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Modulation of the locomotor properties of morphine and amphetamine by uncontrollable stress

Matthew J. Will[a,*], Andre Der-Avakian[b], Julie L. Pepin[b], Brandice T. Durkan[b], Linda R. Watkins[b], Steven F. Maier[b]

[a]*Department of Psychiatry, University of Wisconsin-Madison Medical School, Madison, WI 53719, USA*
[b]*Department of Psychology and Center for Neurosciences, University of Colorado-Boulder, Boulder, CO 80309, USA*

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Abstract

We have recently demonstrated that exposure to a single session of inescapable shock (IS), but not to identical amounts and distributions of escapable shock (ES), increases the rewarding properties of morphine, as measured by conditioned place preference (CPP). Interestingly, we also found that exposure to IS has no effect, or even interferes with amphetamine CPP. The present study explored whether the potentiating effect of IS on morphine reward, but not amphetamine reward, would generalize to the locomotor properties of these drugs. The locomotor response to morphine and amphetamine was measured 120 h following exposure to either IS or home cage control (HCC) treatment. On test day, the activity of all subjects was measured for 1 h before and 3 h after drug administration. The results demonstrated that exposure to IS potentiated the locomotor response to morphine, while having no effect on the response to amphetamine. An additional study investigated whether the effects of IS on the locomotor properties of morphine were sensitive to stressor controllability, by comparing the influence of IS, ES, or control treatment. Again, IS potentiated the locomotor properties of morphine, while exposure to ES and control treatment had no effect.

Keywords: Locomotor activity; Morphine; Amphetamine; Acute stress

1. Introduction

The majority of drug users fail to develop addiction, but rather can use drugs recreationally or on an occasional basis (National Institute of Medicine Report, 1996). However, certain individuals are believed to experience the initial response to a drug as more rewarding, increasing their vulnerability to subsequent drug use and possible dependence. Indeed, the initial rewarding experience of a drug has been shown to be a predictor of subsequent drug addiction (Haertzen et al., 1983). Thus, the evidence suggests that rather than simple exposure to a drug, it is the interaction of specific environmental experiences and a drug that leads to addiction (Piazza and Le Moal, 1996).

Stress is such an experience that has been shown to potentiate or sensitize an organism's reactivity to both the rewarding and locomotor properties of drugs (for review, see Piazza and Le Moal, 1996). Repeated or chronic stress has been shown to enhance the psychomotor response to most abused drugs, including morphine (Leyton and Stewart, 1990; Deroche et al., 1992, 1994; Molina et al., 1994) and amphetamine (Leyton and Stewart, 1990; Deroche et al., 1993). These stressor effects are also present for the rewarding properties of opiates (Alexander et al., 1981; Bozarth et al., 1989) and stimulants (Bozarth et al., 1989; Tidey and Miczek, 1997). However, the influence of acute stressors on the behavioral effects of drugs has been examined less often, and has usually been shown to have no effect (Herman et al., 1984; Hahn et al., 1986; Stohr et al., 1999). However, stressors are not generic events, and different stressors often produce quite different outcomes. For example, exposure to a single session of an uncontrollable stressor such as inescapable shock (IS) often produces outcomes more characteristic of chronic or repeated stressor exposure (Fleshner et al., 1995).

* Corresponding author. Wisconsin Psychiatric Institute and Clinics, 6001 Research Park Boulevard, Madison, WI 53719-1179 USA. Tel.: +1-608-265-4629.

E-mail address: mjwill@facstaff.wisc.edu (M.J. Will).

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Indeed, we have recently demonstrated that exposure to a single session of IS, but not to identical amounts and distributions of escapable shock (ES), increased the rewarding properties of morphine, as measured by conditioned place preference (CPP) (Will et al., 1998). Interestingly, we also found that exposure to IS had no effect, or even interfered with amphetamine CPP (Will et al., 1998).

In the present study, we investigated whether the selective influence of IS on morphine and amphetamine's rewarding properties would generalize to their locomotor properties. Although there have been studies suggesting that there are different neural substrates for the psychomotor and reinforcing properties of drugs (Martin-Iverson et al., 1985; Mithani et al., 1986; Lemaire et al., 1994; Campbell and Spear, 1999), they have more frequently been shown to correlate (for review, see Wise and Bozarth, 1987). In addition, the psychomotor response has been shown to depend on and correlate with dopamine utilization in the mesoaccumbal pathway, a pathway that has been strongly implicated in the reinforcing properties of drugs (for review, see Bardo, 1998). Thus, it might be expected that if exposure to IS alters the rewarding effects of a drug, that the locomotor effects of the drug should be similarly altered.

