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Opioid Modulation of Amphetamine-Stimulated Dopamine Release and Concentration in Rat Striatal Slices

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KOLTA, M. G. AND M. T. BARDO. *Opioid modulation of amphetamine-stimulated dopamine release and concentration in rat striatal slices.* PHARMACOL BIOCHEM BEHAV 46(4) 819–825, 1993.—The effects of morphine and naltrexone on amphetamine-stimulated release and total concentration of dopamine (DA) from rat striatal slices in vitro were examined in this study. Adult male Sprague–Dawley rats were sacrificed and the striata were dissected, sliced, and then incubated in buffer solution at 37°C with amphetamine in the presence or absence of various concentrations of morphine, naltrexone (or both), or the dihydroxyphenylalanine (DOPA) decarboxylase inhibitor (NSD-1015). The concentrations of DOPA, DA, and dihydroxyphenylacetic acid (DOPAC) in the tissue slices and buffer media were measured by HPLC/EC. Amphetamine enhanced DA release and also increased total DA concentration. However, neither morphine nor naltrexone alone altered DA concentration in the media or tissue slices relative to control (no drug added). Moreover, neither morphine nor naltrexone at 1, 10, or 100 μM altered amphetamine-stimulated DA release. However, morphine (1 or 10 μM) inhibited the amphetamine-stimulated increase in total concentration of DA. This effect of morphine was blocked by naltrexone. NSD-1015 alone or in combination with morphine did not alter amphetamine-stimulated DA release, but significantly reduced DA concentration in striatal slices. NSD-1015 alone also increased DOPA accumulation in both media and tissue slices, and this effect was inhibited by the addition of morphine. These results indicate that morphine inhibits the amphetamine-stimulated increase in total DA content, but not the amphetamine-stimulated release of DA.

Opioid Amphetamine Endogenous dopamine In vitro Rat Striatum

THE endogenous opioid system is thought to modulate dopaminergic activity in various areas of the brain. Opioid peptides are located within both the nigrostriatal and mesolimbic regions (16), and opiate receptors have been localized on the DA neurons within these regions (27,28). It has been shown that the administration of opioids to rats produces an increase in the firing rate of DA neurons within the substantia nigra and ventral tegmental area (17,23), as well as an increase in the release and turnover rate of DA within the terminal fields (8,35). These neurochemical effects, which are reversed by naloxone, are thought to involve an indirect action of opioids on GABAergic interneurons (10,19).

Recent evidence indicates that the effects of the DA agonist amphetamine may be altered by opioids. Behavioral studies have shown that opiate antagonists reverse the locomotor-activating effects of amphetamine (31,32), and it has been hypothesized that this effect may reflect an attenuation in the release of DA produced by amphetamine. While the stimulatory effect of amphetamine on DA release has been well characterized both in vivo and in vitro (9,18,20), little is known presently regarding the effect of opioids on amphetamine-stimulated DA release. In one study, however, naloxone has been shown to decrease amphetamine-stimulated DA release in vivo in the caudate nucleus of cats (7).

The present investigation examined the effects of morphine and naltrexone on amphetamine-stimulated DA release from rat striatal slices in vitro. This preparation has been used extensively to assess the effects of opioids on release of DA evoked by potassium, glutamate, and nicotine (5,22,34), but not on the release of DA evoked by amphetamine. In addition to measuring DA release, we also assessed the effect of opiates on DA synthesis and metabolism in this preparation.

METHOD

Animals

Adult male Sprague–Dawley rats (Harlan Sprague–Dawley, Indianapolis, IN) were used in this study. Animals were individually housed in a controlled environment of 25 ± 1°C temperature and 12L : 12D cycle (light on at 0700). Rats were

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provided with food (Purina Lab Chow, St. Louis, MO) and water ad lib throughout the experimental period.

