ELSEVIER

European Journal of Pharmacology 346 (1998) 203–208

ejp

Dissociation of morphine-induced potentiation of turning and striatal dopamine release by amphetamine in the nigrally-lesioned rat

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Received 9 October 1997; revised 12 January 1998; accepted 20 January 1998

Abstract

Morphine has been reported to increase extracellular levels of dopamine in the brain of intact rats and to potentiate turning induced by amphetamine in nigrally-lesioned rats. The present study tested the hypothesis that there is a causal relationship between these two effects of morphine. We tested morphine alone, amphetamine alone, and the combination in separate groups of nigrally-lesioned rats for effects on turning and, by microdialysis, on extracellular dopamine levels. Morphine (3.0 or 10 mg/kg) did not produce significant turning but amphetamine (1.0 mg/kg) did. The lower dose, but not the higher dose, of morphine potentiated amphetamine-induced turning. Amphetamine, but not morphine, produced increases in extracellular dopamine levels. In contrast to what occurred with turning, 10 mg/kg but not 3.0 mg/kg morphine potentiated amphetamine-induced increases in extracellular dopamine levels. These results show that the potentiation of amphetamine-induced turning by morphine in nigrally-lesioned rats is not due to the potentiation of dopamine release in the intact striatum. © 1998 Elsevier Science B.V.

Keywords: 6-Hydroxydopamine; Microdialysis, in vivo; Morphine; Rotational behavior; Striatum; Substantia nigra

1. Introduction

Presynaptic dopamine neurons are destroyed when rats are given a unilateral nigrostriatal lesion and postsynaptic dopamine receptor supersensitivity develops in the lesioned striatum (Robinson and Becker, 1983). Administration of the psychomotor stimulant amphetamine to nigrally lesioned rats produces ipsilateral turning (Lynch and Carey, 1989; Ungerstedt and Arbuthnott, 1970). Amphetamine preferentially releases newly synthesized dopamine from presynaptic cells (Arbuthnott et al., 1991; Kuczenski and Segal, 1989; Zetterström et al., 1986). In vivo microdialysis studies show that amphetamine increases extracellular dopamine levels in the striatum and nucleus accumbens of the rat (Di Chiara and Imperato, 1988a,b; Kalivas and Stewart, 1991). This evidence suggests that amphetamine produces turning by increasing extracellular dopamine levels in the striatum.

Amphetamine-induced turning can be modified by μ-opioid receptor agonists. The μ-opioid receptor agonists levorphanol, meperidine, methadone, and morphine potentiated amphetamine-induced turning in the nigrally-lesioned rat (Kimmel and Holtzman, 1997). In addition, μ-opioid receptor agonists themselves can induce turning and dopamine release. For example, buprenorphine, levorphanol, and methadone produced turning greater than saline did in nigrally-lesioned rats (Kimmel and Holtzman, 1997). Fentanyl, methadone, and morphine also increased extracellular dopamine levels in the striatum and ventral tegmental area of rats (Di Chiara and Imperato, 1988a,b; Kalivas and Stewart, 1991). Thus, opioid drugs can increase dopamine release as well as produce turning on their own and potentiate amphetamine-induced turning.

μ-Opioid receptors are localized upon inhibitory γ-aminobutryic (GABA) neurons that project from the striatum to the substantia nigra (Mansour et al., 1995). The stimulation of the μ-opioid receptors inhibits GABAergic activity, thus increasing dopamine release from nigrostriatal dopamine neurons (Kalivas and Stewart, 1991). This evidence suggests that stimulation of μ-opioid receptors by morphine increases dopamine release in the striatum, leading to an increase in dopamine-mediated behaviors.

