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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.

Keywords: Morphine; Novelty; Individual differences; Oral consumption; Conditioned place preference; Rat

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,

as previously described (Pelloux et al., 2004). Rats were placed in individual cages (L=40 cm, W=25 cm, H=18 cm) with food ad libitum and free access to two drinking bottles. The position of the bottles was changed daily to control for position preference. Both bottles contained tap water for 4 days and water consumption was measured daily. Animals were then given a continuous free choice between water and solutions of morphine (25 mg/l or 50 mg/l) for 32 days. The concentrations were selected on the basis of preliminary experiments.

For HNS and LNS rats selected from a distinct population of 54 rats, bottles contained sucrose (5% w/v) for 4 days. Then, animals were given a continuous free choice between sucrose and morphine (50 mg/l) dissolved in a sucrose solution (5% w/v) for 32 days.

Morphine intake and water (or sucrose solution) consumption were determined daily for a period of 32 days. The animals were weighed every 4 days. Mean daily drug intake (mg/kg/day) was calculated on successive 4-day periods during the experimental period. Morphine ratio was calculated to represent morphine consumption (ml/day) as a percentage of total fluid consumption.

2.5. Quinine oral consumption

In HNS and LNS rats selected from a separate population of 52 animals, rats were tested for their voluntary intake of quinine solutions at increasing concentrations (quinine HCl: from 1.6 to 50 mg/l) using a two-bottle, free-choice paradigm. Rats were habituated to two bottles that both contained tap water for 4 days and then allowed to drink either water or the quinine solution. Rats were exposed to each concentration for 8 days. Quinine consumption (ml/day) was expressed as a percentage of total fluid consumption.

2.6. Conditioned place preference (CPP)

The rewarding effect of morphine was assessed in the conditioned place preference paradigm in HNS and LNS rats selected from a separate population of 106 rats. The apparatus consisted of an enclosure (L=80 cm; W=25 cm; H=35 cm) divided into two main compartments (32×25 cm) separated by a small neutral compartment (14×15 cm) as previously described (Le Pen et al., 1998; Pelloux et al., 2004). Two openings to the main compartments could be closed by sliding doors. The neutral compartment had grey walls. One of the main compartments had black smooth floor, the wall in front of the door was black and the others were white. The other main compartment had a black floor with a grid, and its walls were striped vertically black (width 1 cm) and white (width 2 cm). The experiment consisted of three distinct phases: preconditioning, conditioning and post-conditioning.

The preconditioning phase was carried out over 2 consecutive days. Rats were placed in the neutral compartment and allowed free access to the entire apparatus for 15 min. On the second day, the amount of time spent in each compartment was monitored by a video analysis system (see below) to assess unconditioned preference. Rats showing a strong unconditioned preference (>700 s for the neutral compartment or >500 s for one of the main compartments and <100 s for the other) were discarded in order to obviate any bias towards either test environment.

Place preference conditioning was conducted using an unbiased procedure. Rats were counterbalanced according to their initial preferences, so that in each group, half of the rats received the drug in the preferred compartment and half in the least preferred one. Immediately after drug injection, subjects were confined in the appropriate compartment for 30 min. On alternate days, they were injected with saline and confined to the other compartment. Each animal received three drug pairings (on days 1, 3, 5) and three saline pairings (on days 2, 4, 6). Different groups of rats, counterbalanced according to the period of the day, were conditioned with morphine at doses of either 1.25 or 5 mg/kg.

The post-conditioning test was conducted 1 day after the last conditioning session. Subjects were allowed free access to the apparatus for 15 min and the time spent in each compartment was monitored.

