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Attenuation of methamphetamine-induced behavioral sensitization in mice by systemic administration of naltrexone

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Abstract

Repeated intermittent exposure to psychostimulants was found to produce behavioral sensitization. The present study was designed to establish a mouse model and by which to investigate whether opioidergic system plays a role in methamphetamine-induced behavioral sensitization. Mice injected with 2.5 mg/kg of methamphetamine once a day for 7 consecutive days showed behavioral sensitization after challenge with 0.3125 mg/kg of the drug on day 11, whereas mice injected with a lower daily dose (1.25 mg/kg) did not. Mice received daily injections with either 1.25 or 2.5 mg/kg of methamphetamine showed behavioral sensitization after challenge with 1.25 mg/kg of the drug on days 11, 21, and 28. To investigate the role of opioidergic system in the induction and expression of behavioral sensitization, long-acting but non-selective opioid antagonist naltrexone was administrated prior to the daily injections of and challenge with methamphetamine, respectively. Our results show that the expressions of behavioral sensitization were attenuated by pretreatment with 10 or 20 mg/kg of naltrexone either during the induction period or before methamphetamine challenge when they were tested on days 11 and 21. These results indicate that repeated injection with methamphetamine dose-dependently induced behavioral sensitization in mice, and suggest the involvement of opioid receptors in the induction and expression of methamphetamine-induced behavioral sensitization.

Keywords: Induction and expression of behavioral sensitization; Locomotor activity; Methamphetamine; Naltrexone; Opioid receptors

1. Introduction

Methamphetamine (METH) is a synthetic drug and chemically related to amphetamine (AMPH) but has a higher potential for abuse. AMPH and related compounds mainly elicit impulse-independent release of monoamines from cytosolic stores by reversal of reuptake carrier activity [42]. Continued use of psychostimulants is typically associated with the development of tolerance. However, repeated intermittent exposure to these psychostimulants such as AMPH, METH, and cocaine was found to produce behavioral sensitization, which is characterized by progressive and enduring augmentation of the behavioral effects in response to subsequent exposure to the same dose of the drug [38,39]. The potential clinical relevance of behavioral sensitization has been associated with development of craving in addicts and psychosis that arise from repeated exposure to these psychostimulants [13,39]. The most important characteristic of behavioral sensitization to psychostimulants is long lasting, which persists for months even years after cessation of drug treatment [7,13,38]. Therefore, rearrangement and structural modification of neural networks and circuitry in the CNS must be involved in the development of behavioral sensitization.

The ventral tegmental area (VTA) is the somatodendritic region of the mesolimbic dopamine neurons, whose nerve terminals project primarily to the nucleus accumbens (NAcc), an important structure which has been described to mediate spontaneous and pharmacologically stimulated locomotor activity [9]. The behavioral activating effects of AMPH are thought to depend primarily on its ability to increase dopamine release in the terminal regions of the mesoaccumbens and neostriatum [16]. In addition, by regulating dopamine release in the midbrain, glutamate

Abbreviations: AMPH, amphetamine; METH, methamphetamine; NAT, naltrexone; NAcc, nucleus accumbens; VTA, ventral tegmental area

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also plays an important role in regulation of motor activity [32]. Therefore, the majority of studies related to behavioral sensitization were focused on dopaminergic and glutamatergic systems. Neuroadaptations in the VTA and NAcc are now believed to be associated with the induction and expression of behavioral sensitization to psychostimulants, respectively [15,51]. An abundance of neuroadaptive phenomena observed during the establishment of behavioral sensitization was occurring in a time-dependent fashion [58], and some of these alterations appear to be vanished at post-treatment periods [54,57]. Therefore, the expression of behavioral sensitization after short-term and long-term periods of abstinence may be dependent on different cellular mechanisms, and other neurotransmitter systems may be involved in and contribute to the expression of behavioral sensitization during the period of abstinence.