2. Method

2.1. Subjects

Adult male Sprague–Dawley rats (Harlan Sprague–Dawley, Indianapolis, IN) weighing 300–400 g were housed in groups of two in Plexiglas cages in a climate-controlled colony room of 22 °C. The subjects were maintained on a 12-h light–dark cycle and all experiments were conducted during the light phase. They had free access to food and drinking water prior to and throughout the experiment. All subjects were naive and allowed a minimum of 1 week of adaptation followed by 2 days of handling before the beginning of all experiments. Experimental and control groups contained seven to nine subjects. All experimental procedures were in accord with protocols approved by the University of Colorado Institutional Animal Care and Use Committee.

2.2. Apparatus and materials

2.2.1. Activity apparatus

Locomotor activity was measured in Plexiglas boxes ($30 \times 30 \times 30$ cm) that were striped horizontally or vertically (assignment was counterbalanced) with alternating 3/4 in. black and white electrical tape on the walls. The floor of all boxes was black sanded Plexiglas. One week prior to experimentation, all rats had a conical cap that would allow an LED light assembly to be attached for tracking purposes surgically attached to the top of their heads.

2.2.2. LED light assembly

Subjects were tracked utilizing Chromotrack computer tracking software that received images from a CCD camera mounted 4 ft above the center of the apparatus. One week prior to the experiment, each subject had the outer portion of a screw cap from a 15-ml conical centrifuge tube fixed upside-down to the skull with acrylic and four screws. Prior to placing subjects in test boxes, a light assembly consisting of a red LED and two 1.5-V watch batteries encased in a half-inch portion of plastic tubing was threaded into the screw cap previously mounted on their heads.

2.2.3. IS apparatus

The stressor environment was a dimly lit room with dimensions of approximately $3 \times 2.5 \times 2.5$ m. IS occurred in Plexiglas restraining tubes that were 17.5 cm in length and 7.0 cm in diameter. The rat's tail extended from the rear of the tube and was taped at the base to a Plexiglas rod 4.0 cm in length. The front end of the tube was blocked by a Plexiglas plunger that contained several airholes. Unscrambled shocks (1.0 mA) were delivered by a source modeled after Grason-Stadler Model 700. Electrodes, coated with a small amount of electrode paste, were taped to the midsection of the tail.

2.2.4. ES–IS apparatus

ES and yoked IS were administered in small Plexiglas wheel-turn boxes. The entire box was made of clear Plexiglas. A small wheel extended 1.7 cm into the front of the chamber through a hole 8.0 cm from the floor of the box. The wheel required a force of about 0.50 N to turn. The rat's tail was extended through a slot in the rear wall of the chamber and was taped to a Plexiglas rod parallel to the floor of the chamber. Shock was applied through electrodes attached to the rat's tail and augmented with electrode paste. The shock sources were modeled after Grason-Stadler Model 700.

2.3. Procedure

2.3.1. IS procedure

IS-treated subjects received 100 inescapable tailshocks (IS: 5-s duration, average intertrial interval of 60 s, 1 mA) in Plexiglas restrainer tubes in a different room than where locomotor testing was performed, while home cage control (HCC)-treated subjects remained in their home cages.

2.3.2. ES–yoked shock procedure

Rats either received 100 escapable tailshocks (ES), 100 identical yoked inescapable tailshocks (IS), or remained in their home cages (HCC). In the escape condition, rats received 100 trials of an unsignaled 1.0-mA shock on a variable interval 60-s schedule (range: 30–90 s). The initial 0.8 s of the shock was not under the subject's control. The shock following this period could be terminated by the appropriate wheel-turn response. The initial response requirement was a 90° turn of the wheel, the basic unit of response that was measured, and the subsequent require-

ments were dependent upon the prior response latencies. Three responses under 5.0 s increased the requirement by one unit for the next trial. If that trial had a response latency under 5.0 s, the requirement was increased two units, and every subsequent trial response under 5.0 s resulted in a doubling of the previous unit requirement. The maximum response requirement was 16 units, or four full rotations of the wheel. Any interruption of the increment sequence by response latencies over 5.0 s caused the sequence to restart with a requirement of three consecutive rapid-response trials. Response latencies of 10–29 s decremented the response requirement for the next trial by one unit; failure to complete a response, or a response latency of 30 s, the maximum shock duration allowed, reset the response requirement to one response unit. Response latency was measured from shock onset to the completion of the response requirement. Intertrial interval was measured from response completion to shock onset. This procedure was used because it produces shock durations similar to those in the first two experiments conducted here (i.e., 5-s shocks).

