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# Novelty preference predicts place preference conditioning to morphine and its oral consumption in rats

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**Abstract**

Sensation seeking is frequently observed among drug addicts. This behaviour has been modelled in non-primate animals as novelty seeking. We previously determined that novelty preference did not predict amphetamine-induced place conditioning but was positively correlated with the consumption of a low concentrated amphetamine solution. Here, we studied the relationship between novelty seeking and the vulnerability to rewarding and reinforcing effects of morphine.

Wistar rats were selected according to their novelty preference. In this model, animals have free choice between a new compartment and a "familiar" compartment to which they were previously exposed during two 30-min sessions, 24 h apart. We measured oral morphine consumption when this drug was presented in tap water (25 or 50 mg/l) in free choice with water or when it was presented (50 mg/l) in a 5% (w/v) sucrose solution in free choice with a sucrose solution. The oral consumption of quinine was also measured. The rewarding effect of morphine (1.25 and 5 mg/kg; i.p.) was determined in a conditioned place preference paradigm.

Whereas high and low novelty seekers did not differ in reactivity to the aversive taste of quinine, preference for novelty was associated with a greater oral morphine consumption as well as an increased conditioned place preference induced by the 5 mg/kg dose of morphine. The present results support the hypothesis that novelty preference predisposes to drug abuse.
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## 1. Introduction

Individual variability in susceptibility to drug addiction has been well established in human and rodents (Piazza et al., 1989; Volkow et al., 1999; DeWit et al., 2003). For some individuals, the first drug experience is perceived as aversive, whereas others rate it as a positive experience that could lead to recreational consumption. Moreover, although some individuals can maintain recreational use for long periods of time without any debilitating consequences, a proportion of individuals become rapidly addicted. It is therefore important to determine the factors that predispose to drug consumption.

In the three dimensions theory of personality proposed by Cloninger (1987), "the dimension of novelty seeking is hypothesized to be a heritable tendency towards exhilaration or excitement in response to novel stimuli or cues for potential rewards or potential relief of punishment, which leads to frequent exploratory activity in pursuit of potential rewards as well as active avoidance of monotony and potential punishment". Zuckerman (1994) who includes the novelty seeking as a subscale in the sensation seeking personality super-trait, has defined it as the preference for new, complex and ambiguous stimuli. Numerous studies have shown the importance of this feature in predisposition to addiction.

Novelty seeking remains the best predictive index of drug use (Jaffe and Archer, 1987, Masse and Tremblay, 1997) probably because high sensation seekers would be more likely to experiment with recreational drugs. In men, novelty seeking also predicts the amount and frequency of alcohol consumption (Andrucci et al., 1989, Cherpitel, 1993) as well

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as the predisposition to relapse (Kravitz et al., 1999; Meszaros et al., 1999).

A number of rodent models have been devised to measure novelty-seeking behaviour (Dellu et al., 1996; Bardo et al., 1996). Novelty-induced place preference paradigm evaluates more specifically novelty-seeking behaviour in a non-stressful situation. In this model, animals having free-choice access to a novel or familiar environment spend more time in the novel one. In this situation, animals fail to display an increase in corticosterone levels suggesting that behaviours in this situation are not guided by stress (Misslin and Cigrang, 1986).

Only a few studies thus far have analysed the relationship between individual differences in novelty preference in free-choice situations and predisposition to drugs of abuse, mostly with amphetamine. In rats, novelty preference does not predict subsequent amphetamine-induced stimulation of locomotor activity (Robinet et al., 1998), but is positively correlated with oral consumption of amphetamine solution at a low concentration when measured in a two-bottle free-choice paradigm (Pelloux et al., 2004). By contrast, amphetamine self-administration is not influenced by individual differences in novelty preference (Klebaur et al., 2001). In the conditioned place preference paradigm, a procedure currently used to assess rewarding effects, high novelty seekers (HNS) show a greater amphetamine-induced CPP compared to low novelty seekers (LNS) (Robinet et al., 1998; Klebaur and Bardo, 1999). However, using fewer conditioning sessions, the relationship between preference for novelty and amphetamine-induced place conditioning is not apparent (Pelloux et al., 2004).

