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Effects of Naloxone on Morphine Induced Sedation and Hyperactivity in the Hamster

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SCHNUR, P AND V P RAIGOZA *Effects of naloxone on morphine induced sedation and hyperactivity in the hamster* PHARMACOL BIOCHEM BEHAV 24(4) 849–854, 1986 —Three experiments investigated the effects of naloxone on morphine elicited changes in hamster locomotor activity In Experiment 1, a prior subcutaneous injection of naloxone (0 4 mg/kg) converted morphine (15 mg/kg) elicited hypoactivity into hyperactivity Compared with saline controls, naloxone pretreated animals were hyperactive following a subcutaneous injection of morphine Experiment 2 investigated the effects of four doses of naloxone (0, 0 04, 0 1, 0 4 mg/kg) on morphine elicited hyperactivity Results indicated that naloxone reversal of morphine elicited hyperactivity is directly related to dose of naloxone In Experiment 3, naloxone (0 4 mg/kg) was administered one and two hours after a morphine injection Compared with saline controls, morphine treated animals were hypoactive for approximately 40 minutes after each of the naloxone injections Results are discussed in terms of a modified dual-action hypothesis

Naloxone Morphine Hamsters Locomotor activity

IT has long been known that morphine has both inhibitory and excitatory effects. In both rat and hamster, for example, low doses have predominantly excitatory effects, whereas high doses have predominantly inhibitory effects [2, 5, 13] Moreover, for a wide range of doses, both effects are evident in morphine's biphasic time effect curve [2, 5, 13]. For example, after morphine administration in the hamster, locomotor activity is first suppressed and then elevated compared with saline controls [11,13] Furthermore, with repeated administration, morphine's sedative effects decrease in magnitude and duration (tolerance), while its excitatory effects increase in magnitude and decrease in latency of onset (sensitization) [2, 11, 12, 18]. There is some evidence that morphine's biphasic effects are the result of independent pharmacological actions, mediated by different neuroanatomical mechanisms [9,19]

The dual-action hypothesis was proposed, in part, to account for morphine's biphasic effects [4, 15, 17]. According to this hypothesis: "(1) Morphine produces both depression and stimulation in the integrated nervous system as a direct pharmacologic effect, (2) Depression dominates during the early phases of drug action, masking and even antidoting the stimulant effects, (3) Since stimulation outlasts depression, the later phases of drug action are characterized by hyperexcitability; (4) As the dosage increases, stimulation dominates, ultimately with tetany and convulsions as the net effect, (5) Since tolerance exists only to the depressant actions of morphine, rapid incrementation of dosage and rapid development of tolerance results in unopposed accumulation of excitatory effects." ([14] p 514).

Recent findings in our laboratory provide partial support for the dual-action hypothesis. We reported that the opioid antagonists, naloxone and naltrexone, were effective in blocking morphine elicited sedation as well as morphine elicited hyperactivity [10]. Such results are consistent with the dual-action hypothesis insofar as it implies that both locomotor hypoactivity and hyperactivity are independent pharmacological effects of morphine Furthermore, these results suggest that both portions of morphine's biphasic time effect curve are opioid mediated. Also consistent with the dual-action hypothesis was the finding that, following the administration of naloxone, morphine elicited sedation was *reversed* [10]. That is, when naloxone was administered prior to an injection of morphine, hyperactivity occurred in place of sedation. This finding suggests that naloxone antagonizes locomotor sedation and thereby unmasks hyperactivity. But we also found that when naloxone or naltrexone was administered one hour after a morphine injection, sedation occurred in place of hyperactivity [10]. This finding, not specifically anticipated by the dual-action hypothesis, suggests that opioid antagonists block morphine elicited hyperactivity and thereby unmask sedation A modified dual-action hypothesis could account for these results by proposing that morphine elicits two concurrent, mutually inhibitory processes in the hamster, one that mediates hyperactivity and another that mediates sedation. Initially, morphine elicited sedation masks the effects of the process that promotes hyperactivity and subsequently, morphine elicited hyperactivity masks the effects of the process that promotes sedation. However, when opioid antagonists are used to block morphine elicited effects, the effects of the complementary processes are revealed.