In the IS condition, each rat was paired with an escape rat. Each shock began for an inescapable subject at the same time as for the escape partner and was terminated whenever its escape subject performed the criterion escape response. Therefore, within each escape/yoked pair, both rats received the identical number, pattern, intensity, and duration of shocks. The wheel-turn responses made by the yoked animal had no effect on the shock's termination or onset.

2.3.3. Locomotor assessment procedure

One hundred twenty hours following stress treatment, at approximately 11:00 h, all subjects had an LED assembly screwed into their cap, and then were placed in the boxes for 1 h to assess baseline activity. At the end of the hour, subjects were removed from the box, injected with either vehicle or drug, and immediately placed back into the box. Locomotor activity was measured for an additional 3 h.

2.4. Drugs

The drugs used included morphine (Mallinkrodt, St. Louis, MO) and D-amphetamine (Sigma, St. Louis, MO) both dissolved in physiological saline. Injection volume of both drugs and saline was 1.0 ml/kg body weight.

2.5. Statistical analyses

Data were analyzed by analysis of variance (ANOVA). The dependent variable in all experiments was centimeters traveled.

3. Results

Experiments 1 and 2 determined the locomotor response to morphine (0.25, 1.0, or 3.0 mg/kg sc), amphetamine (0.025, 0.25, or 2.5 mg/kg sc), or saline (1 mg/kg sc) administered 120 h following either HCC or IS treatment.

3.1. Experiment 1: IS effects on the locomotor response to morphine

The mean locomotor activity during the 120 min following administration of each of the four morphine doses (0, 0.25, 1.0, and 3.0 mg/kg) to either HCC- or IS-treated subjects is shown in Fig. 1. Following injection of morphine, HCC subjects displayed an overall increase in activity in response to the two highest doses of 1.0 and 3.0mg/kg, but did not increase activity to the lowest dose of 0.25 mg/kg. Prior treatment with IS significantly increased the locomotor response to morphine, with the largest increase occurring at the lowest dose of 0.25 mg/kg. A 2×4 ANOVA on the first 120 min of the drug trial revealed a significant main effect of drug [$F(3,53) = 11.915$, $P < .0001$] and IS treatment [$F(1,53) = 4.34$, $P < .05$], while the interaction between dose and IS was not quite reliable [$F(3,51) = 2.075$, $P = .11$]. Prior to administration of morphine or vehicle, IS- and HCC-treated subjects displayed no differences in activity levels (data not shown). A 2×4 ANOVA conducted on total activity levels for the 60 min before drug revealed no significant group difference between stress [$F(3,53) = 0.209$, $P > .05$] or drug dose condition [$F(3,53) = 0.469$, $P > .05$].

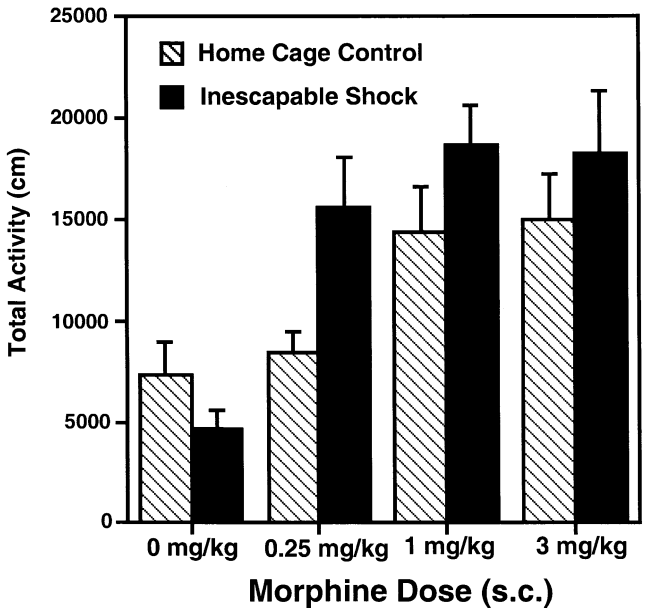

Fig. 1. Locomotor response to morphine (0.25, 1.0, and 3.0 mg/kg) or saline administered 120 h following exposure to IS or HCC treatment. Values represent the mean (±S.E.M.) of the total centimeters traveled over the first 120 min of the drug trial.

