbens. However, the role of such interactions within the nucleus accumbens on the regulation of motility has not been well characterized. Furthermore, morphine interaction with nondopaminergic stimulators of hypermotility has not been reported. The goal of the present work was to determine how morphine-sensitive opiate mechanisms in the nucleus accumbens might interact with neuronal pathways that control locomotor stimulation. Towards this end, we have coinjected into the nucleus accumbens morphine along with compounds that elicit hypermotility and have measured the resultant locomotor activity. Using this procedure, the interaction of morphine with compounds that activate dopaminergic and glutamatergic neurotransmission and that inhibit GABAergic neurotransmission were compared. In addition, effects of intraaccumbens morphine on hypermotility elicited by systemic injection of caffeine and scopolamine were studied.

METHOD

Measurement of Locomotor Activity

Male rats (Harlan Sprague-Dawley, Indianapolis, IN), weighing 250 to 350 g, were housed 4 to a cage in a temperature-controlled (23 ± 1°C) room with a 12-hour light-dark cycle. For direct injection into the nucleus accumbens, the rats were anesthetized with a halothane/oxygen mixture and placed in a stereotaxic frame (David Kopf Instruments, Tajunga, CA) with the toothbar set at −3.3 mm. A midline incision was made in the scalp, and holes were drilled bilaterally into the skull at the coordinates: 10.2 mm anterior to the intraaural line and 1.2 mm lateral to the sagittal suture (24). The needle of a 10 μl Hamilton syringe (Hamilton Co., Reno, NV) was then inserted into the holes to a position 2.0 mm above the intraaural line. Drugs or vehicle were injected in a 0.5 μl volume at a rate of 0.5 μl/min. The needle was left in place for an additional minute to allow for diffusion of the solution. After removal of the needle, the incision was closed with wound clips and swabbed with 5% (w/v) lidocaine ointment.

After injections into the nucleus accumbens, anesthesia was discontinued, and the animals were removed from the stereotaxic frame. Animals recovered from the anesthesia within 5 minutes, after which they were placed in motor activity cages (Opto Varimex-Minor, Columbus Instruments, Columbus, OH) where they were allowed 10 minutes to adapt to the cages. The motor activity cages contained a grid (12 × 12) 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 2 consecutive beams were interrupted. Measurement of locomotor activity was done between 8:00 a.m. and 4:00 p.m. in an isolated environmental room maintained at a temperature of 23 ± 1°C.

After each experiment, animals were decapitated, and their brains were removed and fixed in a 4% solution of formalin for 48 hours. Frozen sections (40 μm) were cut using a Cryo-Cut microtome (American Optical Corp., Buffalo, NY) to check the location of the tip of the injection needle track. When the tips of the needle tracks were found to lie outside the nucleus accumbens, the data for that animal were excluded from the study. The histological examination showed that the majority of injections were localized to a relatively small subsection of the nucleus accumbens just medial and ventral to the anterior commissure at an anterior-ventral level corresponding to 10.2 mm ventral to Bregma according to the atlas of Paxinos and Watson (24).

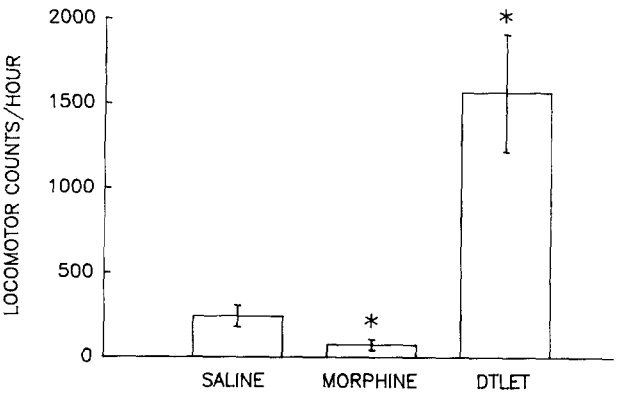

FIG. 1. Effects of morphine and DTLET on locomotor activity in the rat after bilateral injection into the nucleus accumbens. Animals received 5 μg of morphine (n = 8), 1 μg of DTLET (n = 5), or saline (n = 4). After injection, the animals were placed in motor activity cages, and locomotor activity was recorded for 1 hour. Each point represents the mean ± S.E.M. *$p<0.05$ with respect to vehicle control.