The purpose of the present experiments was to provide additional documentation of naloxone's effects on morphine elicited activity in the hamster Experiment 1 tested the effects of naloxone on morphine elicited sedation, whereas Experiments 2 and 3 investigated the effects of naloxone on morphine elicited hyperactivity

EXPERIMENT 1

Experiment 1 was designed to replicate the previously reported effects of naloxone on morphine elicited sedation [10] As described above, naloxone reversed morphine elicited hypoactivity in the hamster, naloxone pretreated animals given morphine were hyperactive, compared with saline controls. However, in a similar experiment using the long acting opioid antagonist naltrexone, morphine elicited hypoactivity was blocked, but not reversed, naltrexone pretreated animals given morphine were no different from saline controls [10] A procedural difference distinguished the naloxone and naltrexone experiments the naltrexone challenge was given after three days of exposure to morphine alone, the naloxone challenge on the first day of morphine administration. Perhaps naloxone's reversal of morphine induced hypoactivity to produce hyperactivity would not occur following three days of morphine administration The present experiment therefore administered a naloxone challenge following three days of morphine administration

METHOD

Subjects

Eight female golden Syrian hamsters with a mean weight of 99 3 grams, obtained from Sasco, Inc (Omaha, NE), were used The hamsters were housed individually, maintained on a 12 12 hr lighting cycle (lights on at 7 a m.) and given free access to tap water throughout the experiment Animals received a daily food ration (Purina rodent lab chow) after each experimental session sufficient to maintain 90% of their ad lib weights

Apparatus and Materials

The apparatus consisted of eight identical activity wheels (Wahmann Co., Model LC-34) which were housed in a room dimly illuminated by two 15 watt bulbs Running wheels were fitted with microswitches and interfaced (Lafayette minicomputer interface, Model 1180) to an Apple II Plus computer to record the number of wheel revolutions An ambient noise level of 79 dB (re. 0 0002 dynes/cm^2, A scale) was maintained

Morphine injections consisted of 15 mg/kg doses of morphine sulfate (Lilly) and naloxone injections consisted of 0 4 mg/kg doses of naloxone hydrochloride (Endo) All injections were administered subcutaneously in the dorsal surface of the neck in 1 ml/kg volumes

Procedure

The experiment was conducted on nine successive days On each of the first three days, animals were given saline injections and placed in the running wheels for a three hour baseline session. Animals then were randomly assigned to one of four treatment groups· Groups SAL/SAL (n=4), NLX/SAL (n=4), SAL/MS (n=4), NLX/MS (n=4) On Days 4, 5 and 6, Groups SAL/SAL and NLX/SAL received saline injections and Groups SAL/MS and NLX/MS received morphine injections 15 min before being placed in the running wheels for three hours On Day 7, animals were tested in a three hour running wheel session following two injections, 10 min apart Group SAL/SAL received two saline injections, Group NLX/SAL received a naloxone injection followed by a saline injection, Group SAL/MS received a saline injection followed by a morphine injection, Group NLX/MS received a naloxone injection followed by a morphine injection On Day 8, all animals received a single injection of saline or morphine (as on Days 4–6) before being placed in the running wheels for three hours On Day 9, animals were tested as they were on Day 7, except that group assignments were reversed between animals in Groups SAL/SAL and NLX/SAL and between animals in Groups SAL/MS and NLX/MS (cf , [10]) The number of wheel revolutions was recorded at 20-minute intervals for each animal