Topographic overlaps between opioid and dopamine neurons were found in the VTA, substantia nigra, striatum, and limbic areas, suggesting that there are interactions between these two systems [21,43]. Acute administration of AMPH or METH is known to increase endogenous opioid contents [35], and mesolimbic structures such as VTA and NAcc receive β-endorphin containing fibers [29]. Although opioid agonists had been known to increase the firing rate of dopamine neurons [31] and increase dopamine levels [20] in the VTA, the character of opioidergic system in chronic use of psychostimulants still remains unclear. Numerous studies strongly suggest the involvement of opioidergic system in some effects of AMPH or METH. For example, METH is more toxic in morphine-dependent mice than in normal mice (LD_{50}: 20.6 mg/kg versus 43.2 mg/kg) [10]. METH-induced conditioned place preference was found to be additively enhanced by co-administration with morphine [30], but inhibited by pretreatment with opioid receptor antagonist [49]. In various laboratory animal species, specific opioid receptor antagonist naloxone was found to decrease both AMPH-induced locomotor activity and AMPH-induced increase in extracellular levels of dopamine [12,41]. Moreover, morphine given alone not merely increases locomotor activity, but cross-sensitizes the behavioral effects to direct dopamine agonist, apomorphine, and indirect dopamine agonist, AMPH or METH [10,14,50]. These findings provided us an interest to determine whether opioidergic system is involved in the chronic actions of METH. Therefore, the present study was designed to investigate the role of opioidergic system in METH-induced behavioral sensitization. This may lead not only to a better understanding of how this drug affects the behavior, but also to a better understanding of the underlying interactions between neurotransmitter systems.

2. Materials and methods

2.1. Animals

Male NIH Swiss mice (Harlan, Indianapolis, IN), weighing 20–25 g at the beginning of the experiment were used. Upon arrival, mice were housed in groups of four in animal colony room on a 12 h light–dark cycle, and at constant temperature ($22 \pm 2\,^{\circ}C$). Before any treatment, mice were maintained in the colony room for at least 7 days without disturbance. Food and water were available ad libitum except during the behavioral testing. All procedures for animal handling and experiments were approved by *Institutional Animal Care Committee* of the University of Mississippi Medical Center, and performed in compliance with the NIH *Guide for the Care and Use of Laboratory Animals*.

2.2. Drug administration

Although extravascular routes of administrations such as intraperitoneal (i.p.) or subcutaneous injection do not resemble those preferred by human drug abusers (intravenous injection and smoking), they are more convenient and accurate for repeated drug administration into small size animals such as mice. Therefore, i.p. injection was used to administer METH or naltrexone (NAT) into mice in this study. METH hydrochloride and NAT hydrochloride dihydrate (Sigma, St. Louis, MO) were freshly dissolved in saline before use and injected at a volume of 10 ml/kg of body weight.

2.3. Measurement of locomotor activity

In order to minimize the external, environmental influences, physically identical home cages (28.5 cm × 17.5 cm × 12 cm) without bedding were used as the locomotor arena. On the day of experiment, mice were transferred to the behavioral testing room in their home cages and allowed to acclimatize to the testing room for 60 min undisturbed with food and water. Following the acclimatization period, the mice were placed individually in locomotor arena and habituated in the arena for 60 min. Locomotor activity during the last 30 min of habituation period in the locomotor arena was considered as baseline activity. After the habituation period, mice were injected with saline or METH and their locomotor activities were measured immediately for 120 min. The locomotor activities in 12 mice were monitored simultaneously and measured as the distance traveled in 5 min intervals using a video tracking system (SMART, San Diego Instruments, San Diego, CA), which recorded and analyzed the real time position of the animal. All experiments were performed during the animals' light cycle. The locomotor activity in each mouse was monitored only once with the exception of those to determine the effects of repeated injection of METH.

2.4. Induction and expression of behavioral sensitization

For induction of behavioral sensitization, each mouse was injected i.p. with either METH or saline once daily for 7 consecutive days. Except those for examination of the effects of repeated injection of METH, mice were kept in animal colony room and received all injections in their home