It appears important to determine whether the influence of novelty seeking on the vulnerability to the effects of psychostimulants could be extended to the effects of drugs belonging to distinct pharmacological classes. Indeed, the different drugs of abuse produce different subjective effects. For example, whereas amphetamine is a powerful mental and motor stimulant, opiates have relaxing and sedative effects. Recently, Zheng et al. (2003) found that the magnitude of morphine place conditioning was positively correlated with novelty-seeking behaviour in a free-choice situation, but not with activity in an inescapable novel environment. However, perseverance of exploration (i.e. delayed activity) in novel environments was shown to predict morphine place conditioning (Nadal et al., 2005). In the present study, we further analysed the relationship between free-choice novelty seeking and vulnerability to morphine. Rats were initially screened for their novelty preference in novelty test chambers. Then, voluntary oral consumption of morphine solutions was measured in a two-bottle free-choice procedure. In order to elucidate whether the bitter taste of morphine affected its intake, HNS and LNS were compared for their oral morphine consumption when the drug was diluted either in tap water or in a sweetened solution (5% sucrose). In addition, we studied whether high and low novelty seekers differed in oral consumption of quinine, a substance known for its bitter taste but that is devoid of abuse liability. Furthermore, the rewarding effect of morphine in high and low novelty seekers was assessed in the conditioned place preference paradigm (Carr et al., 1989; Bardo and Bevins, 2000).

## 2. Materials and methods

### 2.1. Animals

Male outbred Wistar rats (180–200 g upon arrival, corresponding to 7 weeks old) were purchased from Charles River/IFFA CREDO (Saint Germain sur l'Arbresle, France). Four rats were housed in large Makrolon cages (L = 40 cm, W = 25 cm, H = 18 cm). They were maintained on a 12-h/12-h light/dark cycle (lights on at 07:00 a.m.), at a constant temperature (21 ± 1 °C), with laboratory chow and water ad libitum. The experiments were carried out between 09:00 a.m. and 7:00 p.m. They were conducted in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC) and approved by the regional ethical committee for animal experimentation (Normandy).

### 2.2. Drugs

Morphine hydrochloride was purchased from la Cooperation Pharmaceutique Francaise (Melun, France). For conditioned place preference experiments, morphine was dissolved in saline and injected intraperitoneally (i.p.) in a volume of 2.5 ml/kg. For oral consumption experiments, morphine was diluted in tap water or in a 5% sucrose solution. Doses always refer to the free base. Sucrose and quinine hydrochloride were purchased from Sigma-Aldrich (L'isle d'Abeau Chesnes, France).

### 2.3. Preference for novelty

Novelty preference was assessed using boxes with two compartments, each compartment measuring L = 35 cm; l = 35 cm; W = 30 cm, as previously described (Pelloux et al., 2004). Rats from a same home-cage were tested simultaneously. An opening between the two compartments could be occluded by a sliding door. The floor was black and smooth. One compartment had grey walls and the other had bare wooden walls. Rats were confined to the grey compartment for two 30-min sessions, 24 h apart. On the third day, the sliding door was removed and rats were placed in the "familiar" grey compartment, from which they could freely access the novel compartment. The time spent (s) and the number of entries into the novel compartment were measured for 15 min by a video analysis system (described later).

Rats were designated as HNS or LNS according to the time they spent in the novel compartment. Animals that spent less than two or greater than two standard errors to the mean (S.E.M.) were considered as low novelty seekers (LNS) or high novelty seekers (HNS), respectively.

### 2.4. Oral consumption of morphine in a free-choice paradigm

One hundred and four rats were tested for their voluntary intake of morphine using a two-bottle, free-choice paradigm,

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