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The purpose of this study was to test the hypothesis that morphine potentiates turning induced by amphetamine by potentiating the amphetamine-induced release of dopamine in the intact striatum. To do this, we examined the effects of morphine (3.0 and 10 mg/kg) alone, amphetamine (1.0 mg/kg) alone, and the combination, on turning in nigrally-lesioned rats over a 4-h time period. In a second group of nigrally-lesioned rats, we placed a microdialysis probe into the intact striatum and measured extracellular dopamine levels after the administration of the same drugs that were tested in the first group. The doses of amphetamine and morphine selected for this study each increased dopamine release in the striatum of rats (Di Chiara and Imperato, 1988a,b) and this dose of amphetamine and the lower dose of morphine had a synergistic effect on turning (Kimmel and Holtzman, 1997). Based on earlier microdialysis studies, we expected that morphine would potentiate amphetamine-induced dopamine release in the striatum and that this would correlate with turning.

2. Methods

2.1. Subjects

Male Sprague–Dawley rats (Sasco, Omaha, NE) weighing 240–260 g were used. All rats were group housed in polycarbonate cages and maintained in a temperature-controlled colony room with a 12L:12D light cycle. Rats had free access to food (Purina Rodent Chow, Purina Mills, St. Louis, MO) and water.

2.2. 6-Hydroxydopamine lesions

The right nigrostriatal pathway of rats was lesioned by a single injection of 6-hydroxydopamine. Rats were anesthetized with 3.3 mg/kg Equithesin (i.p.) and placed into a stereotaxic frame. Stereotaxic coordinates used relative to bregma were: AP = −4.5, ML = −2.3, DV = −7.1 (Paxinos and Watson, 1986). A 25-μl Hamilton syringe was used to inject 8 μg/4 μl of 6-hydroxydopamine into the right substantia nigra at a rate of 1.0 μl/min for 4 min. Upon completion, the injection needle was kept in place for an additional minute to minimize back flow of the solution. This procedure results in greater than 90% depletion of dopamine on the lesioned side relative to the intact side (Kimmel et al., 1997).

2.3. Rotational behavior

Rotational activity was measured in eight stainless steel rotometer stations (MED Associates, East Fairfield, VT). Each station consisted of a round metal bowl (40.6 cm diameter and 25.4 cm high) with a transparent Plexiglas cover. A spring tether, connected to a direction sensitive rotation sensor mounted above the bowl, was attached to the rat by means of a Velcro belt. Rotational activity was recorded by the Roto-Rat Version 1.2 computer program (MED Associates). Measurements were taken of full (360°) clockwise and counterclockwise turns. During experimental test sessions, counts were taken in 15-min intervals for 4 h, resulting in 16 time points per animal per session. Rats were allowed to recover from surgery for at least 14 days, then they were tested with 0.3 mg/kg *R*(−)-apomorphine s.c. twice weekly for 2 weeks. Rats exhibiting at least 50 contralateral turns during each 10-min interval for 1 h were used for further experiments. The amount of turning in response to apomorphine has been found to be directly correlated with the extent of the nigral lesion (Hudson et al., 1993). Behavioral testing or microdialysis procedures did not begin until at least 1 week following the last apomorphine administration, to prevent any possible carry-over effects of the drug.

On test days, animals were weighed and placed into the test chambers and allowed to habituate for approximately 5 min before drug injections. Rats ($n = 8$) received morphine (3.0 or 10 mg/kg, s.c.) or saline (1.0 ml/kg, s.c.). Five minutes later, amphetamine (1.0 mg/kg, s.c.) or saline s.c. was injected. Measurements of rotational behavior began 5 min after the second injection. Each animal was tested twice weekly with a 3–4 day interval between testing. Every animal received each of the six combinations of drugs, which were administered in a random order.

2.4. In vivo microdialysis

A second group of nigrally-lesioned rats was anesthetized with 3.3 mg/kg Equithesin (I.P.) and placed into a stereotaxic frame with the incisor bar set at +5 mm. A 21-gauge stainless steel guide cannula (Plastics One, Roanoke, VA) was lowered to the dorsal surface of the left striatum, using the stereotaxic coordinates of AP = +2.5, ML = +2.7, DV = −2.7 (Pellegrino et al., 1979). The guide cannula were secured with skull screws and cranioplastic cement (Plastics One). Rats were given 3–5 days of recovery before probes were implanted. All surgeries were performed in accordance with the guidelines of the Emory University Institutional Animal Care and Use Committee.

