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ORIGINAL INVESTIGATION

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Nantenine: an antagonist of the behavioral and physiological effects of MDMA in mice

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Abstract *Rationale:* No selective antagonists for the effects of MDMA have yet been identified. The structurally-similar, naturally-occurring plant alkaloid nantenine (9,10-methylenedioxy-1,2 dimethoxyaporphine) may represent such a compound. *Objectives:* To investigate the capacity of nantenine to block and/or reverse MDMA-induced hyperthermia, lethality, locomotor stimulation, and head twitches in mice, and to compare these actions with those of the selective α_1 antagonist prazosin and the selective 5-HT_{2A} antagonist M100907. *Methods:* Pretreatments of either 10 mg/kg nantenine or 1 mg/kg prazosin were administered 15 min before 32 mg/kg MDMA; core temperature and locomotor stimulation were then monitored via radiotelemetry for at least 3 h. In further hyperthermia studies, 32 mg/kg MDMA was administered first and temperature was allowed to rise for 30 min; 10 mg/kg nantenine, 1 mg/kg prazosin, or 1 mg/kg M100907 was then administered in an attempt to reverse MDMA-induced hyperthermia. In lethality assays, percent lethality was quantified 2 h after MDMA injection in two distinct housing conditions, one or 12 mice per cage, with or without 15 min pretreatments of 10 mg/kg nantenine or 1 mg/kg prazosin. Drug elicited head twitches were quantified for 10 min following administration of either MDMA enantiomer, with and without pretreatments of 1 mg/kg nantenine, 0.1 mg/kg prazosin, or 0.001 mg/kg M100907. *Results:* Nantenine blocked and rapidly reversed MDMA-induced hyperthermia, attenuated lethality in both housing conditions, and reduced MDMA-induced locomotor stimulation and head twitches in mice. Prazosin blocked, but did not reverse, MDMA-induced hyperthermia, attenuated lethality (more effectively in singly-housed animals), and reduced MDMA-induced locomotor stimulation and head twitches. M100907 did not reverse MDMA-induced hyperthermia, but effectively blocked drug-elicited head twitches. *Conclusions:* Nantenine functions as an effective antagonist against a wide range of MDMA-induced effects in mice. The antagonist actions of this compound at serotonin and adrenergic receptors may be differentially implicated across endpoints.

Keywords MDMA · Nantenine · Toxicity · Hyperthermia

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Introduction

Various substitutions to the basic phenethylamine structure yield a diverse group of compounds (Fig. 1). In this regard, oxygenated substituents on the phenyl ring produce hallucinogenic drugs of the phenylisopropylamine type, while side-chain modifications result in stimulant drugs of the amphetamine type. Recent interest has focused on a third class of substituted phenethylamine—the methylenedioxy congeners—which have come to be known as entactogens (Nichols 1986). Included within this group of compounds are 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxyethylamphetamine (MDE), all of which are "club drugs" often sold under the name of ecstasy. Perhaps the most widely abused of these compounds is MDMA, which is the focus of this issue.

In recent years, MDMA appears to be involved in an increasing number of emergency room mentions and

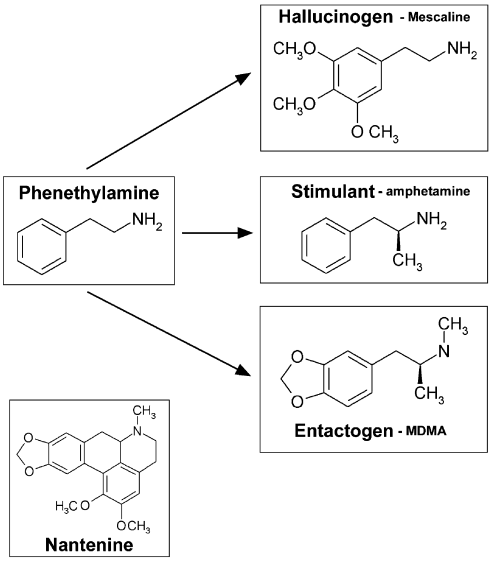

Fig. 1 Variations on the basic phenethylamine structure give rise to diverse classes of drugs of abuse. The structure of the novel compound nantenine is quite similar to that of MDMA and mescaline

