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Research report

Individual differences in initial morphine sensitivity as a predictor for the development of opiate addiction in rats

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HIGHLIGHTS

- Individual differences in sensitivity to initial morphine analgesia may predict the subsequent development of opiate addiction.
- Certain animals that are less sensitive to initial morphine antinociception may be susceptible to developing morphine addiction.
- The current findings may have clinical implications for future research on the molecular mechanisms of opiate addiction and preclinical medication development.

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ABSTRACT

Individuals report a wide range of analgesia to similar doses of opiates, and not all opiate users become addicted. This suggests that there may be certain predispositions that influence one to develop opiate addiction. We investigated the relationship between the individual differences in initial morphine sensitivity and the subsequent development of opiate addiction-like behavior using a hot plate test and an intravenous morphine self-administration (MSA) paradigm in rats. Using a median split of initial morphine antinociception, animals were defined as low antinociception (LA) and high antinociception (HA) groups. Thus, the LA group represents the animals that were less sensitive to initial morphine antinociception as compared to those of the HA group. The animals were allowed to self-administer either saline or morphine (0.5 mg/kg/infusion, 4hr/day) 5 days per week for 3 weeks. Spontaneous locomotor activity was measured on self-administration days 10 and 15. Individual differences in initial morphine sensitivity were not correlated with the amount of morphine self-administered by the animals on day 1. In the second-week of MSA, the LA group exhibited increased morphine intake and locomotor hyperactivity as compared to those of the HA group. Therefore, certain animals that are less sensitive to initial morphine antinociception may be susceptible to developing opiate addiction. The current findings may have clinical implications for future research on the biological mechanisms of opiate addiction and preclinical medication development.

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1. Introduction

Opiates are the most widely prescribed drugs for pain management, and many preclinical studies have characterized their analgesic properties [1], reinforcing properties [2], and molecular mechanisms of action [3–5]. Psychomotor and analgesic tolerance develops with repeated opiate use [6–9]. However, it remains unclear why certain individuals are more vulnerable to opiate abuse. This gradual development of tolerance subsequently requires progressively higher doses of opioids to achieve comparable analgesia. However, simply increasing the dosage of opioids may not be ideal because an escalation of drug taking may shift vulnerable individuals from drug use to drug abuse as suggested previously [10,11].

Abbreviations: MSA, morphine self administration; SSA, saline self-administration; HA, high antinociception; LA, low antinociception.

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There is a great deal of variation in the effectiveness of opiates, as they do not invoke a strong analgesia in all individuals [9,12,13]. Previous studies have examined the individual differences in psychomotor and analgesic measures to opiates in animals [14–18]. These studies demonstrated that animals with high locomotor activity to novelty exhibited addiction-like behaviors and poor morphine-induced analgesia. Moreover, Lewis rats (an addiction-prone strain) showed poor antinociception to a high dose of morphine (20 mg/kg) as compared to Fisher rats (an addiction-resistant strain) [15]. However, the relationship between the individual differences in initial morphine sensitivity and the subsequent development of opiate addiction remains unclear. This is surprising given the increased mortality and morbidity from opiate abuse and addiction in the past years. Thus, studies are necessary to understand the underlying mechanisms of these observed individual differences. Early identification and understanding of the individual differences are important in order to prevent any unnecessary exposure to these addictive substances.

Recent studies suggested that individuals vulnerable to developing drug addiction exhibit two important phenotypes such as the escalation of drug taking and the loss of control over drug use [10,11,19–21]. Researchers can study these phenotypes using different aspects of intravenous drug self-administration in rodents [22]. Locomotor sensitization is another example of addiction-like behavior as it is well established that repeated drug administration leads to increased locomotor activity, especially upon an acute low-dose drug challenge during withdrawal [23]. This increased locomotor activity is regulated by dopaminergic pathways, which also mediate the rewarding and reinforcing properties of morphine [24–26]. Thus, the expression of locomotor sensitization has been extensively used as a measure of drug addiction-like behavior in rodents.