Microdialysis probes consisted of two lengths of fused silica (40 μm ID: 100 μm OD; Polymicro Technologies, Phoenix, AZ) inserted into a piece of cellulose dialysis fiber (220 μm OD; 6000 MW cutoff; Spectrum Medical Industries, Houston, TX). The ends of the dialysis fiber were sealed with polyimide sealing resin (Alltech). The distance between the silica inlet and outlet lines was 4.0 mm. A 375 series single channel small animal cannula swivel (Instech Laboratories, Plymouth Meeting, PA) was incorporated into each probe to allow free movement of the animals. Approximately 30 min before probe implantation, the inlet line of the probe was connected to a 500 μl Hamilton syringe containing artificial cerebrospinal fluid (CSF). Artificial CSF was composed of 149 mM NaCl, 2.8

mM KCl, 1.2 mM $MgCl_2$, 1.2 mM $CaCl_2$, 0.25 mM ascorbic acid, and 5.4 mM D-glucose and was adjusted to a pH of 7.2–7.4 with 0.5 M sodium hydroxide. All chemicals were obtained from Fisher Scientific except L-ascorbic acid, which was obtained from Sigma Chemical.

Microdialysis experiments were carried out in Plexiglas cages (40 × 25 × 25 cm). A 4-in long fluorescent light on the roof of each cage provided illumination, and cages were enclosed within a ventilated, sound-attenuating chamber to minimize external disturbances. The evening before the experiment, animals were transferred to the experimental cages and allowed to habituate for 4–5 h. The rats were then weighed and the dialysis probes inserted. The perfusion of artificial CSF was initiated at a flow rate of 0.1 μl/min in order to allow dopamine concentrations to equilibrate after the disturbance of probe implantation. Approximately 7 h after probe implantation, the artificial CSF flow rate was increased to 0.6 μl/min and the collection of baseline samples began.

Following the collection of 4 baseline samples, rats were given morphine (3.0 or 10.0 mg/kg, s.c.) or saline s.c. Amphetamine (1.0 mg/kg, s.c.) or saline s.c. was administered 5 min later. Each animal was tested only one time.

Dialysate samples were collected at 15-min intervals for 4 h after amphetamine administration, then immediately frozen on dry ice for later analysis. Dialysate samples were analyzed by injecting a 5.0-μl volume of perfusate onto a small-bore high performance liquid chromatography (HPLC) system. The HPLC apparatus consisted of a 0.5 mm ID × 10 cm column (5 μm particle size C-18 stationary phase). Electrochemical detection of dopamine was analyzed using an EG&G Princeton Applied Research amperometric detector using a working electrode (model MF-1000; Bioanalytical Systems) with an applied potential of +700 mV vs. an Ag/AgCl reference electrode (model RE1; Bioanalytical Systems). Dopamine standard solutions were used to generate calibration curves.

Following the experiments, animals were anesthetized with 400 mg/kg chloral hydrate and perfused transcardially with 0.9% NaCl followed by 10% formalin. The brain was removed and stored in 10% formalin. Probe placement was verified by examining 40 μm-thick coronal sections that were stained with thionine.

2.5. Statistical analysis

Rotational behavior time course data were subjected to a one-way analysis of variance (ANOVA) with repeated measures on time and a two-factor ANOVA (drug treatment × time) with repeated measures on both factors. When appropriate, Tukey's protected *t*-test was used for multiple pair-wise comparisons. Dialysate dopamine concentrations (expressed as nM dopamine) were analyzed by a one-factor ANOVA with repeated measures on time and by a two-factor ANOVA (drug combination × time), with repeated measures on time. The area under the curve was determined from the rotational behavior and microdialysis data of each animal, and then analyzed using a one-factor ANOVA (with repeated measures, in the case of the rotational behavior data). When appropriate, post-hoc tests were performed using Tukey's protected *t*-tests.