fatalities (Drug Abuse Warning Network 2002). These acute MDMA toxicities are characterized by malignant hyperthermia, for which there are currently no selective pharmacological treatments in clinical use, perhaps due to the complex neuropharmacology of MDMA itself. In this regard, MDMA has previously been shown to interact with pre- and postsynaptic receptors across several neurotransmitter systems. For example, in rodents, MDMA induces a large presynaptic release of 5-HT (Rudnick and Wall 1992), although dopamine and norepinephrine are also released in lesser amounts, possibly via a similar transporter-mediated effect (Schmidt et al. 1987; Rothman et al. 2001). Recent evidence has shown that MDMA also induces acetylcholine release, both from rat striatal slices in vitro (Fischer et al. 2001) and as measured in vivo in rat prefrontal cortex and striatum by microdialysis (Acquas et al. 2001). In addition to stimulating release, MDMA has direct affinity for serotonin 5-HT_2 and adrenergic α receptors, as well as histamine H_1 receptors and muscarinic M_1 receptors (Battaglia et al. 1988). Finally, MDMA has been shown to act as an agonist at the rat trace amine receptor (Bunzow et al. 2001). Given the ubiquity of MDMA binding across such diverse brain recognition sites, the potential targets for therapeutic drugs seem quite numerous. However, the exact mechanisms underlying many of the effects of MDMA on physiology and behavior have not yet been clearly elucidated, and without similar binding promiscuity, it seems unlikely that any novel antagonists would be capable of blocking a range of MDMA effects, each of which may be mediated by different neurotransmitter systems.

In this regard, the identification (Shoji et al. 1984) and confirmation of biological activity (Indra et al. 2002a) of the alkaloid nantenine (9,10-methylenedioxy-1,2 dimethoxyaporphine), a naturally occurring compound from the fruit of the *Nandina domestica* Thunberg plant, might represent a first step in the discovery of a selective MDMA antagonist. Nantenine shares remarkable structural similarities to MDMA (Fig. 1) and binds as an antagonist with μM affinity at serotonin 5-HT_{2A} (Indra et al. 2002b) and adrenergic α_1 receptors in rat aorta (Indra et al. 2002c) and in mouse brain membrane preparations (K_i=0.4 μM at 5-HT_{2A} and 2.1 μM at α_1, Indra et al. 2002a). 5-HT_{2A} receptors have previously been implicated in MDMA-induced lethality, locomotor stimulation, and hyperthermia in mice (Fantegrossi et al. 2003), in the locomotor stimulant effects of MDMA in rats (Kehne et al. 1996) and in the reinforcing effects of MDMA in rhesus monkeys (Fantegrossi et al. 2003). Recently, α_1 receptors have also been shown to be involved in the hyperthermic response to MDMA in rats (Sprague et al. 2003). Recent in vitro evidence suggests that, at high concentrations, nantenine may also block Ca^{2+} channels (Orallo 2003) and Na^+/K^+ exchange pumps (Ribeiro and Rodriguez de Lores Arnaiz 2001). Whether or not such concentrations (>1 μM) are attained in vivo is presently unknown.

In the present report, we studied the antagonist effects of nantenine and the selective α_1 antagonist prazosin against the induction of racemic MDMA-induced hyperthermia, locomotor stimulation, and lethality in male NIH Swiss mice. Further hyperthermia experiments were conducted with these compounds and the selective 5-HT_{2A} antagonist M100907 (formerly MDL100907) in order to gauge the capacity of these agents to reverse MDMA-induced hyperthermia once established. Finally, experiments were also conducted to assess the actions of nantenine, prazosin, and M100907 against the head-twitch response (HTR) elicited by S(+)- and R(−)-MDMA. The HTR is a selective behavioral model for 5-HT_2 activity in rodents, as a wide range of direct and indirect 5-HT agonists have been shown to induce this effect (Peroutka et al. 1981; Colpaert and Janssen 1983; Green et al. 1983; Goodwin and Green 1985; Darmani et al. 1990a, 1990b, 1992). Further, HTR can be selectively blocked by 5-HT_2 receptor antagonists (Lucki et al. 1984; Handley and Singh 1986), and the potency with which an antagonist blocks HTR is highly correlated with its affinity for 5-HT_2 receptors (Peroutka et al. 1981; Ortmann et al. 1982). Thus, the antagonist effects of nantenine against several behavioral and physiological effects of MDMA were compared to those of prazosin and M100907 in order to gauge the contribution of serotonergic and adrenergic systems to nantenine's antagonist effects in these assays.