Drugs

The following compounds were purchased from Sigma Chemical Co. (St. Louis, MO): morphine sulphate, d-amphetamine sulphate, nialamide, dopamine, ascorbic acid, caffeine HCl, scopolamine, and [D-Thr^2]-leucine enkephalin-Thr (DTLET). α-Amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA) and (+)-MK-801 hydrogen maleate were purchased from Research Biochemicals Inc. (Natick, MA). Morphine sulphate and AMPA were dissolved in distilled H_2O; all other drugs were dissolved in sterile saline. The doses of morphine refer to the free base; for all other drugs the doses refer to the weights of the salts. The doses shown refer to the amount injected on each side of the nucleus accumbens.

Statistics

Data were expressed as the mean and the standard error of the mean (SEM). The data were evaluated statistically using the one-tailed Mann-Whitney U-test with $p<0.05$ accepted as significant.

RESULTS

Effects of Morphine and DTLET on Normal Locomotor Activity in the Rat

The bilateral injection of DTLET (1.0 μg), a specific δ agonist, into the nucleus accumbens produced a significant increase in locomotor activity. Conversely, administration of morphine (5.0 μg) into the nucleus accumbens markedly inhibited locomotor activity (Fig. 1). However, this degree of akinesia did not impair performance on a rotorod. Animals placed thirty minutes after injection (time of maximum akinetic response) on a 45-mm diameter rod rotating at 1.25 rpm maintained themselves on the rod for the entire five-minute testing period.

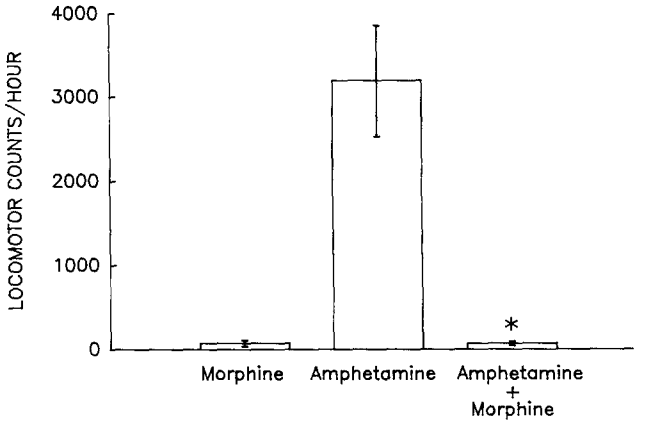

FIG. 2. Morphine inhibits d-amphetamine-induced locomotor activity in the rat after bilateral injection into the nucleus accumbens. Animals received 5 μg of morphine (n = 8), 10 μg of amphetamine (n = 6), or both morphine and amphetamine (n = 7). The animals were placed in motor activity cages, and locomotor activity was recorded for 1 hour. Each point represents the mean ± S.E.M. *$p<0.05$ with respect to stimulant alone control. The data for the morphine group are the same as shown in Fig. 1.

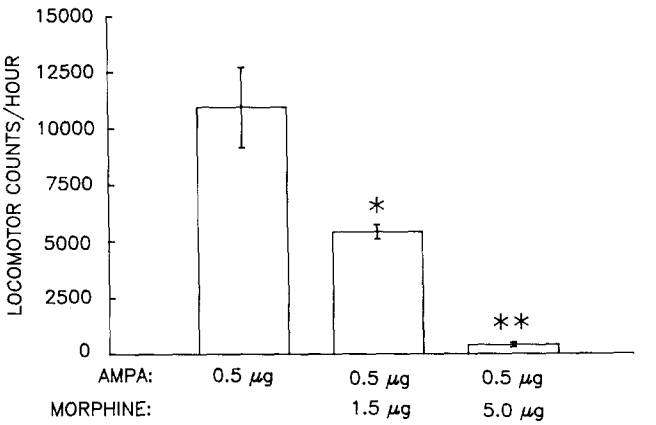

FIG. 3. Effect of morphine on AMPA-induced locomotor activity in the rat after bilateral injection into the nucleus accumbens. A solution of morphine (1.5 or 5.0 μg) or vehicle was coinjected with AMPA (0.5 μg) in a 0.5 μl volume. The animals were placed in motor activity cages, and locomotor activity was recorded for 1 hour. Each point represents the mean ± S.E.M. for 4 rats in the AMPA-treated groups or 5 rats in the control group *$p<0.05$, **$p<0.01$ with respect to stimulant alone control.

