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Naltrindole, a δ-Opioid Antagonist, Blocks MDMA's Ability to Enhance Pressing for Rewarding Brain Stimulation

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REID, L. D., C. L. HUBBELL, J. TSAI, M. D. FISHKIN AND C. A. AMENDOLA. *Naltrindole, a δ-opioid antagonist, blocks MDMA's ability to enhance pressing for rewarding brain stimulation.* PHARMACOL BIOCHEM BEHAV 53(2) 477–480, 1996.—Twelve rats were each fixed with a chronically indwelling bipolar electrode for stimulation of the medial forebrain bundle as it courses through the hypothalamus. These rats were trained to press a bar for intracranial stimulation of 0.3-s trains of 60 Hz sine waves for 10 min daily at three intensities. One intensity was just above threshold for maintaining pressing, one intensity was a high intensity that sustained considerable pressing, but not maximum pressing, and the other was intermediate to the others. After stable rates of pressing were obtained, rats received MDMA daily. MDMA significantly increased rates of pressing. Prior to a day when rats received MDMA, they also received an injection of naltrindole, a selective δ-opioid receptor antagonist. Naltrindole blocked MDMA's enhancement of pressing for reinforcing brain stimulation.

MDMA Naltrindole δ-Opioid receptor Drug reinforcement

METHYLENEDIOXYMETHAMPHETAMINE (MDMA, ecstasy, or XTC) is an addicting drug as manifest (a) by its reoccurring popularity as a recreational drug even though its use is illegal and known to be dangerous (1,16), and (b) by its activity in rats within procedures designed to assess addictive liability. MDMA, for example, readily establishes a conditioned place preference among rats (2–4,17) using procedures within which morphine establishes such a preference (14).

Naltrindole (NTI) is a selective δ-opioid receptor antagonist (10,15,19). Recently, NTI has been shown to block cocaine's ability to establish a conditioned place preference (9), to block cocaine's enhancement of pressing for rewarding intracranial stimulation (ICS) (6,13), and to modulate responding for IV injections of cocaine (12). NTI, at doses affecting cocaine's effects, however, does not reliably affect morphine's (4.0 mg/kg) ability to establish a place preference (6), morphine's (4.0 mg/kg) enhancement of pressing for ICS (6), or morphine's self-administration (12). These observations lead to the suggestion that NTI's selective antagonist effects (in terms of binding to a class of receptor) are, in turn, selective (in terms of indices of drug reinforcement) for kinds of addictive agents. This suggestion, however, should be taken cautiously because only a few doses of each kind of addictive agent have been assessed.

In addition to their propensity to be repeatedly self-administered, addictive drugs share a number of salient characteristics. One of those characteristics is that they enhance rats' pressing for rewarding ICS and reduce the threshold for intracranial reinforcement (5,8,11). MDMA characteristically shares this feature with other addictive agents [(7) and data presented here].

Because addictive agents enhance pressing for rewarding ICS and because this characteristic reflects a particularly relevant effect of addictive agents (8), rats' pressing for ICS can be used to assess germane effects of addictive agents (11). Here, we assessed NTI's effects on the ability of MDMA to facilitate rats' pressing for ICS.

There are no logical reasons, before the complete facts are known, to hypothesize that an opioid antagonist will modulate MDMA's addictive potential. MDMA is not apt to act di-

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rectly, for example, at opioid receptors (1). MDMA has been shown to increase dopamine levels in systems associated with the medial forebrain bundle (MFB) and that might be sufficient, according to current theory (18), to account for MDMA's reinforcement. There is also evidence that MDMA affects serotonergic processes. MDMA, for example, has been shown to be toxic to serotonergic neurons (1). Also, MDMA's ability to establish a place preference can be blocked by a 5-HT_3 antagonist (4). Thus, it is reasonable to theorize that MDMA produces an increment in serotonergic activity that, in turn, increases dopaminergic activity and, thus, increases activity in the MFB system. Increased activity of the MFB system can be considered as increased positive affect that, when arranged contingently, is positive reinforcement (4,18). It follows from this narrative that any opioidergic effects are apt to be superfluous to MDMA's addicting properties. Nevertheless, it has been shown that naloxone (7,8) and naltrexone (2) modulate MDMA's reinforcing properties. Also, here we show that a selective δ-opioid receptor antagonist is effective in blocking a relevant effect of MDMA.