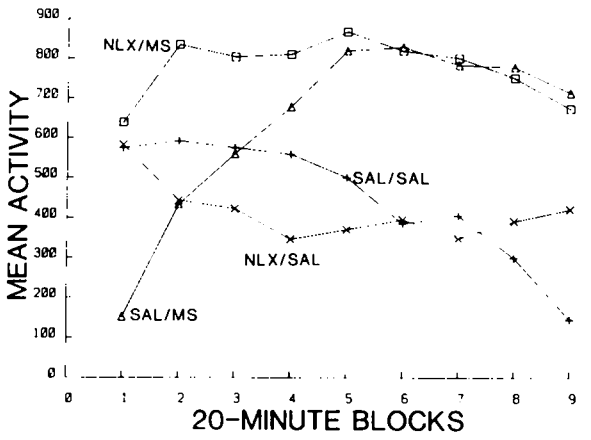

FIG 1 Mean activity (number of wheel revolutions) as a function of 20-minute time blocks during test days in Experiment 1

RESULTS AND DISCUSSION

Figure 1 shows mean running wheel activity as a function of time for all groups during test days The effect of morphine is evident in the comparison of Group SAL/MS with Group SAL/SAL Consistent with earlier reports [11, 12, 13], morphine in the present experiment induced sedation followed by hyperactivity The present results also confirm our earlier observations concerning naloxone's effects on morphine induced sedation in the hamster [10] A comparison of Group NLX/MS with Group SAL/MS indicates that the sedation elicited by morphine in Group SAL/MS was completely blocked in Group NLX/MS by a prior injection of 0 4 mg/naloxone. Moreover, as expected, animals given naloxone plus morphine (Group NLX/MS) were *hyperactive* compared with saline controls Naloxone itself had no effect on hamster locomotor activity, Groups NLX/SAL and SAL/SAL maintaining similar activity levels during the test sessions [10]

These conclusions are corroborated by a 2 (first injection) × 2 (second injection) × 9 (time blocks) mixed factorial analysis of variance (ANOVA) which indicated that there was no effect of the second injection, $F(1,6)=2\ 38$, $p>0\ 17$, but that the effect of the first injection, $F(1,6)=5\ 58$, $p<0\ 05$, and the interaction between the first and second injections, $F(1,6)=15\ 66$, $p<0.01$, were significant In addition, the in-