2.6. Drugs

D-Amphetamine sulfate (Sigma Chemical, St. Louis, MO) and morphine sulfate (Penick, Newark, NJ) were dissolved in 0.9% saline. *R*(−)-Apomorphine hydrochloride (Research Biochemicals, Natick, MA) and 6-hydroxydopamine hydrobromide (Sigma Chemical) were dissolved in a solution of 0.1% ascorbic acid in 0.9% saline. All drugs except for 6-hydroxydopamine were administered in a volume of 1.0 ml/kg body weight, with all doses expressed as the free base.

3. Results

Morphine (3.0 mg/kg) produced slight turning ($F(7,15) = 2.15$, $P = 0.014$), while 1.0 mg/kg amphetamine produced slightly more turning that peaked at 42 turns/15 min for the first 45 min after administration, then tapered off over 3 h ($F(7,15) = 9.01$, $P < 0.0001$) (Fig. 1A). The administration of 3.0 mg/kg morphine with 1.0 mg/kg amphetamine produced a large increase in turning, with a maximum of 108 turns/15 min, 75 min after administration. A two-way ANOVA with repeated measures on both factors revealed a significant main effect of drug treatment ($F(2,14) = 20.7$, $P < 0.0001$) and of time ($F(15,105) = 16.9$, $P < 0.0001$), as well as a significant interaction between treatment and time ($F(30,210) = 6.92$, $P < 0.0001$). At 30 and 45 min, turning produced by the combination was significantly greater than turning produced by morphine alone. From 60 to 135 min, turning produced by the combination was significantly greater than turning produced by either morphine or amphetamine alone.

Morphine (3.0 mg/kg) did not produce a detectable change from baseline in extracellular dopamine levels in the intact striatum of nigrally-lesioned rats ($F(4,19) = 1.10$, NS) (Fig. 1B). Amphetamine (1.0 mg/kg) produced significant increases in dopamine release ($F(4,19) = 40.6$, $P < 0.0001$). Dopamine levels peaked at 125 nM 30 min after administration, and were significantly greater than baseline levels from 30 to 90 min after administration. A two-way ANOVA with repeated measures on time revealed a significant main effect of drug treatment ($F(2,12) = 8.26$, $P = 0.006$) and of time ($F(15,180) = 32.5$, $P < 0.0001$), as well as a significant interaction between treatment and time ($F(30,180) = 9.59$, $P < 0.0001$). At no time point did the combination of morphine and amphetamine produce extracellular dopamine levels greater than amphetamine alone did.

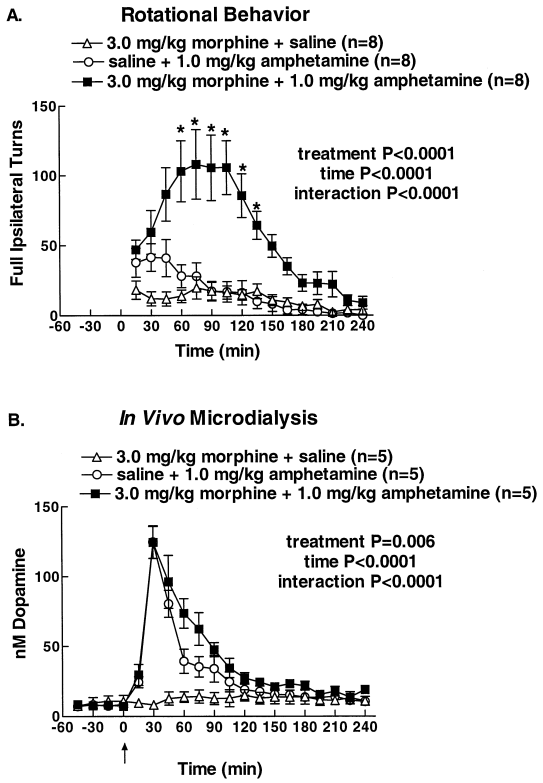

Fig. 1. (A) Time-course of turning produced by 3.0 mg/kg morphine, 1.0 27 mg/kg amphetamine, and the combination. The combination produced more turning than either morphine or amphetamine alone. A two-way ANOVA (treatment×time) with repeated measures on both factors showed a significant main effect of both treatment and time, as well as a significant interaction. Asterisk, * combination greater than amphetamine alone, $P < 0.05$. (B) Striatal dopamine levels measured after the administration of 3.0 mg/kg morphine, 1.0 mg/kg amphetamine, or the combination. A two-way ANOVA (treatment×time) with repeated measures on time showed a significant main effect of both treatment and time, as well as a significant interaction. At no time point did the combination of morphine and amphetamine produce extracellular dopamine levels greater than amphetamine alone.