Materials and Methods

Animals

Male NIH Swiss mice (Harlan Sprague Dawley Inc., Indianapolis, Ind., USA) weighing approximately 20–30 g were housed 12 animals per 44.5×22.3×12.7 cm Plexiglas cage in a temperature-controlled room that was maintained at an ambient temperature of 22±2°C at 45–50% humidity. Lights were set to a 12-h light/dark cycle. Animals were fed Lab Diet rodent chow (Laboratory Rodent Diet #5001, PMI Feeds, Inc., St Louis, Mo., USA) and water ad libitum until immediately before testing. Animals were not used in experiments until at least 2 days after arrival in the laboratory. Each animal was used only once, and was killed immediately after use. Studies were carried out in accordance with the Declaration of Helsinki and with the Guide for Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health. The experimental protocol was approved by the University of Michigan's University Committee on the Use and Care of Animals.

Procedure

Core temperature and locomotor activity experiments

Following appropriate anesthetization with ketamine (100 mg/kg, IP) and xylazine (10 mg/kg, IP), the abdominal area of each mouse was shaved and sanitized with iodine swabs. A rostral-caudal cut approximately 1.5 cm in length was made with skin scissors, providing access to the intraperitoneal cavity. A cylindrical glass-encapsulated radiotelemetry probe (model ER-4000 E-Mitter, Mini Mitter, Bend, Ore., USA) was then inserted, and the incision was closed using absorbable 5-0 chromic gut suture material. Surgeries were carried out at least 7 days before initiation of experimental conditions, allowing time for incisions to heal and for the mice to recover normal body weights. Following surgery, all implanted mice were individually housed in 15.24×25.40×12.70 cm Plexiglas mouse cages for the duration of all temperature and locomotor activity experiments. Implanted transmitters produced activity- and temperature-modulated signals, which were sent to a receiver (model ER-4000 Receiver, Mini Mitter Co. Inc.) underneath each mouse cage. On experimental days, mice were weighed, marked, and returned to their individual cages. MDMA and pretreatment doses were then calculated and prepared for injection. Animals were subsequently removed from their cage, injected IP with saline, 1 mg/kg prazosin or 10 mg/kg nantenine, then returned to their cage. Fifteen minutes after the initial injection, mice were injected IP with 32 mg/kg MDMA and returned to their cage, while temperature and locomotor activity data were collected at 5-min intervals and processed simultaneously by the Vital View data acquisition system (Mini Mitter Co.) for 24-h. These experiments investigated the capacity of nantenine and prazosin to block the induction of hyperthermia elicited by MDMA. Further "rescue" experiments were later conducted with nantenine, prazosin and M100907 to assess the capability of these compounds to reverse MDMA-induced hyperthermia once established. In these experiments, mice were injected IP with 32 mg/kg MDMA and were left untreated for 30-min while temperature rose. Mice were then injected IP with 10 mg/kg nantenine, 1 mg/kg prazosin, 1 mg/kg M100907, or an equivalent volume of nantenine vehicle or saline.