Effects of Morphine on Amphetamine- and AMPA-Stimulated Locomotor Activity in the Rat

d-Amphetamine, which induces hyperlocomotion in the rat primarily by releasing dopamine from dopaminergic nerve terminals and by preventing its reuptake, induced a pronounced locomotor effect (Fig. 2). The locomotor effect was characterized by the animals running along the periphery of the cage. They would typically stop at the corner and sniff for a moment before resuming ambulatory movement. Rats did not bump into the walls of the cage, and they would avoid obstacles placed in their path. However, when morphine (5.0 μg) was coinjected with d-amphetamine (10 μg) into the nucleus accumbens, the d-amphetamine-induced increase in locomotor activity was abolished (Fig. 2). Rats given morphine along with amphetamine tended to stay in the middle of the activity cages, in contrast to animals receiving only saline which stayed in the corner of the cage.

AMPA, an excitatory amino acid and quisqualate receptor agonist which appears to require dopamine to induce locomotion, produced a large increase in locomotor activity after bilateral injection (0.5 μg) into the nucleus accumbens (Fig. 3). The locomotion elicited by AMPA was qualitatively similar to that elicited by amphetamine; however, the amount of ambulatory movement after AMPA was greater. Coadministration of morphine (1.5 and 5.0 μg) into the nucleus accumbens inhibited AMPA-induced locomotor activity in a dose-dependent manner, with the dose of 5 μg almost totally abolishing activity (Fig. 3).

Data presented above demonstrate that 5 μg of morphine completely inhibits hypermotility elicited by either 10 μg d-amphetamine (Fig. 2) or 0.5 μg of AMPA (Fig. 3). To determine whether this interaction is competitive in nature, the ability of higher doses of d-amphetamine and AMPA to overcome morphine inhibition was studied. The dose of each stimulant was increased three-fold. While this resulted in a partial reversal of the morphine inhibitory effect when AMPA was the locomotor stimulant (Fig. 4), the locomotor responses to higher doses of amphetamine (30 and 50 μg) were still completely blocked by morphine (Fig. 4).

Effects of Morphine on Other Agents That Stimulate Locomotor Activity in the Rat

The observation that morphine attenuated both normal locomotor activity and the hypermotility elicited by amphetamine or AMPA suggests that morphine injected into the nucleus accumbens can nonspecifically inhibit locomotor activity. Therefore,

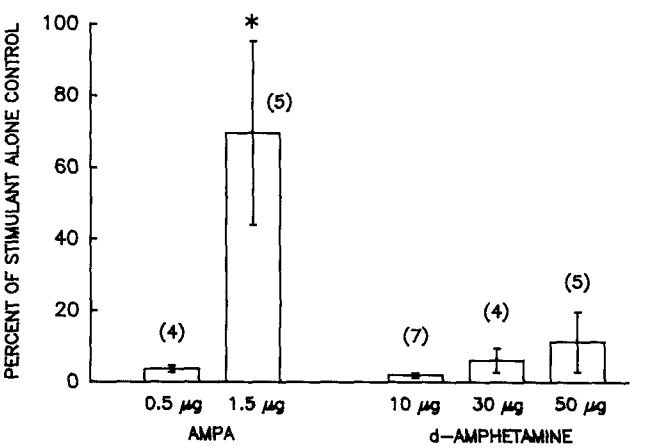

FIG. 4. Effect of morphine on locomotor activity induced by high concentrations of AMPA or d-amphetamine in the rat after bilateral injection into the nucleus accumbens. A solution of morphine (5.0 μg) was coinjected with AMPA (0.5 or 1.5 μg) or d-amphetamine (10, 30 or 50 μg) in a 0.5 μl volume. The animals were placed in motor activity cages, and locomotor activity was recorded for 1 hour. Data are expressed as a percentage of the stimulant control mean. Each point represents the mean ± S.E.M. of the percentage values for the number of rats shown in parentheses. Control locomotor responses to AMPA; 0.5 μg (10930 ± 1781) and 1.5 μg (14053 ± 5737 counts), were not statistically different. Control responses to d-amphetamine; 10 μg (3202 ± 663 counts), 30 μg (4946 ± 586 counts), and 50 μg (8214 ± 526); significantly increased with each successive dose (Mann-Whitney U-test). Asterisk indicates stimulant counteracted morphine effect ($p>0.05$ compared to stimulant alone control).