General Neurochemical Procedures

On the day of the experiment, animals were sacrificed by decapitation and the striata were dissected on an ice-cold plate, as previously described (14). The striata were sliced into 0.3 × 0.3 mm sections using a McIlwain tissue chopper. All of the tissue slices from one rat were dispersed in 1.0 ml ice-cold Krebs-Ringer-Hepes buffer medium. This buffer was made of the following composition (mM): NaCl (118), KCl (4.8), $CaCl \cdot 2H_2O$ (1.3), $MgSO_4 \cdot 7H_2O$ (1.2), KH_2PO_4 (1.2), EDTA (0.03), ascorbic acid (0.6), Hepes (22.0), and D-glucose (11.0). The buffer was aerated on ice for 15 min with 95% O_2 plus 5% CO_2, then the pH was adjusted to 7.2 using 3.0 M Tris solution. The slices were washed with 1.0 ml ice-cold buffer and centrifuged at 2000 × *g* for 2 min. The supernatant was discarded and the slices were then resuspended in ice-cold buffer. The final incubation volume was 1.0 ml of which 890 or 900 μl was medium containing tissue slices and the remaining 110 or 100 μl was the buffer containing the appropriate drug. All of the tissue slices from one rat were exposed to only one drug treatment, with a minimum of six rats used per treatment.

In all of the experiments described below, tissue slices were preincubated for 2 min at 37°C in a shaker water bath before the appropriate drug was added to the medium. At the completion of incubation, samples were placed on ice and then the medium was separated from the tissue slices by centrifugation for 5 min at 5000 × *g* and 4°C. The supernatant was transferred to another tube containing 10.0 μl of concentrated $HClO_4$ to give a final concentration of about 0.1 N. The pellets (tissue slices) were homogenized by sonication in 1.0 ml of 0.1 N $HClO_4$, centrifuged for 10 min at 40,000 × *g* and 4°C. The supernatants were separated and all samples were kept at −70°C until analysis.

Sample Preparation for Dopamine Assay

The concentrations of DA, its precursor DOPA, and its acidic metabolite DOPAC in tissue slices and media were determined by high performance liquid chromatography (HPLC) as described elsewhere (30). The HPLC system (Bioanalytical Systems, West Lafayette, IN) consisted of an LC-304-T Liquid Chromatograph coupled with an electrochemical detector and connected to a temperature-controlled (25°C) ODS, C-18 column (5 μm, 4.6 × 250 mm). An aliquot of 20 μl from each sample was injected directly onto the column and the system was run at a flow rate of 1.5 ml/min at operating potential of +650 mV. The amounts of DOPA, DA, and DOPAC in each sample were calculated using external standards that were assayed daily. The final concentrations were based on the tissue wet weight (g).

Drugs

The opioid agonist, morphine sulfate, and opioid antagonist, naltrexone HCl, were obtained from the National Institute on Drug Abuse (NIDA). The dopamine agonist, *d*-amphetamine sulfate, and the DOPA-decarboxylase inhibitor, *m*-hydroxybenzylhydrate HCl (NSD-1015), were purchased from Sigma Chemical Company (St. Louis, MO).

Experimental Design

The first experiments were designed to determine the in vitro effects of amphetamine (1 or 10 μM), morphine (1, 10, or 100 μM), and naltrexone (1, 10, or 100 μM) on the release of endogenous DA. Each drug was assessed separately in an independent experiment. After a 2-min preincubation period, tissue slices were incubated for 15 min with one dose of the drug or with an equivalent volume of buffer. Dopamine concentrations were then measured in both medium and tissue slices.

The second experiment was designed to determine whether morphine or naltrexone alone or in combination would alter amphetamine-induced DA release. Striatal slices were incubated with either: a) buffer (control, no drug), b) amphetamine alone (10 μM), c) morphine (1, 10, or 100 μM) + amphetamine (10 μM), d) naltrexone (1, 10, or 100 μM) + amphetamine (10 μM), or e) morphine (1, 10, or 100 μM) + naltrexone (10 μM) + amphetamine (10 μM). The incubation period with naltrexone was for 2 min, followed by morphine for 5 min. After this, amphetamine was added and the incubation was continued for an additional 15 min and DA concentrations were determined in both medium and tissue slices as described above.