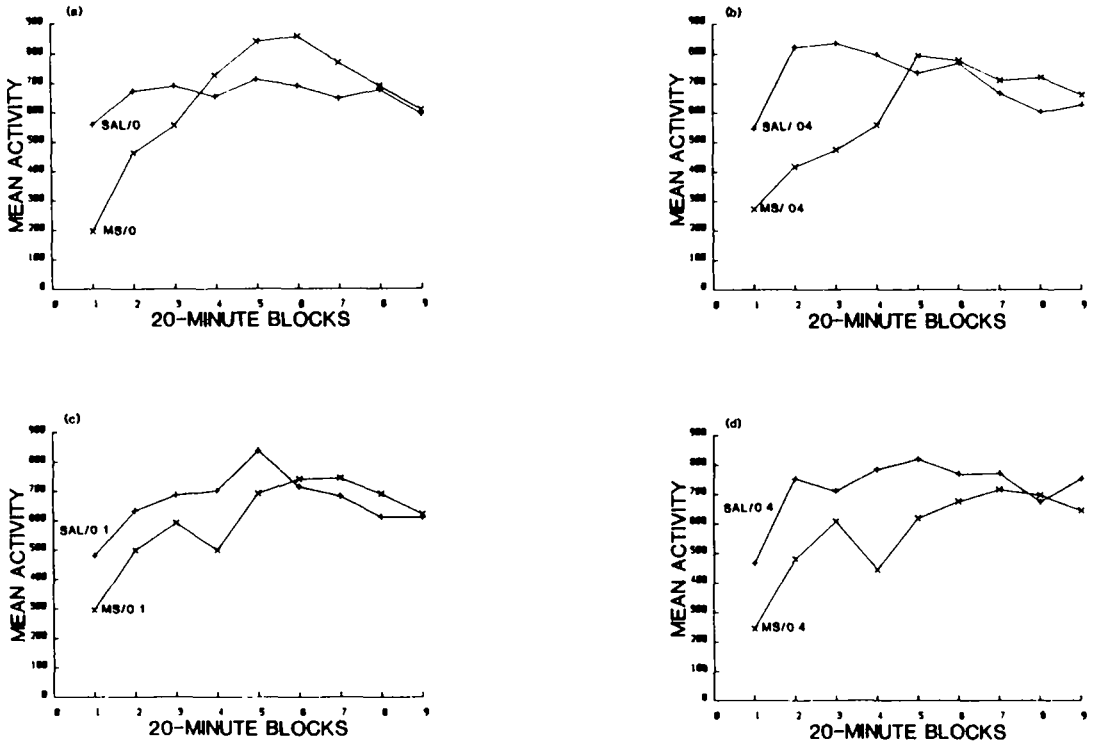

FIG 2 Mean activity (number of wheel revolutions) as a function of 20-minute time blocks during test days in Experiment 2 Each panel shows the data for a different naloxone dose.

teraction between time and the second injection was significant, $F(8,48)=4.17$, $p<0.001$, as was the interaction between time, the first injection and the second injection, $F(8,48)=3.59$, $p<0.002$ Post hoc comparisons using Fisher's least significant difference test revealed that Group NLX/MS was significantly ($p<0.05$) more active than Group SAL/SAL after 40, 60 and 80 minutes of the test session; that is, times when Group SAL/MS was not yet hyperactive.

Thus, the present findings indicate that, after three days of morphine administration, naloxone can reverse morphine elicited sedation to produce hyperactivity. Such results are consistent with previous results [10] and with the hypothesis that naloxone acts on morphine elicited sedation to "unmask" an underlying process that promotes hyperactivity.

EXPERIMENT 2

According to the modified dual-action hypothesis proposed above, morphine elicited hyperactivity masks the effects of an underlying process that mediates sedation Evidence consistent with that hypothesis is given by the finding that opiate antagonists induce sedation when administered during morphine elicited hyperactivity [10]. Experiment 2 was designed to extend that finding by testing the effects of four doses of naloxone (0, 0.04, 0.1, 0.4 mg/kg) on morphine induced hyperactivity Morphine was administered for three successive days before the naloxone challenge. As in previous work [10], the naloxone challenge was given one hour after animals began running under the influence of morphine in order to synchronize the naloxone injection with the excitatory portion of morphine's time effect curve [11,12].

METHOD

Subjects

Sixteen adult golden Syrian hamsters (11 females, 5 males) with a mean weight of 97 grams were used. The hamsters were descended from animals obtained from Sasco, Inc. (Omaha, NE). Housing and maintenance conditions were the same as described in Experiment 1

Apparatus and Materials

The apparatus was identical to that used in Experiment 1. Morphine injections consisted of 15 mg/kg doses of morphine sulfate (Lilly). Naloxone injections consisted of 0 (saline), 0.04, 0.1 or 0 4 mg/kg doses of naloxone hydrochloride (Endo). All injections were administered subcutaneously in the dorsal surface of the neck in 1 ml/kg volumes

Procedure

The experiment was conducted on ten successive days. During each of the first three days, the animals were given a saline injection and placed in the running wheels for a three hour baseline session. On Days 4 through 6, half the animals received saline and half received morphine injections before being placed in the running wheels for three hours Animals were tested on Days 7 through 10. On each test day, animals received saline or morphine as they had on Days 4–6 and then were placed in the running wheels. One hour later, they were removed from the running wheels, given an injection of one of the four doses of naloxone, and replaced in the wheels for two additional hours. The order of administering