The higher dose of morphine (10 mg/kg) produced slight turning similar to the lower dose (3.0 mg/kg) ($F(7,15) = 3.57$, $P < 0.0001$) (Fig. 2A). The amphetamine curve is reproduced from Fig. 1a. The administration of 10 mg/kg morphine with 1.0 mg/kg amphetamine produced turning that was not significantly different from the turning produced by amphetamine alone. A two-way ANOVA with repeated measures on both factors revealed a significant main effect of time ($F(15,105) = 10.1$, $P < 0.0001$), as well as a significant interaction ($F(30,210) = 2.24$, $P = 0.001$), but not a significant main effect of treatment ($F(2,14) = 1.84$, NS).

Morphine (10 mg/kg) produced a slight increase in extracellular dopamine levels in the intact striatum of nigrally-lesioned rats ($F(4,19) = 2.96$, $P < 0.0001$) (Fig. 2B), with a peak at 105 min after administration. The amphetamine curve was reproduced from Fig. 1B. A two-way ANOVA with repeated measures on time revealed a significant main effect of drug treatment ($F(2,12) = 36.3$, $P < 0.0001$) and of time ($F(15,180) = 49.8$, $P < 0.0001$), as well as a significant interaction between treatment and time ($F(30,180) = 16.6$, $P < 0.0001$). The combination of 10 mg/kg morphine and 1.0 mg/kg amphetamine at 15, 30 and 90 min produced greater increases in extracellular dopamine than morphine alone did. From 45 to 75 min, the combination of morphine and amphetamine produced extracellular dopamine levels greater than amphetamine alone did.

To examine the rotational behavior and microdialysis data further, we performed area under the curve analyses on the data presented in Figs. 1 and 2. Fig. 3A shows the area under the curve for the rotational behavior and the microdialysis data for the groups that received 3.0 mg/kg morphine, 1.0 mg/kg amphetamine, or the combination. A one-way ANOVA revealed a significant difference between the effects of the drug treatments upon turning ($F(2,14) = 18.7$, $P < 0.0001$) and upon dopamine levels ($F(2,12) = 7.51$, $P = 0.008$). For turning, a post-hoc test