The third experiment was designed to study the effect of morphine on amphetamine-stimulated striatal DA synthesis and metabolism as measured by the accumulation of DOPA and DOPAC in the presence of NSD-1015. Striatal slices were incubated with either: a) buffer (control, no drug), b) NSD-1015 alone (200 μM), c) NSD-1015 (200 μM) + amphetamine (10 μM), d) NSD-1015 (200 μM) + morphine (10 μM), or e) NSD-1015 (200 μM) + morphine (10 μM) + amphetamine (10 μM). The incubation period with NSD-1015 was for 5 min, followed by another 5 min with morphine, then for an additional 15 min after amphetamine was added to the medium. The concentrations of DOPA, DA, and DOPAC were measured in both the medium and tissue slices.

Statistical Analysis

Data from all experiments were analyzed using analyses of variance (ANOVA). For the overall effect, significant differences were determined by *F*-tests. Subsequent comparison between individual means were performed using Tukey's, Newman-Keuls' and two-tail LSD test of significance.

RESULTS

Effect of Amphetamine, Morphine, or Naltrexone Alone on DA Release

Figure 1 (A–C) presents the results of the experiment assessing the ability of amphetamine, morphine, or naltrexone to release DA. When striatal tissue slices were incubated with amphetamine (Fig. 1A), there was a dose-dependent release of DA into the medium. Total DA concentration (medium + tissue slices) was significantly higher ($p < 0.05$) following 10 μM than 1 μM amphetamine or control (no drug added), indicating that DA synthesis may have been enhanced by the highest concentration of amphetamine. Data obtained from the morphine and naltrexone experiments are presented in Fig. 1B and C, respectively. Neither morphine nor naltrexone alone altered the release or total content of DA as measured by the amount recovered from the medium and tissue slices when compared to controls (no drug added).

Effect of Morphine and Naltrexone on Amphetamine-Stimulated DA Release

Figure 2 shows the results of the experiment assessing the effect of morphine on amphetamine-stimulated DA concen-