Lethality experiments

On experimental days, mice were weighed, marked, and returned to the home cage. MDMA and pretreatment doses were then calculated and prepared for injection. Animals were subsequently removed from the home cage, injected IP and placed into 15.24×25.40×12.70 cm Plexiglas mouse cages singly, or in groups of 12. All aggregation groups were drawn from the same home cage in order to minimize aggression. Lethality experiments were conducted in the colony room at an ambient temperature of 22±2°C, and neither food nor water was available during the tests. Mice were observed for 2-h post-injection, and lethality was quantified at 15-min intervals until the end of this period. No mice were removed from their respective cages before the expiration of the 2-h test period. Doses of racemic MDMA that produced equivalent lethality (approximately 75%) across cage densities (56 mg/kg in crowded animals, 110 mg/kg in singly housed animals; previously determined in Fantegrossi et al. 2003) were studied with and without a pretreatment of nantenine (10 mg/kg) or the selective α_1 adrenergic antagonist prazosin (1 mg/kg). These pretreatment doses were chosen because they were the highest doses that lacked effects on core temperature and spontaneous locomotor activity in mice (unpublished observations) and were injected IP 15-min prior to MDMA administration. The effects of M100907 against MDMA-induced lethality in these caging conditions were previously reported (Fantegrossi et al. 2003). The lethal effects of MDMA, with and without the various pretreatments, were doubly determined for each caging condition.

Head-twitch response

On experimental days, mice were weighed, marked, and returned to the home cage. MDMA and pretreatment doses were then calculated and prepared for injection. Individual animals were subsequently removed from the home cage, injected IP with saline, 0.1 mg/kg prazosin, 0.001 mg/kg M100907 or 1 mg/kg nantenine, then placed into a 15.24×25.40×12.70 cm Plexiglas mouse cage. Ten minutes after the initial injection, mice were injected with various doses of S(+)- or R(−)-MDMA or saline and returned to the small observation cage. Five minutes after MDMA injection, a camera mounted above the observation cage began recording behavior, and continued to do so for 10-min. Videotapes were later scored by two blind observers for HTR, here defined as a rapid rotational jerk of the head that is not contiguous with any grooming or scratching behaviors. All HTR experiments were conducted in the colony room at an ambient temperature of 22±2°C, and neither food nor water was available during the tests.

Data analysis

Data from the lethality experiments are presented as mean±SEM and were compared using Fisher's exact test. For the core temperature and HTR experiments, data are presented as mean±SEM and were compared to values obtained from equivolume saline controls (n=6, data not shown) using Student's one-sample t-tests (one-tailed). Locomotor activity data were compared by repeated measures ANOVA and analyzed post-hoc by Tukey's HSD. All statistical tests were performed using commercially available software, and significance was judged at $P<0.05$.

Drugs

Racemic MDMA and its enantiomers were supplied by the National Institute on Drug Abuse (Research Technology Branch, Research Triangle Park, N.C., USA) and was dissolved in physiological saline prior to injection. M100907 was synthesized at the Laboratory of Medicinal Chemistry at the National Institutes of Diabetes, Digestive and Kidney Disorders at the National Institutes of Health (Bethesda, Md., USA), and dissolved in sterile water and 0.5 N HCl. Prazosin was purchased from Sigma-Aldritch (St Louis, Mo., USA) and was dissolved in physiological saline solution. Nantenine was synthesized at the Department of Pharmaceutical Molecular Biology, Tohoku University, Graduate School of Pharmaceutical Sciences (Sendai, Japan), and dissolved in a solution comprised of ethanol (10% volume), Alkamuls (10% volume), and sterile water (80% volume). All injections were administered IP in a volume equal to body weight (g)/100.