naloxone doses on Days 7–10 was counterbalanced across subjects

RESULTS AND DISCUSSION

Figure 2 shows mean locomotor activity on test days as a function of 20-minute blocks of time for all groups in Experiment 2 Each panel presents the data for a different naloxone dose Recall that the second injection for all groups was given after one hour of running under saline or morphine Figure 2a shows the data for Groups SAL/0 and MS/0 Compared with saline controls, morphine produced sedation followed by hyperactivity As expected, a saline injection after one hour had no detectable effect on morphine's time effect pattern Figures 2b, 2c and 2d show the data for Groups SAL/0 04 and MS/0.04, Groups SAL/0 1 and MS/0 1, and Groups SAL/0 4 and MS/0 4, respectively Compared with saline controls (Fig 2a), naloxone interfered with morphine elicited hyperactivity in a dose dependent manner At the lowest dose of naloxone, the recovery from sedation was slowed and little hyperactivity occurred during the three hour session. At the 0 1 dose of naloxone, sedation occurred in place of hyperactivity, recovery was slowed and again, little hyperactivity was evident during the session At the highest naloxone dose, even greater sedation occurred in place of hyperactivity, recovery was slowed and no hyperactivity was evident

These conclusions are corroborated by a 2 (first injection) × 4 (naloxone dose) × 9 (time blocks) mixed factorial ANOVA The effect of the first injection was not significant ($F<1$), nor was the effect of the second injection ($F<1$) However, the effect of time was significant, $F(8,112)=9\ 94$, $p<0\ 001$, as were the Time × First Injection, $F(8,112)=2\ 84$, $p<0\ 01$, and the Time × First Injection × Naloxone Dose, $F(24,336)=1\ 84$, $p<0\ 01$, interactions Post-hoc comparisons using Fisher's least significant difference test indicated ($p<0\ 05$) that Group MS/0 was significantly more active than Group SAL/0 after 120 minutes, that Group MS/0 04 was significantly less active than Group SAL/0 04 after 80 minutes, that Group MS/0 1 was significantly less active than Group SAL/0.1 after 80 and 100 minutes, and that Group MS/0 4 was significantly less active than Group SAL/0 4 after 80 and 100 minutes

These results confirm previous findings by demonstrating that a 0 4 mg/kg dose of naloxone reverses morphine elicited hyperactivity In addition, the present data indicate that naloxone reversal of morphine elicited hyperactivity is directly related to dose of naloxone An alternative interpretation of these data is that naloxone elicits opiate withdrawal in morphine treated animals However, since opiate withdrawal is characterized by *increased* levels of activity in hamsters [1], in mice [16] and sometimes in rats [3], this hypothesis seems implausible

EXPERIMENT 3

According to the dual-action hypothesis, morphine induced stimulation outlasts morphine induced depression and thus hyperactivity appears as the second phase of morphine's time effect pattern. However, the results of Experiment 2 (and our previous observations [10]) suggest that an underlying process that promotes sedation accompanies behavioral hyperactivity, that morphine's excitatory actions are superimposed on and mask the sedation Nevertheless, it remains reasonable to consider the hypothesis that "stimulation outlasts depression" If that is true, then a naloxone challenge should reveal a smaller inhibitory process as a function of time since morphine administration The purpose of Experiment 3 was to test the effects of two naloxone injections on morphine induced hyperactivity Naloxone injections were given one and two hours after morphine administration It was expected that the first naloxone injection would produce a greater reversal of hyperactivity than the second

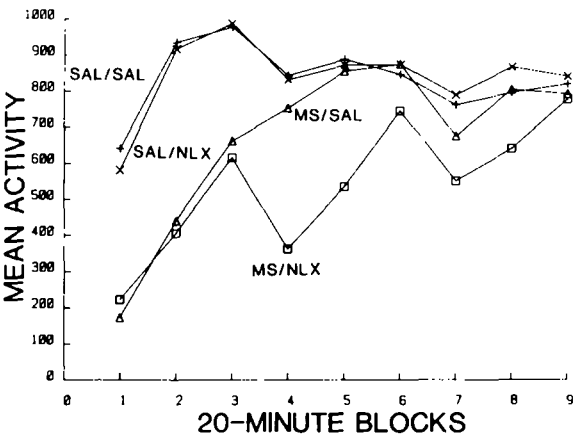

FIG 3 Mean activity (number of wheel revolutions) as a function of 20-minute blocks of time during test days in Experiment 3