3.2. Experiment 2: IS effects on the locomotor response to amphetamine

The mean locomotor activity during the 120 min following administration of each of the four amphetamine doses (0.025, 0.25, 2.5 mg/kg) to either HCC- or IS-treated subjects is shown in Fig. 2. Following injection of amphetamine, HCC subjects displayed an overall increase in activity in response to both the two highest doses of 0.25 and 2.5 mg/kg, while only showing a modest increase at the lowest dose of 0.025 mg/kg. Prior treatment with IS had no effect on activity levels at any of the four amphetamine doses tested. A 2×4 ANOVA conducted on the first 120 min of the drug trial revealed no main effect of IS treatment [$F(3,46) = 3.656$, $P > .05$], but a significant main effect of dose [$F(3,46) = 362.415$, $P < .0001$].

Prior to administration of amphetamine or vehicle, IS- and HCC-treated subjects displayed no differences in activity levels (data not shown). A 2×4 ANOVA conducted on total activity levels for the 60 min before injection revealed no main effect of stress [$F(1,46) = 3.831$, $P > .05$], or drug dose condition [$F(3,46) = 0.432$, $P > .05$].

3.3. Experiment 3: Effects of IS, ES, or HCC treatment on the locomotor response to 0.25 mg/kg of morphine

The mean locomotor activity during the 120 min following administration of 0.25 mg/kg of morphine or vehicle to IS- and HCC-treated subjects is shown is Fig. 3. As in Experiment 1 above, 0.25 mg/kg of morphine did not lead to an increase in activity in HCC subjects. Furthermore, exposure to ES did not potentiate activity to morphine.

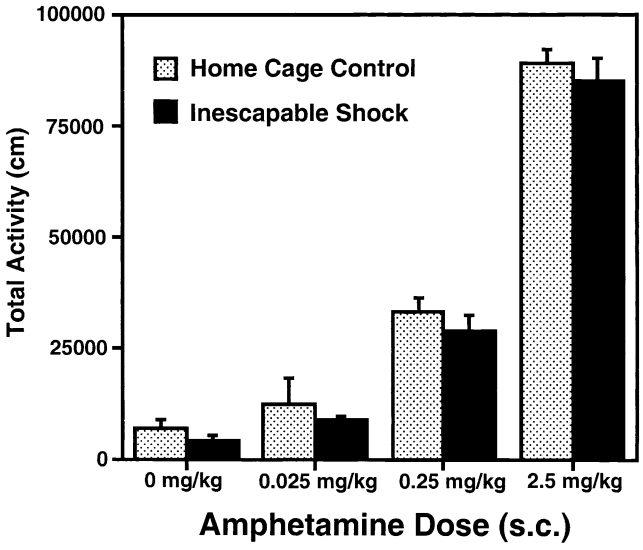

Fig. 2. Locomotor response to amphetamine (0.025, 0.25, and 2.5 mg/kg) or saline administration 120 h following exposure to IS or HCC treatment. Values represent the mean (±S.E.M.) of the total centimeters traveled over the first 120 min of the drug trial.

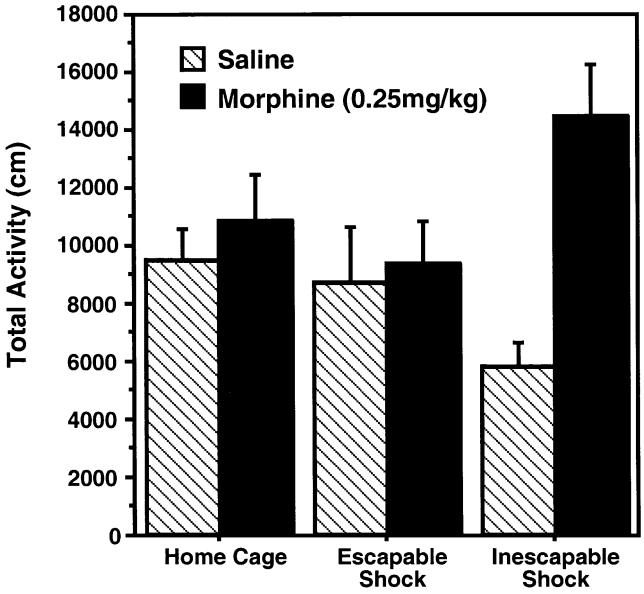

Fig. 3. Locomotor response to morphine (0.25 mg/kg) or saline administration 120 h following exposure to ES, IS, or HCC treatment. Values represent the mean (±S.E.M.) of the total centimeters traveled over the first 120 min of the drug trial.