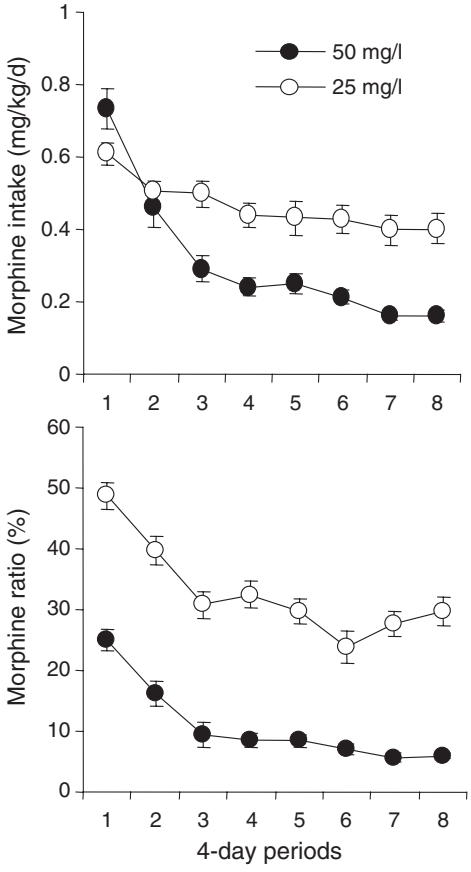

Fig. 1. Oral morphine consumption during the 32-day free-choice period. Rats were allowed free choice between tap water and solutions of morphine diluted in tap water. Mean (±S.E.M.) of morphine intake (mg/kg/day; upper panel) and morphine ratio (lower panel). The morphine ratio represents the morphine consumption (ml/day) as a percentage of total fluid consumption. $N=52$ rats per group.

2.7. Image analysis system

The image analysis system (Videotrack 512, Viewpoint, Lyon, France) consisted of video cameras positioned above the apparatus, a video interface and a microcomputer. It converted the video input signal into binary images so that each animal corresponded to a white spot against a black background. During experimentation, the movements of the spot were translated into the time (s) spent, distance (cm) travelled, and entries in each compartment by the centre of gravity of the spots.

2.8. Statistical analysis

For the oral consumption experiments, data were analysed by two-way repeated measures ANOVA, followed by Fisher's least significant difference (LSD) test for multiple comparisons. Correlations between consumption and the preference for novelty were evaluated by the Pearson's correlation test. For the CPP test, the scores (±S.E.M.) were expressed as the change in time (s) spent in the drug-paired compartment before and after conditioning. A paired Student's *t*-test was used to determine whether an individual dose of morphine produced significant place preference. A significantly greater amount of time spent on the post-conditioning test, as compared with the preconditioning phase, was defined as a CPP. CPP scores were compared by two-way ANOVA with novelty level (HNS vs. LNS) and dose (1.25 vs. 2.5 mg/kg) as main factors, followed by a Fisher's LSD test for post-hoc analysis.

3. Results

3.1. Oral consumption of morphine in a free-choice paradigm

The time course of oral morphine consumption as a function of the concentration of the morphine solution is shown in Fig. 1. For both concentrations (25 and 50 mg/l), we observed a progressive decline in morphine intake during the 32-day free-choice period ($F(7,705)=57$; $P<0.001$). The morphine ratio defined as the consumption of morphine on the total fluid consumption also differed across time ($F(7,705)=55$, $P<0.001$). The main effect of concentration on morphine intake ($F(1,705)=13.4$, $P<0.001$) and morphine ratio ($F(1,705)=133$, $P<0.001$) was significant. The time course of morphine intake also differed as a function of the concentration ($F(7,705)=11.2$; $P<0.001$). Animals exposed to the 25 mg/l concentration adapted their consumption more progressively than rats exposed to the 50 mg/l concentration. At the end of the 32-day period, both groups maintained a stable consumption of 0.4 and 0.16 mg/kg/day for the 25 and