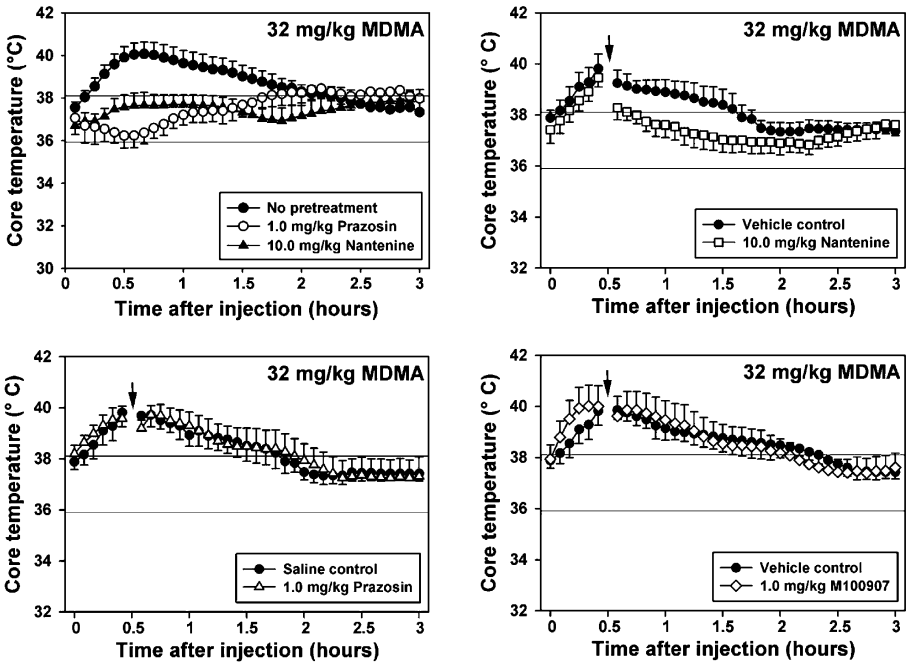

Fig. 2 Blockade of induction of MDMA-induced hyperthermia (*top left*) and reversal of MDMA-induced hyperthermia by nantenine (*top right*), prazosin (*bottom left*) and M100907 (*bottom right*). Each point represents the mean±SEM (n=6 mice per dose). *Abscissae*: time after injection (h). *Ordinates*: core temperature (°C). The defined region between approximately 36°C and 38°C represent the normal range of rodent core temperature measured over a 24-h period following equivolume saline injection

Results

Core temperature and locomotor activity experiments

Racemic MDMA produced a time-dependent hyperthermic effect in mice, which was significantly elevated over saline-treated animals from 25- to 85-min post-injection (P<0.05). The peak temperature reached was approximately 40°C (Fig. 2, top left, filled circles). By approximately 2.5-h post-injection, temperatures returned to basal values and did not subsequently deviate outside this range over the remainder of the 24-h sampling period (data not shown). The dose of MDMA here used to induce hyperthermia (32 mg/kg) did not result in any deaths up to 24-h post-injection. Pretreatment with either 10 mg/kg nantenine or 1 mg/kg prazosin completely abolished the hyperthermic effects of MDMA (Fig. 2, top left), although these pretreatments did not alter core temperature on their own (data not shown.) In addition to blocking the induction of hyperthermia produced by MDMA, 10 mg/kg nantenine was also able to reverse MDMA-induced hyperthermia when administered 30-min after MDMA (Fig. 2, top right). Neither prazosin (1 mg/kg, Fig. 2, bottom left) nor M100907 (1 mg/kg, Fig. 2, bottom right) reversed MDMA-induced hyperthermia.

Racemic MDMA also produced a long-lasting stimulation of locomotor activity, peaking at approximately 175 activity counts 1-h after administration (Fig. 3, filled circles). MDMA-stimulated locomotor activity was significantly higher than saline controls (P<0.05) for the first 3-h after injection. Pretreatment with 1 mg/kg prazosin attenuated MDMA-induced locomotor stimulation, while pretreatment with 10 mg/kg nantenine had similar, but more pronounced effects (Fig. 3). In both instances, locomotor activity counts were significantly lower

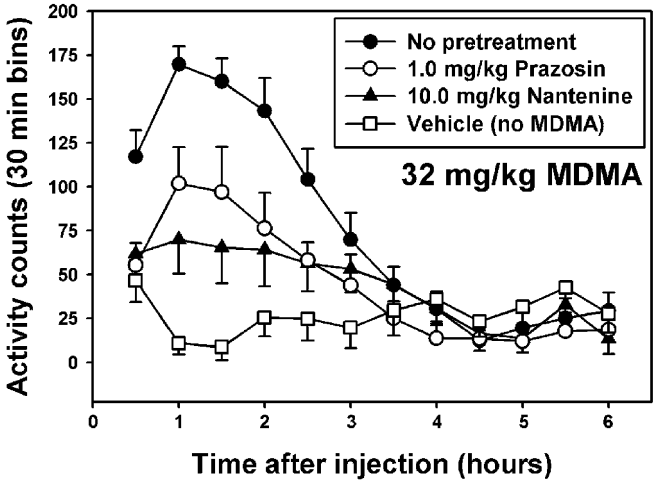

Fig. 3 Blockade of induction of MDMA-induced locomotor stimulation by prazosin and nantenine. Each point represents the mean±SEM (n=6 mice per dose). *Abscissae*: time after injection (h). *Ordinates*: activity counts (measured by implanted telemetry probe)