In the current study, we utilized the intravenous morphine self-administration (MSA) paradigm to expose the animals to morphine 5 days per week for 3 weeks. This model has been used in preclinical drug addiction studies [27–29] because morphine has an abuse potential in humans and also is self-administered by animals. Compared to the passive administration of drugs, the self-administration paradigm has several advantages when studying drug addiction, including voluntary intravenous drug administration, self-regulation of drug intake, and the gradual development of tolerance and sensitization. The main goal of the current study was to investigate the relationship between the individual differences in initial morphine sensitivity and the subsequent development of addiction-like behavior in rats that self-administered intravenous morphine.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (7 weeks old upon arrival) were obtained from the Taconic Farms (German Town, NY), and they were allowed to acclimate to our facilities for a minimum of 1 week. Following surgical implantation of an indwelling jugular vein catheter, animals were single-housed in standard rat cages (42.5 × 20.5 × 20 cm) on hardwood chip bedding (Pine-Dri) with free access to food (Harlan Teklad 4% Mouse/Rat Diet 7001) and water. Single housing was necessary to preserve the integrity of each animal's indwelling catheter. The animal housing room was maintained at 68–72 °F with 40% humidity and a reversed 12 h light-dark cycle (lights off at 0600). The experimental protocol was approved and conducted in full compliance with the USUHS Institutional Animal Care and Use Committee.

2.2. Drugs

Morphine sulfate (Medisca Inc., Plattsburgh, NY) was dissolved in 0.9% sterile saline daily. All drug doses were expressed as the weight of the salt.

2.3. Catheter surgery

Male Sprague-Dawley rats (250–300 g) were anesthetized with a cocktail of ketamine/xylazine (80 mg/kg and 10 mg/kg, i.p.), and small portions of the animal's back and lower neck were shaved. Two incisions were made, one on the back (2.5 cm) and one on the neck (1 cm), and the right jugular vein was isolated. The catheter was passed subcutaneously over the shoulder from the animal's back and implanted into the animal's right jugular vein as described previously [30]. The cannula was flushed daily with a saline solution (0.2 ml) containing heparin (10 USP units/mL) and gentamycin (1 mg/mL) to maintain catheter patency and infection prophylaxis.

2.4. Experimental design

Experiment 1: Hot plate latencies were measured one day prior to the initiation of self-administration (baseline), self-administration days 1, 3, and 5. Animals with hot plate latencies above the median of the group were defined as HA, while the remainder were defined as LA (self-administration day 1). All animals were individually placed in the operant chambers to begin self-administration of either morphine or saline. Each self-administration session lasted 4 h and was conducted 5 days per week for 3 weeks. After the self-administration session, animals were allowed to habituate to the hot plate testing room for 20 min before the hot plate test. Locomotor activity was measured in all animals immediately after the self-administration session on days 10 and 15.

Experiment 2: Hot plate latencies were measured at 30 and 60 min after a bolus morphine (2.5 mg/kg, iv) administration one day prior to the initiation of MSA. Animals with hot plate latencies above the median of the group were defined as HA, while the remainder were defined as LA. Animals were allowed to self-administer intravenous morphine 5 days per week over 3 weeks. Hot plate latencies were measured for all animals on self-administration days 1, 3, and 5 after the session. Animals were allowed to habituate to the hot plate testing room for 20 min before the hot plate test. Locomotor activity was measured in all animals immediately after the self-administration session on days 10 and 15.

2.5. Hot plate test

Morphine-induced antinociception was measured using the Omnitech Hot Plate Analgesiometer (Omnitech Electronics, Columbus, OH). The latency was measured from the placement of the rat onto the metal plate (51 °C) until the rat licked a hind paw. The test was cut off at 60 s to prevent excessive heat exposure to the hot plate and potential damage to paws.

2.6. Self-administration

Following one-week of recovery from the catheter surgery, all animals were individually placed in the operant conditioning chambers (Med Associates Inc., St. Albans, VT) and allowed to self-administer either morphine (N = 30) or saline (N = 18). Each chamber was equipped with two levers, a Razel Model A infusion pump (Stamford, CT), and a 10 ml glass syringe connected to a fluid swivel (Instech, Plymouth Meeting, PA) by Teflon tubing. This setup allowed the animals to self-administer morphine