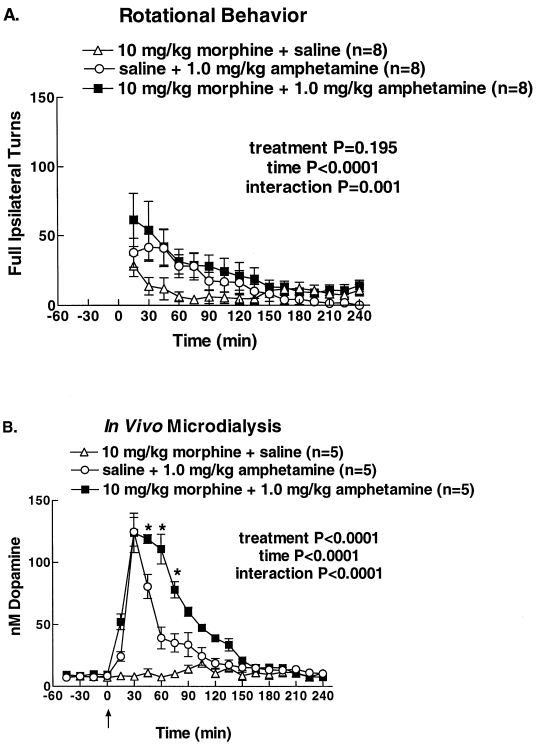

Fig. 2. (A) Time-course of turning produced by 10 mg/kg morphine, 1.0 mg/kg amphetamine, and the combination. The combination did not produce more turning than either morphine or amphetamine alone. A two-way ANOVA (treatment×time) with repeated measures on both factors showed a significant main effect of time and a significant interaction, but not a significant main effect of treatment. Asterisk, * combination greater than amphetamine alone, $P < 0.05$. At no time point did the combination of morphine and amphetamine produce turning greater than amphetamine alone. (B) Striatal dopamine levels measured after the administration of 10 mg/kg morphine, 1.0 mg/kg amphetamine (as shown in Fig. 1b), or the combination. A two-way ANOVA (treatment× time) with repeated measures on time showed a significant main effect of both treatment and time, as well as a significant interaction. Asterisk, * combination greater than amphetamine alone, $P < 0.05$.

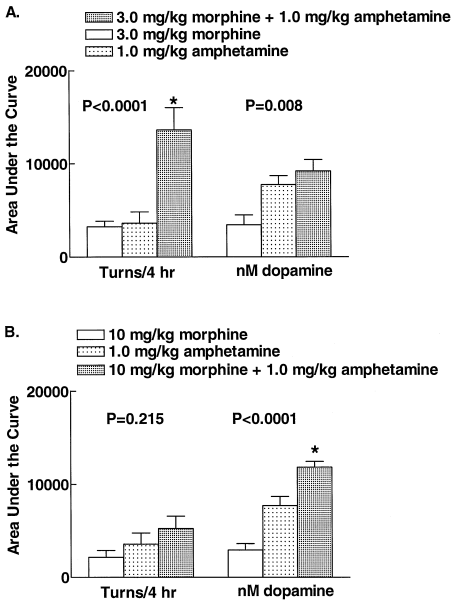

Fig. 3. (A) Area under the time-course curve of turning and dopamine levels following treatment with 3.0 mg/kg morphine, 1.0 mg/kg amphetamine, and the combination. One-way ANOVAs showed a significant difference among the effects of 3.0 mg/kg morphine, 1.0 mg/kg amphetamine, and the combination upon turning and upon dopamine levels. Asterisk, * combination greater than amphetamine alone, $P < 0.05$. (B) Area under the time-course curve of turning and dopamine levels following treatment with 10 mg/kg morphine, 1.0 mg/kg amphetamine (as shown in A), and the combination. One-way ANOVAs showed a significant difference among the effects of 10 mg/kg morphine, 1.0 mg/kg amphetamine, and the combination upon dopamine levels, but not upon turning. Asterisk, * combination greater than amphetamine alone, $P < 0.05$.

revealed that the area under the curve for the 3.0 mg/kg morphine and 1.0 mg/kg amphetamine combination was significantly greater than the area under the curve for amphetamine alone. Fig. 3B shows the area under the curve for the rotational behavior and the microdialysis data in the groups that received 10 mg/kg morphine, 1.0 mg/kg amphetamine, or the combination. A one-way ANOVA revealed a significant difference between the effects of the drug treatments upon dopamine levels ($F(2,12) = 32.2$, $P < 0.0001$), but not upon turning ($F(2,14) - 1.72$, NS). A post-hoc test revealed that the area under the curve of the combination of 10 mg/kg morphine and 1.0 mg/kg amphetamine was significantly greater than the area under the curve of amphetamine alone for the microdialysis data. These analyses confirmed the results determined by analyzing the time-course data using two-factor ANOVAs; 3.0 mg/kg morphine significantly potentiated amphetamine-induced turning, while 10 mg/kg morphine significantly potentiated amphetamine-induced dopamine release in the striatum.

4. Discussion

In this study, we found that while 3.0 mg/kg morphine alone and 1.0 mg/kg amphetamine alone produced low amounts of turning in nigrally-lesioned rats and that the combination produced large, significant amounts of turning that lasted for 4 h. These data agree with those found in earlier studies in this laboratory, in which 3.0 mg/kg morphine potentiated amphetamine-induced turning (Kimmel and Holtzman, 1997). In contrast, 10 mg/kg morphine combined with 1.0 mg/kg amphetamine produced turning that was not different from the turning produced by this dose of amphetamine alone. The high, but not the low, dose of morphine altered amphetamine-induced increases in striatal dopamine levels; however, these changes did not parallel those observed in turning.