METHOD

Subjects

The 12 subjects of these procedures were male, Sprague–Dawley rats purchased from Taconic Farms (Germantown, NY) when they weighed about 200 g. Upon arrival at the laboratory, each was housed individually with food and water always available. The vivarium was maintained at 22°C with 12 h of incandescent light a day beginning at 0800 h.

Subsequent to acclimation to the conditions of the laboratory, each rat was fixed, using standard procedures including deep anesthesia (11), with a chronically indwelling bipolar electrode for stimulation of the MFB as it courses through the lateral hypothalamus. The electrodes (Plastic One, Roanoke, VA, product No. MS 302/2) were insulated except at the cross section of their stimulating tips.

Apparatus

The rats were trained to press a bar, for direct electrical stimulation of tissue at the tip of the electrode, in a standard experimental space. The space was a 24 × 24 × 38 cm plastic box with a bar extending through one wall. The depression of the bar actuated a switch, thereby providing a signal for programming the events of ICS and for counting the rat's responding. ICS was delivered from the stimulator, through a slip-ring assembly, by way of flexible electrode leads. The arrangement allowed a rat complete freedom of movement within the box.

The ICS was 60-Hz sine waves of 0.3 s duration of varying intensities but always less than 50 μA, rms. Each bar press produced a single ICS except when the press occurred during an ICS. Although a bar press during an ICS did not lead to further ICS, the press was counted.

Drugs

MDMA [(±)-3,4-methylenedioxymethamphetamine HCl] was delivered in a physiological (0.9%) saline solution. NTI is 17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-6,7-2′,3′-indolomorphinan HCl. NTI's carrier was distilled water. Placebos for each drug were the carriers of each drug. MDMA was given in a dose of 2.0 mg/kg (SC) and NTI in a dose of 10.0 mg/kg (IP). All injections were 1.0 ml/kg. The dose of MDMA was chosen because it was known to reliably affect responding for ICS (7). The dose of NTI is a dose that reliably blocks cocaine's enhancement of pressing for ICS, but not that of morphine (6,13).

Procedure

Subsequent to the surgical implantation of the electrodes and during daily sessions lasting about 0.5 h, each rat was brought from its home to an experimental space, attached to the electrode leads, and trained to press the bar for ICS. After the rats learned to press for ICS, the intensity of ICS was varied to select three intensities of ICS: a low, a medium, and a high intensity. The low intensity was just above threshold for maintaining pressing. The high intensity was an intensity sustaining considerable pressing, but not maximum pressing. The medium intensity was intermediate to the others. The 50-μA limit to ICS was maintained throughout training, selection of intensities, and subsequent testing.

The intensities were individually selected for each subject, so they differed slightly across subjects. The mean value for low intensity was 12.0 μA, rms, with limits of the range of 8 and 20 μA. The mean value for medium intensity was 14.2 μA with limits of 9 and 23 μA. The mean value for high intensity was 16.0 μA with limits of 10 and 26 μA. The intensities produced 86.2 ± 14.0, 325.2 ± 34.6, and 713.6 ± 42.8 presses during 10 min, respectively, for low, medium, and high ICS (values are means ± SE of scores under influence of placebos, see below and Fig. 1).

With the selection of intensities, a daily regimen was established that remained constant throughout the balance of the procedures. Each day, during midafternoon, a rat was placed in a box with an opportunity to press for 5 min at the high, medium, low, low, medium, and high intensity, in that order (i.e., 10 min at each intensity). A period with each intensity began only after a rat had experienced the newly introduced intensity at least five times.

Rats were run daily until responding for intensities of ICS became stable. Each rat had at least five daily sessions before testing began under the influence of injections. After rate of pressing became stable across at least 3 days, rats received two injections of placebos daily for either 2 or 3 days (four subjects for 2 days, eight subjects for 3 days). The two injections were carriers of MDMA and NTI, respectively. Then rats were given injections of MDMA for either 5 or 6 days (four subjects for 5 days) and another injection. For the first and last days, the other injection was the placebo for NTI. During one of the middle days of the 5 or 6 days of MDMA, NTI was given.

Because (a) testing did not begin until rats' pressing rates were stable, (b) placebos produced no noticeable effects on the rats' pressing, and (c) it is desirable to reduce the data for presentation, the rats' mean rates of pressing for each intensity across all days of placebo and all days of MDMA preceding administration of NTI were taken as the best estimate of what rats' performances were without an active drug and with MDMA. The rats' performances subsequent to the injection of NTI were similar to that before the injections and are not represented here.