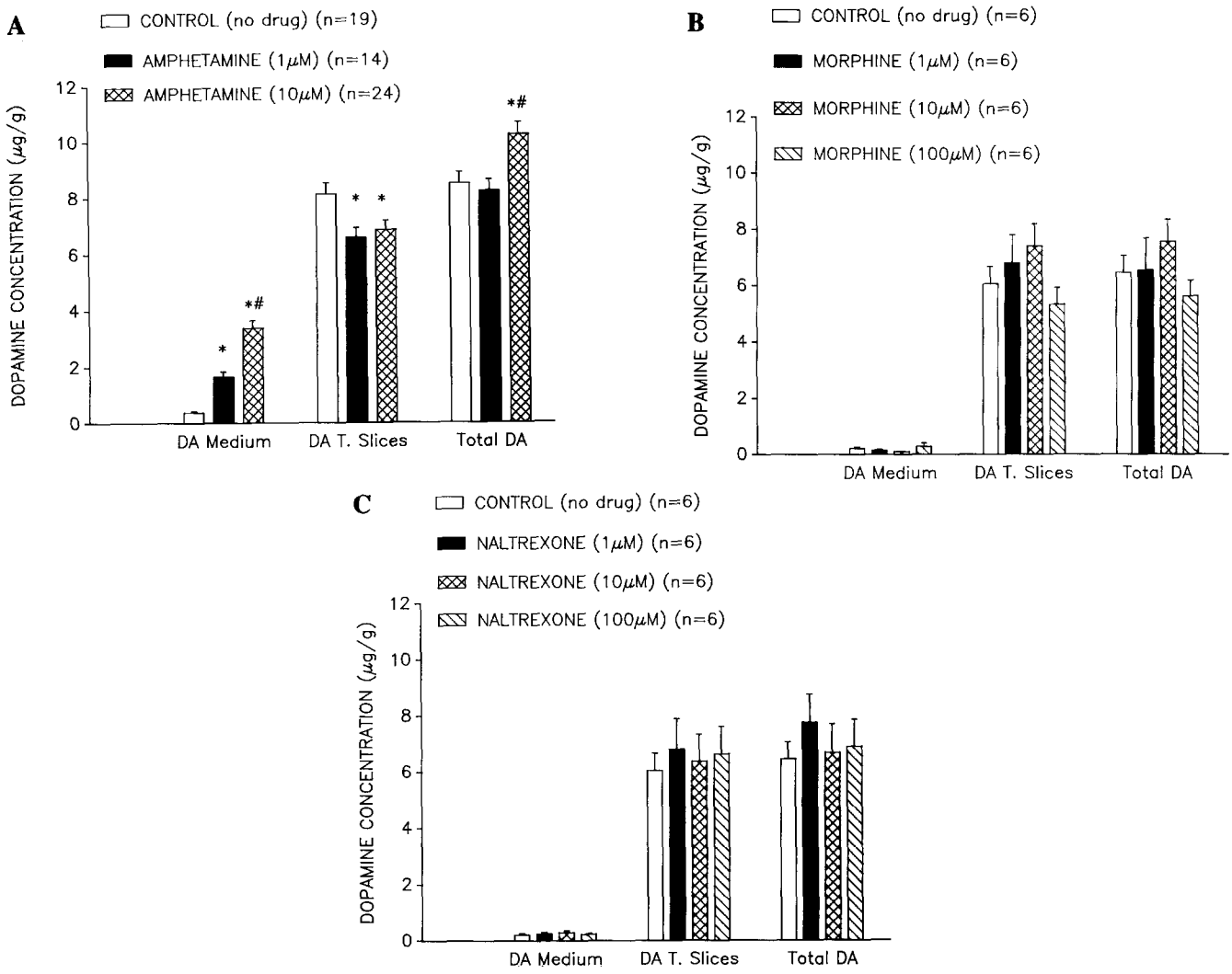

FIG. 1. Effect of amphetamine (A), morphine (B), or naltrexone (C) on striatal DA concentration (μg/g tissue). Each bar represents the mean ± SEM; n = animals/treatment. Significant difference between treatments: *from control, $p < 0.05$, and #from 1 μM amphetamine, $p < 0.05$.

tration in striatal tissue slices. Morphine at a concentration of 1, 10, or 100 μM did not alter amphetamine-stimulated endogenous DA release into the medium (Fig. 2), although there was a clear tendency for 1 and 10 μM morphine to reduce the amphetamine-stimulated DA release ($p < 0.10$). Morphine at 1 and 10 μM did reduce the DA concentration in the slices, as well as blocking amphetamine-stimulated increase in total DA content. The highest concentration of morphine (100 μM) also tended to reduce the amphetamine-stimulated increase in total DA content, but this effect did not reach statistical significance.

Figure 3 shows the effect of naltrexone on amphetamine-stimulated DA concentration in striatal slices. Similar to morphine, there was no significant effect of naltrexone on amphetamine-stimulated DA release into the medium. Naltrexone at 1 or 10 μM in combination with amphetamine was also without any significant effect on DA concentration in both tissue slices and total DA concentration when compared to amphetamine alone, although in both cases there was a strong trend for naltrexone to enhance the effect of amphetamine. The highest concentration of naltrexone (100 μM) combined with amphetamine significantly reduced DA concentration in the tissue slices when compared to control. In addition, 100 μM naltrexone blocked the effect of amphetamine-stimulated increase in total DA concentration, although this treatment did not differ significantly from either controls or amphetamine alone.

Figure 4 shows the effect of amphetamine (10 μM) on DA concentration of striatal tissue slices incubated sequentially with naltrexone and morphine. Morphine at 1 and 10 μM in the presence of 10 μM naltrexone enhanced amphetamine-induced DA release into the medium as compared to either controls or amphetamine alone. When the slices were exposed to the high concentration of morphine (100 μM) and 10 μM naltrexone, amphetamine-induced DA release from these slices was similar to that produced by amphetamine alone. Furthermore, the highest concentration of morphine (100 μM) in combination with naltrexone and amphetamine also re-