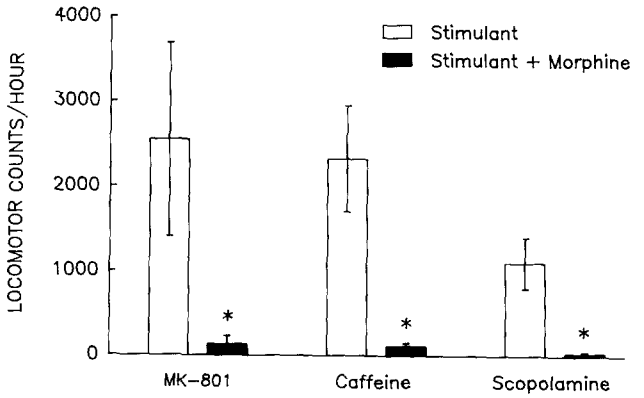

FIG. 5. Effect of morphine on hypermotility elicited by bilateral injection of MK-801 into the nucleus accumbens or by systemic administration of caffeine or scopolamine. A solution of morphine (5.0 μg) or vehicle was coinjected with MK-801 (5.0 μg) in a 0.5 μl volume or administered simultaneously with caffeine (10 mg/kg SC) or scopolamine (0.5 mg/kg SC). The animals were placed in motor activity cages, and locomotor activity was recorded for 1 hour. Each point represents the mean ± S.E.M. for 4 rats in each group. *$p<0.05$ with respect to stimulant alone control.

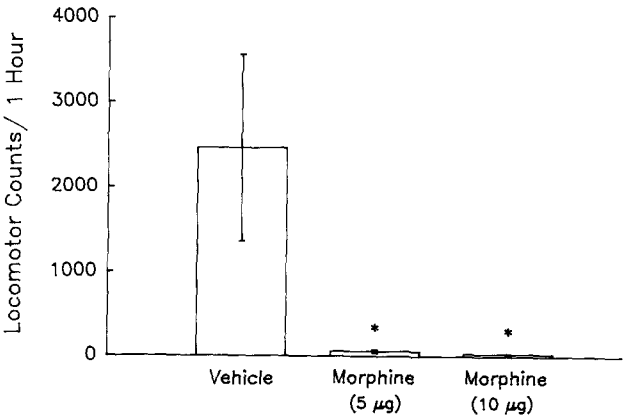

FIG. 6. Effect of morphine on dopamine-induced locomotor activity in the rat after bilateral injection into the nucleus accumbens. Rats were pretreated with nialamide (200 mg/kg IP), and two hours later a solution of morphine (5.0 μg, n=5, or 10.0 μg, n=6) or vehicle (n=6) was coinjected with dopamine (20 μg) in a 0.5 μl volume. The animals were placed in motor activity cages, and locomotor activity was recorded for 1 hour. Each point represents the mean ± S.E.M. for 5 or 6 rats in each group. *$p<0.05$ with respect to dopamine control.

the effects of morphine injected into the nucleus accumbens were tested against several agents that stimulate hypermotility. Bilateral administration of MK-801 (5.0 μg), an antagonist of the NMDA receptor, into the nucleus accumbens stimulated locomotor behavior in the rat, and this effect was abolished by coadministration of morphine (5.0 μg) into the nucleus accumbens (Fig. 5). Similarly, the increases in locomotor activity induced by systemic administration of both the methylxanthine caffeine (10 mg/kg SC) and the cholinergic antagonist scopolamine (0.5 mg/kg SC) were abolished by simultaneous administration of morphine (5.0 μg) into the nucleus accumbens (Fig. 5). In addition, direct administration of dopamine (20 μg) into the nucleus accumbens two hours after pretreatment with nialamide (200 mg/kg IP) produced an increase in locomotor activity (Fig. 6), which was abolished by coadministration of morphine (5 and 10 μg) (Fig. 6). The dopamine hypermotility effect was long-lasting, as the rats were still hyperactive after 3 hours. The inhibition of this behavior by morphine was long-lasting as well, as rats were akinetic as long as three hours after drug injection (data not shown). The dose of each of these agents that was tested was chosen to produce a submaximal response, and a reliable response would be obtained from both the dose used and double that dose. Thus the morphine effect is not likely to result from a shift to the right of a compound with a bell-shaped dose response curve. No overt differences in the pattern of locomotion were observed for the ambulatory movement elicited by these agents.