RESULTS

The results are summarized in Fig. 1 as mean presses for each intensity of ICS. The placebo scores are means across days immediately before injections of MDMA. The MDMA scores are means across the days following scores of placebos and before injections of NTI. The data of MDMA plus NTI are the scores of the day when rats received both drugs. Using

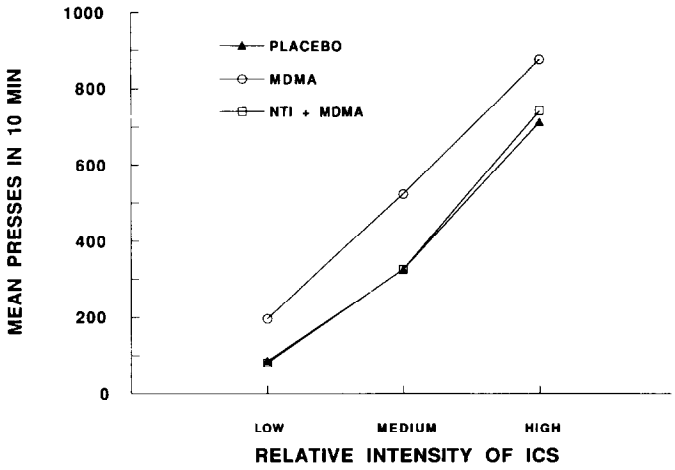

FIG. 1. Mean pressing for each of three intensities of intracranial stimulation (ICS) under each of three conditions of dosing. The placebo means are mean numbers of presses when rats received the placebos for each of the drugs. The means noted as MDMA reflect pressing when rats received MDMA, 2.0 mg/kg, and placebo for naltrindole (NTI). The means noted as MDMA + NTI reflect rats' rate of pressing when they were under the influence of both MDMA and NTI, 10.0 mg/kg.

these scores, the data conform to a 3 × 3 analysis of variance (ANOVA) for repeated measures having factors of the three intensities of ICS and the three drug conditions.

The ANOVA of the scores used to derive Fig. 1 yields $F(2, 22) = 112.0$, $p < 0.0001$ for the factor of intensity of ICS, thereby confirming that we did, indeed, arrange for three levels of pressing. The factor associated with the three drug conditions yields an $F(2, 22) = 18.0$, $p < 0.0001$. The interaction term of the ANOVA yields $F(4, 44) = 1.2$, $p = 0.33$, indicating that drugs' effects are not peculiar to an intensity of ICS.

An ANOVA using only the scores of placebo and MDMA yields an $F(1, 11) = 42.3$, $p < 0.0001$ for the factor of kind of injection, indicating that MDMA, similar to other addicting drugs, enhances pressing for MFB ICS. An ANOVA using only scores of placebos and MDMA plus NTI yields $F(1, 11) = 0.1$, $p = 0.80$, indicating that there is no basis for concluding that scores under the influence of MDMA plus NTI are different from scores under the influence of placebos. The F-value associated with the comparison of scores of MDMA to those of MDMA plus NTI is $F(1, 11) = 25.2$, $p = 0.0004$.

DISCUSSION

The results assessing the effects of NTI on enhanced pressing associated with MDMA are remarkably similar to results from assessing the effects of NTI on the enhanced pressing associated with cocaine. In both assessments, NTI blocked the stimulant's enhancement of pressing for ICS. The results lead to the conclusion that there is a critical δ-opioidergic process involved with addicting stimulants' ability to enhance pressing for MFB ICS.

A number of potential alternative explanations of the results are not concordant with a close inspection of the available findings. It is highly unlikely, for example, that NTI interferes with ability to press or the expression of all affective processes, because NTI does not reduce pressing below levels under placebo and because NTI does not reduce the enhanced pressing seen with 4.0 mg/kg injections of morphine (6). NTI, by itself, did not produce reliable shifts in pressing in a previous test (13) and NTI, by itself, did not lead to a place preference (9).

There are a number of interesting implications of the findings. Current theories of addictions [e.g., (18)], emphasizing the idea that a dopaminergic element is a final common path of events begun by all addictive agents, are not compatible with the finding that an opioid antagonist, NTI, blocks signs of stimulants' reinforcing characteristics and that the same antagonist does not block signs of small doses of morphine's reinforcing characteristics. A dopaminergic element may be an initial event in a cascade of events begun by some addictive agents, but it highly unlikely that dopaminergic processes are sufficient by themselves or are a final pathway for all addictive processes. These findings support the implication that a δ-selective opioid receptor antagonist will be an effective pharmacological adjunct to other treatments for addictions centered about stimulants (9,13).

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