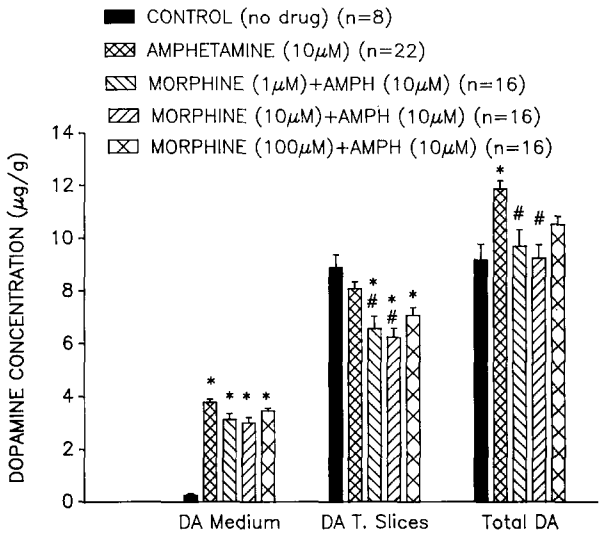

FIG. 2. Effect of morphine on amphetamine-stimulated striatal DA concentration (μg/g tissue). Each bar represents the mean ± SEM; *n* = animals/treatment. Significant difference between treatments: *from control, $p < 0.05$, and #from amphetamine alone, $p < 0.05$.

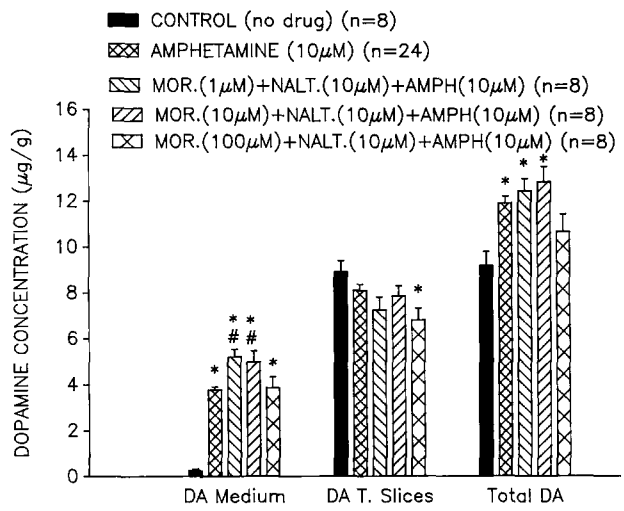

FIG. 4. Effect of naltrexone and morphine on amphetamine-stimulated striatal DA concentration (μg/g tissue). Each bar represents the mean ± SEM; *n* = animals/treatment. Significant difference between treatments: *from control, $p < 0.05$, and #amphetamine alone, $p < 0.05$.

duced DA concentration in the tissue slices compared to control. More important, the amphetamine-stimulated increase in total DA concentration was not significantly altered by the combination of morphine (1 or 10 μM) and naltrexone. The highest concentration of morphine (100 μM) with naltrexone did tend to reduce the amphetamine-stimulated increase in total DA concentration to the control levels, and this treatment did not differ significantly from amphetamine alone as well.

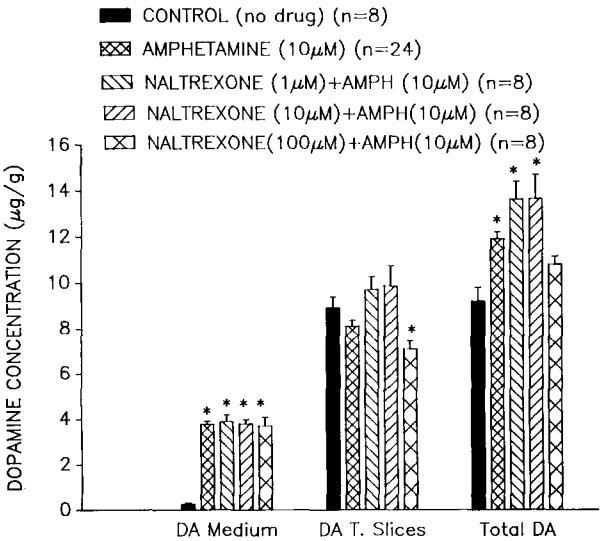

FIG. 3. Effect of naltrexone on amphetamine-stimulated striatal DA concentration (μg/g tissue). Each bar represents the mean ± SEM; *n* = animals/treatment. Significant difference between treatments: *from control at $p < 0.05$.