In agreement with previous studies (23), administration into the nucleus accumbens of picrotoxin (0.15 and 0.5 μg), a blocker of the chloride channel associated with the GABA-A receptor, also markedly stimulated locomotor activity.

However, in sharp contrast to the other stimulants investigated in this study, the picrotoxin-induced stimulation of locomotor activity was not attenuated by coadministration of morphine (5 or 10 μg) into the nucleus accumbens (Fig. 7).

DISCUSSION

The results of the present study clearly demonstrate that morphine injected into the nucleus accumbens blocks the locomotor stimulation elicited by amphetamine, which acts indirectly by releasing endogenous dopamine, and dopamine (in the nialamide-pretreated rat), which directly activates dopaminergic receptors. This effect of morphine was not due to a general impairment in motor function, since morphine treatment did not interfere with performance of the animals on a rotorod, and morphine did not inhibit the locomotor stimulation produced by picrotoxin. The fact that morphine is equally effective against both the direct and the indirect dopaminergic stimulants strongly implies that the morphine inhibition is exerted at a locus at or "downstream" from the dopaminergic receptors in the nucleus accumbens. It is unlikely that morphine is acting directly on dopaminergic receptors as morphine does not compete for dopaminergic receptors in binding assays (5), and important differences between morphine- and neuroleptic-induced catalepsy have been reported (11,32).

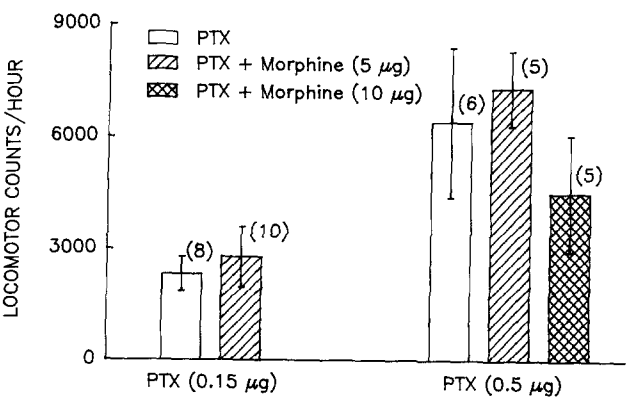

FIG. 7. Effect of morphine on picrotoxin-induced locomotor activity in the rat after bilateral injection into the nucleus accumbens. A solution of morphine (5.0 or 10 μg) or vehicle was coinjected with picrotoxin (0.15 or 0.5 μg) in a 0.5 μl volume. The animals were placed in motor activity cages, and locomotor activity was recorded for 1 hour. Each point represents the mean ± S.E.M. for the number of observations in parentheses.

The inhibition of amphetamine-induced stimulation of locomotion is compatible with the results of several studies suggesting that morphine impairs motor function by inhibiting the depolarization-induced release of dopamine (4, 5, 20, 26, 27, 30, 35). However, several observations do not support this hypothesis. Thus, while opiate receptors have been localized on dopaminergic nerve terminals in the nucleus accumbens (26), opiate receptors have been found in greater quantity on cell bodies and on terminals in the nucleus accumbens that are not dopaminergic (13,33). In addition, while activation of opiate receptors by morphine has been shown to inhibit the depolarization-induced release of dopamine (4,35), the amphetamine-induced release of dopamine is produced by a different mechanism, involving the release of dopamine from a cytoplasmic pool and the inhibition of dopamine reuptake (19). It is, therefore, unlikely that the inhibitory effect of morphine on the depolarization-induced release of dopamine is responsible for the antagonism of the amphetamine response. In our study, the intraaccumbens injection of morphine was able to inhibit the hypermotility response to dopamine (Fig. 6). These observations suggest that the ability of morphine to counteract the effects of amphetamine resides in a postsynaptic rather than a presynaptic action.

In addition to its ability to block locomotion elicited by activation of the dopaminergic system in the nucleus accumbens, morphine also attenuated locomotion elicited by the excitatory amino acid agonist AMPA. The hypermotility effects of AMPA are dependent upon intact dopaminergic neurotransmission within the nucleus accumbens (1, 3, 12). Thus the ability of morphine to inhibit the effects of AMPA may result from its action which counteracts dopaminergic stimulation.