(P<0.05) than those obtained in MDMA-treated animals without pretreatment, but significantly higher (P<0.05) than counts obtained in vehicle-treated mice for the first 3-h after injection. Neither of these pretreatments altered spontaneous locomotor activity on their own (data not shown.)

Lethality experiments

As we have previously reported (Fantegrossi et al. 2003), racemic MDMA produces lethal effects consistent with

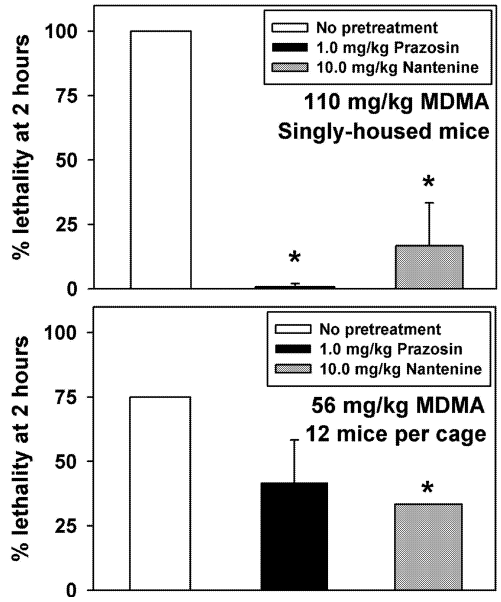

Fig. 4 Lethality-matched (LD_{75}) doses of MDMA with and without prazosin or nantenine pretreatment in singly housed mice (*top*) and in mice housed 12 per cage (*bottom*). Each bar represents the mean±SEM (based on 12 mice for the singly housed group and 24 for the 12 mice-per-cage group). *Ordinates*: percentage lethality assessed at 2 h after injection. *Asterisks* indicate significance (P<0.05) by the Fisher's exact test

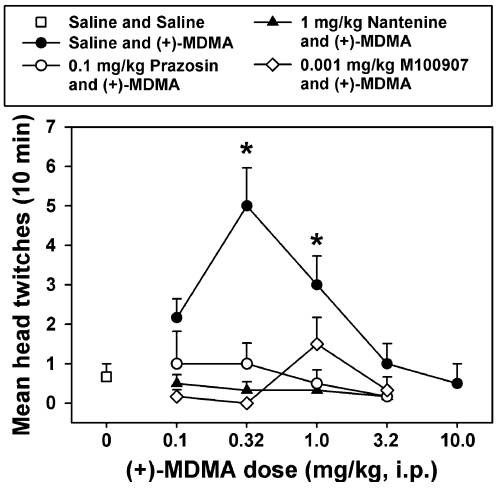

Fig. 5 Blockade of induction of S(+)-MDMA-induced HTR by M100907, prazosin and nantenine. Each point represents the mean±SEM (n=6 mice per dose). *Abscissae*: MDMA dose (mg/kg, IP). *Ordinates*: mean head twitches/10-min. *Asterisks* indicate significant differences from saline controls (P<0.05) by Student's one-sample t-test

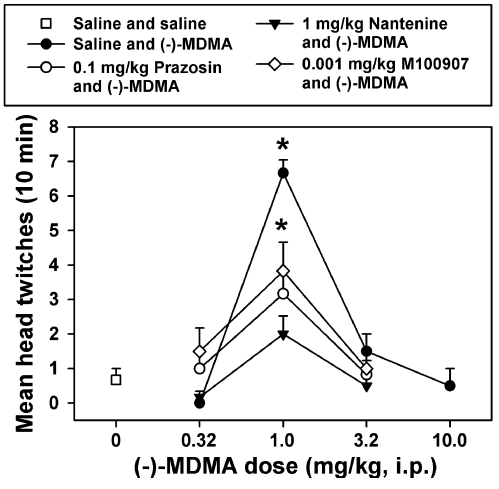

Fig. 6 Blockade of induction of R(−)-MDMA-induced HTR by M100907, prazosin and nantenine. Each point represents the mean±SEM (n=6 mice per dose). *Abscissae* and *ordinates* as described in Fig. 5. *Asterisks* indicate significant differences from saline controls (P<0.05) by Student's one-sample t-test