Effect of Morphine and Amphetamine on DOPA Accumulation and DOPAC

Table 1 shows that when tissue slices were incubated with 200 μM NSD-1015 alone, DA concentration in the medium was increased compared to control. In contrast, NSD-1015 alone decreased DA concentration in the striatal slices, as well as the total DA concentration (medium + tissue slices). Similar results were obtained when morphine (10 μM) was added to the medium in the presence of NSD-1015. Table 1 also shows that even in the presence of NSD-1015, amphetamine stimulated the release of DA into the medium, and this effect of amphetamine was not altered by the presence of morphine.

Table 2 shows that 200 μM of NSD-1015 alone increased DOPA accumulation in both the medium and tissue slices when compared to control. Morphine produced a significant inhibition in DOPA accumulation in tissue slices and total DOPA concentration recovered from both medium + slices. In contrast, the presence of amphetamine with NSD-1015 or in combination with morphine and NSD-1015 was without significant effect compared to NSD-1015 alone.

The concentration of DOPAC in the tissue slices and total content were significantly reduced ($p < 0.05$) in response to NSD-1015 alone. However, neither morphine nor amphetamine, alone or in combination, altered the effect obtained with NSD-1015 alone (data not shown).

DISCUSSION

There are three major points that may be derived from the results of the present study. First, as expected, amphetamine was shown to stimulate the release of striatal DA into the buffer medium in a concentration-dependent manner. This enhanced release into the medium was accompanied by an increase in the total concentration of DA recovered from the medium and tissue slices. Second, while morphine had no significant effect on the amphetamine-stimulated release of DA into the medium, morphine did prevent the amphetamine-stimulated increase in total DA concentration. This effect of

TABLE 1

EFFECT OF MORPHINE ON AMPHETAMINE-STIMULATED STRIATAL DA CONCENTRATIONS (μg/g) IN THE PRESENCE OF NSD-1015

Drug	*n*	Medium	Tissue Slices	Total
None (no drug added)	8	0.58 ± 0.06	10.56 ± 0.51	10.76 ± 0.84
NSD-1015 (200 uM)	12	1.58 ± 0.12*	5.41 ± 0.18*	6.98 ± 0.15*
NSD-1015 (200 uM) + amphetamine (10 uM)	12	3.63 ± 0.29*†	3.98 ± 0.21*†	7.61 ± 0.47*
NSD-1015 (200 uM) + morphine (10 uM)	8	1.88 ± 0.28*	4.90 ± 0.41*	6.78 ± 0.53*
NSD-1015 (200 uM) + morphine (10 uM) + amphetamine (10 uM)	8	3.51 ± 0.28*†	3.96 ± 0.22*†	7.48 ± 0.46*

Each value represents the mean ± SEM; *n* = animals/treatment.
*†Significant difference between treatments: *from control, $p < 0.05$ and †from NSD-1015 alone, $p < 0.05$.

morphine was blocked by naltrexone, demonstrating that opiate receptors are involved. Third, in the presence of a DOPA decarboxylase inhibitor (NSD-1015), morphine was shown to reduce the accumulation of DOPA, while having no significant effect on its metabolite DOPAC. This latter finding suggests that, in the in vitro slice preparation used in the present study, the ability of morphine to prevent the amphetamine-stimulated increase in total DA concentration involves an action on the synthesis of DA, rather than on the metabolism of DA.