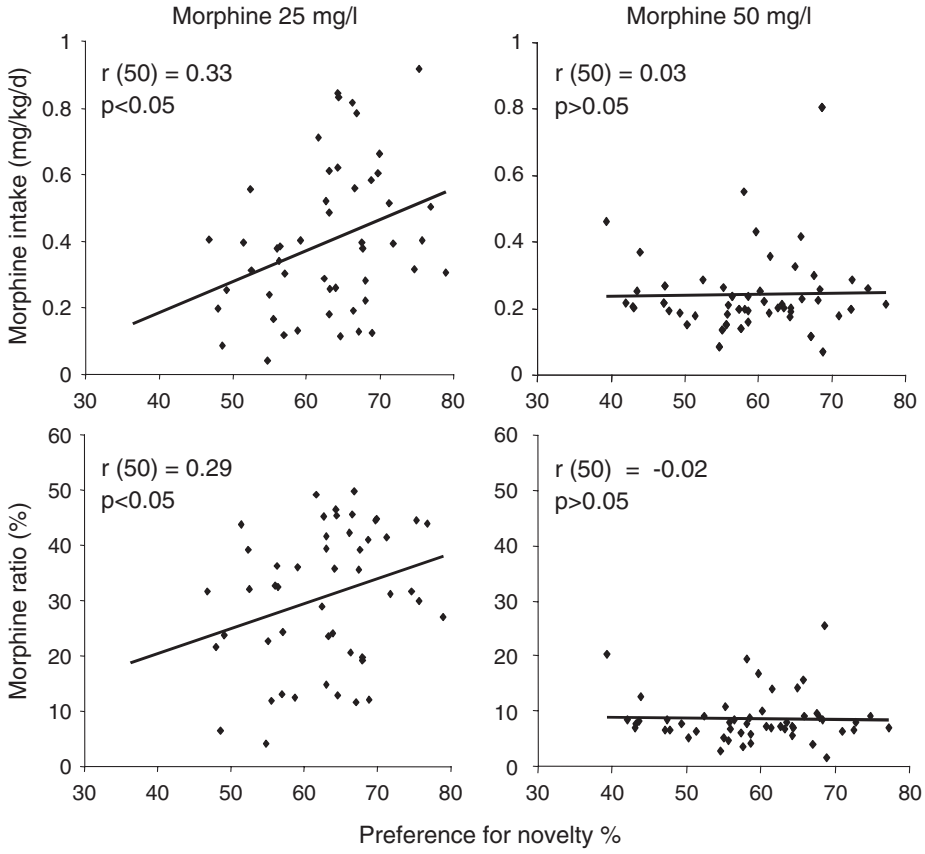

Fig. 2. Correlation between novelty preference and morphine consumption expressed as morphine intake (mg/kg/day; upper panel) or morphine ratio (lower panel) from the 25 mg/l (left part) or 50 mg/l (right part) morphine concentration over 32 days. The morphine ratio represents the morphine consumption expressed as a percentage of the total fluid consumption. Novelty preference represents the time spent in a novel compartment expressed as a percentage of the total time. $N=52$ rats per group.

50 mg/l concentration, respectively. During the experiment, the average total fluid consumption, for the 25 and 50 mg/l concentrations was 26.1± 1.2 and 26.6±0.6 ml/day, respectively.

The relationship between preference for novelty and oral consumption of morphine when it was presented in tap water, is presented in Fig. 2. Preference for novelty was positively correlated with morphine intake and morphine ratio at the 25 mg/l concentration. For the highest concentrated solution (50 mg/l), the correlation between novelty preference and morphine consumption disappeared.

3.2. Oral consumption of a morphine sweetened solution

In a preliminary study, we first assessed the influence of preference for novelty on sucrose 5% consumption. For this purpose, 54 rats tested for their preference for novelty were habituated to drinking from two bottles containing water for 4 days and were then given water in one bottle and sucrose (5% w/v) in the other one for 4 days. Whereas rats presented a water consumption of 34 ml/day during habituation, this one dropped to 0.9 ml/day during the period of free choice between sucrose and water. Rats then presented a sucrose consumption of 120± 6 ml/day as soon as the first day of exposure, revealing an extreme avidity for sucrose. No correlation was observed between sucrose consumption and the level of novelty preference ($R(52)=0.16$).

Then, in other rats selected as HNS and LNS, to test whether the bitter taste of morphine at the high concentration may have affected morphine intake, we studied oral morphine consumption at the 50 mg/l concentration when this drug was presented in a sucrose 5% solution in a free-choice with the sweetened solution (Fig. 3, right panel). These data were compared with those obtained for HNS and LNS rats selected from the total population of the above experiment (Figs. 1 and 2), where morphine (50 mg/l) was diluted with tap water (Fig. 3, left panel).