the concept of aggregate toxicity; the dose required to induce lethality decreases as the number of animals per cage increases. Further, since the dose effect curve for MDMA-induced lethality in single-housed animals is quite steep (see Fantegrossi et al. 2003), we here used a dose of MDMA that was lethal to all animals in the absence of pretreatment. Thus, crowded animals were administered approximately half as much MDMA (56 mg/kg) as singly housed animals (110 mg/kg). In the absence of pretreatment, deaths typically occurred within 30-min and were preceded by convulsions and motor incoordination. In singly housed animals, prazosin completely blocked the lethal effects of MDMA, while nantenine reduced MDMA-induced lethality by approximately 75% (P<0.05, Fig. 4, top). In animals housed 12 per cage during testing, both pretreatments reduced MDMA-induced lethality by approximately 50% (P<0.05, Fig. 4, bottom). Additionally, in each housing condition, both pretreatments increased survival time to at least 1-h (data not shown.)

Head-twitch response

S(+)-MDMA induced a dose-dependent HTR in mice, producing a maximum of approximately five twitches in 10-min at a dose of 0.32 mg/kg (Fig. 5, closed circles). Pretreatment with 0.001 mg/kg M100907, 0.1 mg/kg prazosin, or 1 mg/kg nantenine reduced the HTR for all doses of S(+)-MDMA to saline-like levels. Similarly, R(−)-MDMA produced a significant HTR at a dose of 1.0 mg/kg (Fig. 6, closed circles). The dose effect curve here was steeper than that observed with S(+)-MDMA, but a higher absolute number of twitches were obtained with R(−)-MDMA than with its enantiomer. As with S(+)-MDMA, all pretreatments attenuated the R(−)-MDMA-induced HTR, but in this instance only nantenine reduced the HTR to saline-like levels.

Discussion

The results from the present report suggest that antagonists acting at 5-HT_{2A} and α_1 receptors can attenuate or abolish a wide range of MDMA effects on physiology and behavior in mice. The relative contributions of the serotonergic and adrenergic antagonist properties of nantenine in the mediation of these effects can be gauged by means of comparison with prazosin (selective α_1 antagonist) and M100907 (selective 5-HT_{2A} antagonist). Perhaps surprisingly, adrenergic antagonism seems to be quite effective in the attenuation of MDMA actions in the mouse.

In our previous work with M100907 in mice (Fantegrossi et al. 2003), we found that pretreatments with this compound reduced the lethal effects of racemic MDMA in singly housed and crowded animals, but were more effective in the aggregated caging condition. In the present experiments, however, prazosin was a more effective antagonist against the lethal effects of MDMA in singly housed mice, while the effectiveness of nantenine was basically equivalent across housing conditions. These results suggest that the lethal effects of MDMA may be mediated through different mechanisms depending on the environmental conditions in which it is administered, and imply that pharmacotherapies for MDMA overdose might be more or less successful depending on the individual peculiarities surrounding a given patient's MDMA use. In this regard, a compound such as nantenine with serotonergic and adrenergic antagonist properties might be expected to be less sensitive to these individual dosing conditions, and therefore may represent a promising lead in drug development for indications involving MDMA abreaction.