The exact mechanism of opioid interaction with the dopaminergic system is not completely clear. It has been shown that dopamine-containing neurons overlap with both proenkephalin- and prodynorphin-derived opioid peptides in various regions of the CNS, including the striatum (6,12,24,37). Further, studies have demonstrated that at least three subtypes of opioid receptors exist in the rat striatum, namely the mu, delta, and kappa (26). Activation of these opioid receptor subtypes by various selective agonists has been shown to alter the function of central dopaminergic systems in different ways (36). For example, it has been demonstrated that mu- and delta-selective agonists enhance DA turnover rate in the rat striatum, as reflected by an increased level of DA metabolites (36). Morphine and some other opioid agonists have also been shown to stimulate DA synthesis, as well as the firing rate of dopaminergic neurons (1,13,15). Furthermore, kappa receptor agonists such as U-50,488H, bremazocine, and tifluadom have been shown to decrease DA released in the dorsal caudate and nucleus accumbens of freely moving rats (8). This effect was reversed by naloxone, but only at high doses. Using the rat striatal slice preparation, it has also been shown that kappa agonists such as dynorphin A and ketocyclozocine inhibit K^+-stimulated [^{3}H]DA release. Similarly, U-50,488H, a kappa-selective agonist, inhibits the release of [^{3}H]DA from rat and guinea pig striatal slices in response to 20 mM K^+ (33). This effect is partially blocked by the administration of naloxone. However, selective mu and delta receptor agonists are without effect on [^{3}H]DA from the same preparation. These data, along with our findings, suggest that mu receptor activating agents may influence the rate of DA synthesis, while kappa receptor agonists may modulate the release process of DA.

An increasing number of studies have confirmed that the central stimulant effect of amphetamine is due to an increase in dopaminergic neurotransmission, including facilitating DA release and synthesis, as well as blocking its reuptake and metabolism. The ability of amphetamine to enhance DA re-

TABLE 2

EFFECT OF MORPHINE ON AMPHETAMINE-STIMULATED DOPA ACCUMULATION (μg/g) IN THE PRESENCE OF NSD-1015

Drug	*n*	Medium	Tissue Slices	Total
None (no drug added)	8	0.28 ± 0.04	0.08 ± 0.003	0.03 ± 0.04
NSD-1015 (200 uM)	12	5.36 ± 0.19*	3.25 ± 0.12*	8.53 ± 0.28*
NSD-1015 (200 uM) + amphetamine (10 uM)	12	5.63 ± 0.49*	3.09 ± 0.15*	8.81 ± 0.59*
NSD-1015 (200 uM) + morphine (10 uM)	8	4.93 ± 0.15*	2.73 ± 0.13*†	7.65 ± 0.26*†
NSD-1015 (200 uM) + morphine (10 uM) + amphetamine (10 uM)	8	5.15 ± 0.22*	3.01 ± 0.43*	8.16 ± 0.43*

Each value represents the mean ± SEM; *n* = animals/treatment.
*†Significant difference between treatments: *from control, $p < 0.05$ and †from NSD-1015 alone, $p < 0.05$.

lease has been attributed to its interaction with the uptake system of DA neurons, resulting in a greater release of DA (4,20,21,38). Since morphine in the present study did not alter amphetamine-stimulated DA release, it may be suggested that this mu-opioid agonist does not interfere with the proposed action of amphetamine on DA release.

Several mechanisms regulating DA synthesis in dopaminergic neuronal systems have been described. One mechanism may involve end product feedback inhibition in which the increased levels of DA intraneuronally will inhibit the activity of tyrosine hydroxylase, the rate-limiting step in DA synthesis (3). As the level of DA is reduced by release and metabolism, there is a removal of the enzyme inhibition, with a subsequent enhancement in DA synthesis. Another mechanism thought to be involved in regulating DA synthesis and/or release is related to DA autoreceptors that are located on dopaminergic presynaptic nerve terminals in the striatum (25). These receptors may become saturated when continuously stimulated by DA, thus resulting in the inhibition of DA synthesis and release due to suppression of nerve activity. However, after the level of DA in the synaptic cleft is reduced, stimulation of these autoreceptors is also decreased, leading to an enhanced synthesis and release of DA.

The effects of amphetamine-stimulated DA synthesis appear to be complex, probably involving more than one mechanism. The presence of a high concentration of enkephalin binding sites in the striatum (2,26), as well as enkephalin-containing striatal neurons (11,29), supports our finding of a modulatory role of opioids in amphetamine-stimulated DA synthesis in this region. Furthermore, it has been demonstrated that enkephalinergic neurons terminate on presynaptic dopaminergic nerve terminals in the striatum (28). It may be speculated that activation of these presynaptic opioid receptors may enhance the sensitivity of DA autoreceptors regulating its synthesis. Alternatively, however, the present study cannot rule out the possibility that morphine may also have a direct inhibitory action on tyrosine hydroxylase activity.

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