METHOD

Subjects

Sixteen adult golden Syrian hamsters (15 females, 1 male) with a mean weight of 100 5 grams were used The hamsters were descended from animals obtained from Sasco, Inc (Omaha, NE) Conditions of housing and maintenance were as described in Experiment 1

Apparatus and Materials

The apparatus and materials were identical to those used in Experiment 1

Procedure

The experiment was conducted on eight successive days During each of the first three days, the animals were given a saline injection and placed in the running wheels for a three hour baseline session On Days 4 through 6, half the animals received saline and half received morphine injections before being placed in the running wheels for a three hour session Days 7 and 8 were test days in which the animals received either saline or morphine, as on Days 4 through 6, before being placed in the running wheels Then, one and two hours later in the session the animals were removed from the running wheels and received a second and third injection, respectively, of either saline (Groups SAL/SAL and MS/SAL) or naloxone (Groups SAL/NLX and MS/NLX) On Day 8, the same procedure was followed, but those animals which were given naloxone on Day 7 were given saline and those given saline on Day 7 received naloxone

RESULTS AND DISCUSSION

Figure 3 shows mean activity on the test days as a func-

tion of 20-minute blocks of time for all groups in Experiment 3. Morphine's sedative effects are evident during the first hour, where Groups MS/SAL and MS/NLX were less active than Groups SAL/SAL and SAL/NLX. The effects of naloxone on morphine induced changes in activity can be seen in the comparison of Group MS/SAL with Group MS/NLX after the first and second hour injections. After both injections, Group MS/NLX decreased its activity and was hypoactive compared with saline controls After the first injection, the activity of Group MS/NLX decreased, whereas that of Group MS/SAL increased. After the second injection, the activity of Group MS/NLX decreased again, but the magnitude of the decrease was smaller than it was after the first injection A comparison of Groups SAL/SAL and SAL/NLX indicates that naloxone by itself had no effect on hamster locomotor activity.

One feature of these results that is inconsistent with previous data is the fact that morphine did not elicit hyperactivity in the present experiment. That is, Group MS/SAL was never more active than Group SAL/SAL. Nevertheless, the effects of naloxone are clear. Although Groups MS/SAL and SAL/SAL achieved equivalent levels of activity, the results of the naloxone challenge indicate that activity in these two groups was mediated by *different* mechanisms That is, since naloxone administrations produced hypoactivity in morphine treated animals (Group MS/NLX), but not in saline treated animals (Group SAL/NLX), it is fair to conclude that activity in the former but not in the latter group, was opioid mediated Moreover, since naloxone elicited *hypoactivity* in Group MS/NLX, it appears that naloxone, in blocking recovery from morphine sedation, unmasked a process that promotes decreased locomotor activity.

These conclusions are corroborated by a 2 (first injection) × 2 (second, third injection) × 9 (time blocks) mixed factorial ANOVA which indicated that the effect of the first injection was significant, $F(1,14)=12\ 25$, $p<0.005$, as was the effect of time, $F(8,112)=21\ 83$, $p<0.001$ In addition, the Time × First Injection interaction, $F(8,112)=8.09$, $p<0.001$, and the Time × First Injection × Second, Third Injection interaction, $F(8,112)=2.21$, $p<0.05$, were significant Post-hoc comparisons using Fisher's least significant difference test indicated ($p<0\ 05$) that Group MS/NLX was significantly less active than Group SAL/SAL after 80, 100, 140 and 160 minutes of the test session In other words, compared with saline controls, morphine treated animals were hypoactive for approximately 40 minutes after each of two naloxone injections The decrease in activity evident in Group MS/SAL after 140 minutes was not significantly different from saline controls.

In demonstrating that naloxone elicits hypoactivity in morphine treated animals, the present experiment suggests the existence of an underlying process that promotes decreased activity during the recovery from morphine induced sedation. The present results are consistent with the dual-action hypothesis insofar as the first naloxone injection produced more hypoactivity than the second This was expected on the basis of the hypothesis that stimulation outlasts depression. It is interesting to note, however, that significant hypoactivity was produced by the second naloxone injection, two hours after morphine administration.