Similarly, our previous work demonstrated that M100907 could only partially attenuate the hyperthermic effects of racemic MDMA. Indeed, we were unable to completely block induction of MDMA hyperthermia with M100907 unless exceptionally large doses—doses that induced a profound hypothermia on their own—were administered (unpublished observations.) Prazosin, however, completely blocked the induction of MDMA-induced hyperthermia at a dose that did not alter core temperature on its own, suggesting a significant adrenergic involvement in the hyperthermic effects of MDMA. Pedersen and Blessing (2001) have previously shown that cutaneous vasoconstriction contributes to MDMA-induced hyperthermia, and these vascular effects of MDMA are predominately mediated by α_1 adrenergic receptors (McDaid and Docherty 2001). The incomplete blockade of MDMA-induced hyperthermia by prazosin previously reported by Sprague et al. (2003) in rats may have simply been due to an insufficient prazosin dose. The combination of 5-HT_{2A} and α_1 antagonist properties in nantenine may therefore explain the complete attenuation of MDMA-induced hyperthermia following nantenine pretreatment. This blockade of the induction of MDMA-induced hyperthermia is experimentally interesting, but from a clinical standpoint, the more relevant effect would seem to be reversal of a hyperthermic state previously induced by MDMA. In these initial studies, nantenine was quite effective in this regard, reversing MDMA-induced hyperthermia within 10-min of administration. Interestingly, neither prazosin nor M100907 reduced MDMA-induced hyperthermia when administered 30-min post-MDMA. These data further imply a potential clinical utility of nantenine in the treatment of MDMA overdose.

The antagonist effects of prazosin on MDMA-induced locomotor stimulation were likewise striking as the dose used in the present experiments did not alter spontaneous locomotor activity (data not shown). A similar pattern of results was obtained with M100907 in our previous experiments, and was first demonstrated in rats by Kehne et al. (1996). The current studies with nantenine also revealed an effective blockade of the locomotor stimulant effects of MDMA. It should be noted, however, that the blockade seen with all three compounds presently tested was only partial. Although obviously less than observed following MDMA alone, locomotor activity following pretreatment with all compounds studied was still significantly higher than observed in vehicle controls for up to 3-h post-injection, perhaps implicating other neurotransmitter systems in the mediation of MDMA's locomotor stimulant effects. While larger doses of all compounds could perhaps further reduce MDMA-induced locomotor stimulation, we have found that doses higher than those presently reported begin to suppress basal locomotor activity (unpublished observations), which could complicate interpretations of the antagonist effects of these drugs against MDMA.

In the HTR studies with the MDMA enantiomers, we present for the first time evidence that both S(+)- and R(−)-MDMA induce these twitches in mice. The MDMA doses required to induce HTR were quite low, suggesting that this may be a particularly sensitive assay for MDMA activity. Indeed, the most active S(+)- and R(−)-MDMA doses in this assay were about 100-fold lower than required to induce locomotor stimulation in this species (as reported in Fantegrossi et al. 2003). These HTR effects are likely to be mediated by 5-HT release or by direct agonist activity of the MDMA enantiomers at 5-HT_{2A} receptors as, consistent with previous findings (Lucki et al. 1984; Handleyand Singh 1986), pretreatments with low doses of the selective 5-HT_{2A} antagonist M100907 blocked or attenuated the HTR for both isomers. However, prazosin also blocked or attenuated the HTR for the stereoisomers, perhaps indicating an adrenergic component to MDMA-mediated HTR. In this regard, Dursun and Handley (1996) studied nine monoamine antagonists against spontaneous and 4-iodo-2,5-dimethoxyphenylisopropylamine (DOI)-induced head shakes and found that their potency to inhibit HTR was related to their affinity at both $5HT_{2A}$ and α_1 receptors. In the present studies, nantenine potently inhibited MDMA-induced HTR at a dose 10-fold lower than that required to attenuate MDMA-induced lethality, hyperthermia, or locomotor stimulation. Further experiments to more fully characterize these effects are currently underway.

This report describes the antagonist effects of nantenine, a novel, naturally-occurring plant alkaloid with remarkable structural similarity to MDMA, against several behavioral and physiological effects of MDMA in mice. Nantenine effectively blocked or attenuated MDMA-induced lethality, hyperthermia, locomotor stimulation, and HTR. The antagonist effects of nantenine are likely to be jointly mediated by 5-HT_{2A} and α_1 receptors, and this compound may represent a promising lead in drug development for indications involving MDMA overdose and abreaction. This compound should be further studied in other species and assays to fully characterize its effects as an MDMA antagonist.

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