In earlier studies, Di Chiara and Imperato (1988a,b) found that 10 mg/kg morphine produced a 175% increase in extracellular striatal dopamine from baseline, while Shoaib et al. (1995) found that 10 mg/kg morphine produced a 225% increase in extracellular accumbens dopamine from baseline, both in unlesioned rats. The results of the present study corroborate these earlier findings, showing that 10 mg/kg morphine produced a change in striatal dopamine levels from a baseline of 8.1 nM to a maximum of 18.6 nM, a 230% difference. We also found an overall significant effect of 10 mg/kg, but not of 3.0 mg/kg morphine, on extracellular dopamine release.

In contrast to morphine, amphetamine (1.0 mg/kg) produced a peak effect of 125 nM extracellular dopamine in the striatum 30 min after administration. The peak of striatal dopamine release preceded the peak of turning (42 turns) by 15 min. This finding agrees with that of Clausing et al. (1996), in which the peak of extracellular dopamine after the administration of 2.5 mg/kg amphetamine preceded the peak of amphetamine-induced turning by 20 min. Similarly, the effect of amphetamine on dopamine release lasted about 120 min, while the effect on turning lasted about 150 min. These data suggest there is a delay between the increase in dopamine release and the onset of turning, as well as the cessation of dopamine release (above baseline) and turning.

Other investigators have noted that although dopamine plays a clear role in amphetamine-induced behaviors, no simple relationship appears to exist between the quantitative features of the dopamine response to amphetamine and the appearance of specific drug-induced behaviors (Segal and Kuczenski, 1994). The results of the present study support this observation. One reason for the disparity between microdialysis and behavioral results may be due to the fact that present microdialysis techniques cannot follow rapid fluctuations in extracellular neurotransmitters levels (Westerink and Justice, 1991).

Our results suggest that the potentiation of amphetamine-induced turning in nigrally lesioned rats by morphine is not due to changes in extracellular striatal dopamine levels. Three mg/kg morphine clearly potentiated turning induced by 1.0 mg/kg amphetamine, but this dose of morphine did not potentiate amphetamine-induced increases in extracellular dopamine. Conversely, 10 mg/kg

morphine potentiated the amphetamine-induced increase in extracellular dopamine, but this dose of morphine did not potentiate amphetamine-induced turning. One caveat of this study is that the higher dose of morphine combined with amphetamine may have impaired the motor function of the rats. Drugs that produce motor activity, such as amphetamine, caffeine, and cocaine often have biphasic effects, due to the stereotypy produced at high doses (Garrett and Holtzman, 1996; Jones et al., 1993; Jones and Holtzman, 1994).

Increasing extracellular dopamine levels are a prerequisite for demonstrating an interaction between morphine and drugs that affect dopamine transporters. The experimental procedures used in this study examined the effect of drugs upon the nigrostriatal dopamine system. However, the mesolimbic dopamine system, projecting from the ventral tegmental area to the nucleus accumbens, is also involved in turning (Pycock and Marsden, 1978). The synergistic interaction between morphine and amphetamine on turning could be mediated by a potentiation of amphetamine-induced dopamine release in the nucleus accumbens. Systemic administration of morphine increased extracellular dopamine levels in the nucleus accumbens of the rat (Di Chiara and Imperato, 1988a,b; Pothos et al., 1991; Shoaib et al., 1995). Drugs that increase dopamine release in the accumbens have also been found to increase locomotor activity (Kalivas and Stewart, 1991), and may also increase turning. Nonetheless, this is the first report that we are aware of to show that morphine potentiates amphetamine-induced dopamine release in the striatum.

Acknowledgements

This research was supported by Grant DA00541, Research Scientist Award K05 DA00008, and NRSA Predoctoral Fellowship F31 DA05692-01, all from the National Institute on Drug Abuse, National Institutes of Health.

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