GENERAL DISCUSSION

The experiments reported here extend previous investigations of the effects of opioid antagonists on morphine elicited changes in hamster locomotor activity and may be summarized as follows: (1) morphine elicited sedation is replaced by hyperactivity in naloxone pre-treated animals; (2) naloxone reversal of morphine induced hyperactivity is directly related to dose of naloxone; (3) successive naloxone challenges produce repeated reversal (i.e., hypoactivity) of recovery from morphine sedation. Such results are consistent with the hypothesis that morphine elicits two concurrent, mutually inhibitory processes in the hamster Initially, one process predominates and sedation is the behavioral outcome Subsequently, the opposing process predominates and hyperactivity is the behavioral outcome That the opponent processes co-exist is suggested by the effects of naloxone: When either process was blocked, its complement was revealed in a reversal of behavioral outcome.

The effects reported in these experiments with hamsters have been reported occasionally in other species. For example, Brady and Holtzman [3] studied the effects of naloxone on morphine elicited changes in the activity of nondependent and dependent rats In nondependent rats, doses of morphine (e.g., 30 mg/kg) that produced sedation when administered alone, produced hyperactivity when administered in combination with naloxone (0.3 mg/kg). In dependent rats, doses of morphine (e.g., 1 mg/kg) that produced hyperactivity when administered alone, produced sedation when administered in combination with naloxone (0.3 mg/kg). In mice, hyperactivity induced by morphine (10 mg/kg) was changed into hypoactivity by a low dose (0.05 mg/kg) of naloxone [8]. And, in monkeys, morphine induced sedation was changed into excitation by pre-treatment with the opioid antagonist, nalorphine [15].

These findings raise questions about the mechanisms of morphine's biphasic effects One possibility is that both effects are the result of a single dose related mechanism, with stimulant effects occurring at low doses and depressant effects at high doses [18] Thus, over time, sedation gives way to hyperactivity as initially high blood levels of the drug fall to low blood levels. The present finding that naloxone can reverse sedation to produce hyperactivity and reverse hyperactivity to produce sedation weakens that hypothesis in favor of one that posits two independent actions of morphine (cf., [12]). An alternative hypothesis is that morphine's biphasic effects are the result of drug receptor interaction at different CNS sites For example, the dual action hypothesis [14], proposed that morphine sedation was mediated by receptors on the axon, whereas morphine excitation was mediated by receptors on the cell body. Recently, evidence has been presented to suggest that morphine's excitatory actions are mediated by the mesolimbic dopamine system [7,19], and that its sedative effects are mediated by midbrain [9] or reticular formation structures [4]. Thus, in rats, application of morphine directly to the nucleus accumbens [9], substantia nigra [7], and the ventral tegmentum [7,19] elicits hyperactivity, whereas application of morphine directly to the nucleus raphe pontis elicits sedation [4] It is still too early to choose among these competing hypotheses

The present findings are relevant also to reports of morphine induced *hyperreactivity* [6] This phenomenon is characterized by extreme startle reactions (explosive motor behavior) to relatively mild stimuli and is elicited by microinjections of morphine into the periaqueductal grey region Significantly, however, this form of morphine elicited excitation is not naloxone reversible, whereas the hyperactivity seen in the above experiments is naloxone reversible.

Finally, the present findings, along with previous results

[3, 8, 10], raise difficult questions about the mechanism(s) of naloxone antagonism of morphine induced changes in locomotor activity. In particular, the mechanism by which naloxone "unmasks" opiate effects is at issue. What would be the mechanism by which naloxone blocks sedation and not hyperactivity at one moment, but subsequently blocks hyperactivity but not sedation? Admittedly, it is merely a rephrasing of the problem to state that, in the context of the dual-action hypothesis, opiate antagonists act to oppose the predominant process

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