Although morphine inhibited the hypermotility induced by either AMPA or amphetamine, increasing the dose of AMPA overcame the morphine-induced inhibition, while increasing the dose of amphetamine did not. There are several possible explanations for this difference. The ability of AMPA to counteract the inhibition by morphine could be related to the greater intensity of the locomotor response to this drug as compared to amphetamine. It is also possible that the high dose of AMPA used (1.5 μg) may stimulate locomotion in a manner unrelated to the effects of morphine. Recently, we have compared the abilities of D1 and D2 dopaminergic receptor antagonists to attenuate hypermotility responses to amphetamine and AMPA. Higher doses of antagonists were needed to inhibit the effects of AMPA than were required to block the response to amphetamine (3). Thus results with both dopaminergic antagonists and morphine suggest that AMPA is more powerful than amphetamine in stimulating nucleus accumbens locomotor circuits.

In contrast to the above findings, coadministration into the nucleus accumbens of morphine did not antagonize the locomotor response to picrotoxin, an inhibitor of the chloride channel associated with the GABA-A receptor complex. This observation indicates that morphine does not inhibit the locomotor response to all drugs that stimulate locomotion by acting in the nucleus accumbens. One explanation for this observation is that picrotoxin acts at a site in the nucleus accumbens that is located "downstream" from the morphine site. Alternatively, it is possible that there are at least two divergent neuronal pathways in the nucleus accumbens involved in the regulation of motility. Regardless of which hypothesis is correct, our results are consistant with the observation that picrotoxin-induced hypermotility does not require dopaminergic receptor activation, since haloperidol injected into the nucleus accumbens does not attenuate the locomotor activity elicited by picrotoxin (23).

We observed that morphine in the nucleus accumbens blocked hypermotility elicited by systemic administration of scopolamine and caffeine or by injection of MK-801 into the nucleus accumbens. It has been hypothesized that these compounds stimulate hypermotility by mechanisms other than dopaminergic activation in the nucleus accumbens. Thus monoamine depletion or blockade of dopaminergic receptors does not abolish the locomotor effect of MK-801 (6,28). Furthermore, destruction of dopamine neurons with 6-hydroxydopamine does not significantly inhibit hypermotility elicited by caffeine or scopolamine (17), and the dopamine receptor antagonist, alpha-flupenthixol, does not block hypermotility elicited by caffeine (31). Our results suggest that all three compounds activate a morphine-sensitive pathway in the nucleus accumbens, or that all three compounds activate a pathway elsewhere in the brain that is inhibited as a result of morphine action in the nucleus accumbens. If caffeine, scopolamine, and MK-801 activate pathways in the nucleus accumbens, the focus of activity must be downstream from the dopaminergic receptor or be on a morphine-sensitive pathway that does not contain dopaminergic receptors.

The present results are consistent with the hypothesis that the μ-opiate receptor subtype mediates akinesia in the nucleus accumbens (10,14). Administration of morphine, which is about 125 times more active at μ-sites then at δ-sites (7), resulted in akinesia, while administration of DTLET, a highly selective δ-receptor agonist, resulted in stimulation of locomotor activity. It has been demonstrated elsewhere that administration of other specific μ-agonists such as DAGO into the nucleus accumbens results in akinesia (10), whereas specific δ-agonists into the nucleus accumbens result in hyperactivity (10,14).

One limitation that must be considered in interpreting our results is that residual anesthetic and/or the stress from surgery might cause release of endorphins or other compounds that might affect behavior. Our experience is that injection of amphetamine, morphine, AMPA, and saline via implanted cannula into awake animals and injection into anesthetized animals (as used in the present study) produce identical locomotor responses. Furthermore, our results with MK-801, picrotoxin, and dopamine agree with results obtained by injecting these compounds via implanted cannula (23, 25, 28). Thus complications from the method of drug administration are thought to be minimal.

Based on our results and observations previously reported by others, we propose an explanation for the biphasic effect of systemic morphine and heroin on locomotion in rodents (2). After systemic administration, lower doses of the compounds exert locomotor stimulation by acting primarily on μ-receptors in the ventral tegmental area (15,16). This produces a disinhibition of dopaminergic neurons, resulting in activation of dopaminergic neurotransmission in the nucleus accumbens. Higher doses of the compounds may act primarily on μ-receptors in the nucleus accumbens to produce akinesia which overcomes the increased activity in the dopaminergic system. This latter argument would also explain why drug abusers sometimes use morphine or heroin in combination with amphetamine or cocaine to decrease the hyperactivity and agitation of the stimulant drugs.

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