However, IS-treated subjects administered morphine displayed over a 200% increase compared to IS subjects given saline. ANOVA conducted on activity levels during the first 2 h of the drug trials revealed no main effect of stress [$F(2,26) = 0.355$, $P > .05$], but did show a significant main effect of drug [$F(1,26) = 7.893$, $P < .01$], and a significant interaction between stress and drug [$F(2,21) = 4.182$, $P < .05$]. Post hoc analysis revealed that IS-treated subjects administered morphine demonstrated significantly higher activity levels than both IS-treated subjects given saline and ES-treated subjects given morphine.

Prior to administration of morphine or vehicle, IS-, ES-, and HCC-treated subjects displayed no differences in activity levels (data not shown). ANOVA conducted on predrug activity levels indicated no effect of stress [$F(2,26) = 2.321$, $P > .05$] or drug group [$F(1,26) = 1.464$, $P > .05$].

4. Discussion

In the present study, we examined whether exposure to IS would influence the locomotor response to morphine and amphetamine. We have previously shown that exposure to IS potentiates the rewarding properties of morphine, while having no effect on the rewarding properties of amphetamine (Will et al., 1998). The results of the present study offer further support to the conclusion that the influence of IS is selective to the behavioral effects of morphine, as IS potentiated the locomotor response to morphine, while having no effect on the locomotor response to amphetamine. IS potentiation of the psychomotor effects of morphine, but not amphetamine, occurred over a wide

dose range, from doses having no effect in controls to doses having large effects. IS led to activity increases at a morphine dose that had no effect at all in controls (0.25 mg/kg), as well as at doses that had large effects in controls. IS did not alter activity to amphetamine at any dose. The present results can therefore not be attributed to a biased selection of doses. Additionally, the effect of IS on the locomotor properties of morphine was sensitive to stressor controllability, as exposure to ES had no effect. These effects cannot be explained by IS-induced changes in unconditioned activity, as IS-, ES-, and HCC-treated subjects demonstrated similar levels of activity before drug administration and following saline administration.

Confirming previous reports (Deroche et al., 1992), 1 and 3 mg/kg of morphine led to a significant increase in locomotor activity in nonstressed HCC subjects, compared to HCC subjects administered saline. The lowest dose of morphine (0.25 mg/kg) produced locomotor activity no different than that observed following administration of saline in HCC subjects. Exposure to IS 120 h prior to morphine administration produced a general overall increase in locomotor activity for all doses of morphine, with the greatest increase being observed at the lowest morphine dose (0.25 mg/kg). Amphetamine doses of 0.025, 0.25, and 2.5 mg/kg produced a significant increase in locomotor activity in HCC subjects compared to HCC subjects administered saline. Exposure to IS 120 h prior to amphetamine administration had no effect on these increases. Lastly, the potentiating effect of IS on the locomotor response to 0.25 mg/kg of morphine was sensitive to stressor controllability, as treatment with ES had no effect.

The majority of studies that have investigated stressor effects on the locomotor response to drugs have utilized chronic or repeated stress. With regard to morphine, 14 days of chronic variable stress (Molina et al., 1994) or 7 days of food restriction (Deroche et al., 1993) have both been shown to increase morphine's locomotor properties. In addition, repeated stressors such as 3 days of either restraint or social defeat (Stohr et al., 1999) or several days of restraint (Deroche et al., 1992) have also been reported to increase the locomotor response to morphine. With regard to amphetamine, chronic food restriction (Deroche et al., 1993), repeated footshock (Hahn et al., 1986), or tailpinch (Piazza et al., 1990) have all been shown to increase amphetamine's locomotor activating effects. Therefore, it appears as though chronic and repeated stress influence the locomotor response to both morphine and amphetamine equally. Whether or not acute stressors have this same influence is unclear.

Although a few studies have examined the effects of an acute stressor on the behavioral response to a drug, there has never been an investigation comparing the locomotor response to morphine and amphetamine following the same stressor. However, the studies that have explored only amphetamine are in agreement with the present findings that demonstrated no effect of IS on amphetamine-induced locomotor activity. Indeed, exposure to 10 (Schmidt et al., 1999), 20 (Herman et al., 1984), or 60 footshocks (Hahn et al., 1986) have all failed to influence the locomotor response to amphetamine. The literature regarding the effect of acute stress on the locomotor response to morphine is scarce. Stohr et al. (1999) reported that 2 h of restraint was without effect on the locomotor response to morphine when assessed 3 days later. While the controls in the present study were HCC subjects rather than restraint, we have previously reported that 2 h of restraint had no effect on the rewarding properties of morphine (Will et al., 1998). Indeed, none of the behavioral effects that we have previously shown to be produced by IS have been observed following 2 h of restraint (Short and Maier, 1993; Sutton et al., 1997; Will et al., 1998).

The mesolimbic dopaminergic (DA) pathway projecting from ventral tegmental area (VTA) to the nucleus accumbens (NAc) is believed to be a common substrate underlying the actions of most drugs of abuse (for review, see Bardo, 1998). In addition to the involvement of the DA pathway, drugs of abuse have also been shown to recruit and dysregulate certain "stress systems." such as the hypothalamic–pituitary–adrenal axis (for review, see Kreek and Koob, 1998). However, less is known about the effects of environmental stress on the DA substrate, and whether or not these influences are drug specific. The present findings and those previously reported (Will et al., 1998) suggest that IS induces a state that selectively interacts with morphine to increase both its rewarding and locomotor properties, while failing to influence the same properties of amphetamine. The experiments reported above do not indicate the nature of this state or the underlying persistent physiological alterations produced by IS. However, the physiological substrate that mediate the effects of IS on other behavioral sequelae has been extensively investigated.

Exposure to IS, but not ES or restraint, produces behavioral deficits that have been shown to be mediated by serotonergic (5-HT) pathways originating in the dorsal raphe nucleus (DRN). Indeed, it has been demonstrated that IS selectively activates DRN 5-HT neurons (Grahn et al., 1999) leading them to become sensitized to subsequent input (Amat et al., 1998). Thus, any excitatory input to these sensitized DRN 5-HT neurons for a period of time following exposure to IS results in an exaggerated activation of these neurons leading to exaggerated release of 5-HT in DRN projection regions (Amat et al., 1998).

While both morphine and amphetamine are known to increase DA transmission in the mesolimbic pathway, they have opposite effects on DRN 5-HT activity. Morphine has been demonstrated to activate DRN 5-HT neurons (Jolas and Aghajanian, 1997) and amphetamine has been shown to have either no effect or to inhibit DRN 5-HT activity (Pennington and Reiffenstein, 1986). Assuming that IS produces its behavioral effects predominantly through a sensitized 5-HT pathway, it might be expected that IS should only alter the properties of drugs such as morphine,

which are known to themselves activate DRN 5-HT neurons. On the other hand, IS should be expected to have no effect on the behavioral response of drugs such as amphetamine, which do not activate DRN 5-HT neurons. Additional evidence suggesting a selective role for 5-HT interaction with morphine, but not amphetamine, comes from 5-HT antagonist and 5-HT lesion studies. Administration of 5-HT_3 antagonists block morphine, but not amphetamine CPP (Carboni et al., 1989; Higgins et al., 1992). In addition, 5,7-DHT lesions of the NAc prevent morphine, but not amphetamine-induced CPP (Spyraki et al., 1988).

Recent studies in our laboratory have shown that IS potentiates the DA efflux in the NAc produced by systemic administration of morphine while ES does not (Sparks et al., 1999). Moreover, NAc 5-HIAA levels were higher in IS-treated subjects, suggesting increased utilization of NAc 5-HT (Sparks et al., 1999). Indeed, 5-HT/DA interactions do occur in the NAc, and electrical stimulation of the DRN can facilitate DA release in the NAc (De Deurwaerdere et al., 1998). It is conceivable that the exaggerated NAc 5-HT utilization observed in IS-treated subjects who are administered morphine, in turn facilitates NAc DA release, which then potentiates the locomotor effect of the drug.

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