First, the time course of morphine consumption under both experimental conditions (presentation of morphine in a sweetened solution or not) was compared by ANOVA two-way for repeated measures, with conditions and 8-day periods as main factors. Consumption profiles varied according whether morphine was presented in tap water or in sweetened water (interaction condition × period: $F(3,234)=12.75$; $P<0.001$) although there was no main effect of period ($F(3,234)=0.35$) or condition ($F(1,234)=1.52$). Morphine ratio differed as a function of time ($F(3,234)=8.06$; $P<0.001$) and the profiles of consumption also differed depending on whether morphine was

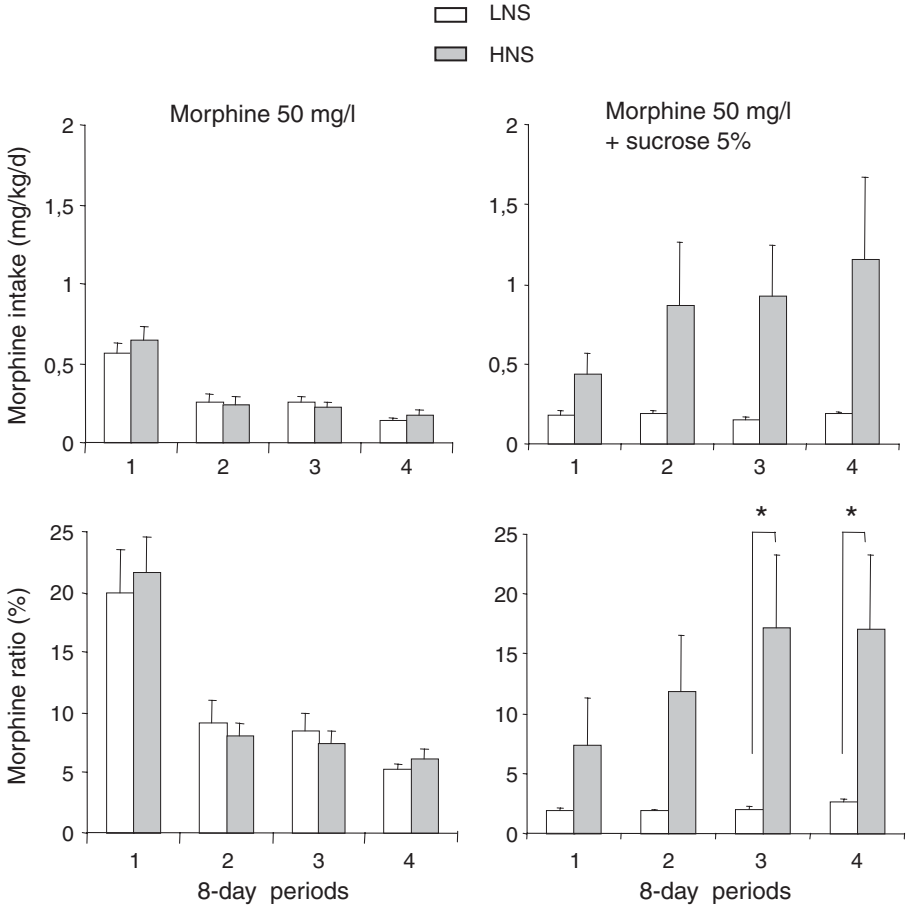

Fig. 3. Influence of novelty preference on oral consumption of morphine (50 mg/l) diluted in tap water (left panel) or in a sucrose 5% solution (right panel). Rats were selected as high-novelty seekers (HNS) or low-novelty seekers (LNS) according to the time they spent in the novel compartment. Mean (±S.E.M.) of morphine intake (mg/kg/day; upper panel) and morphine ratio (lower panel); $N=18$–22 rats per group. Difference between HNS and LNS groups: $*p<0.01$ (Fisher's LSD test).

presented in a sweetened solution or in tap water (interaction condition × period: $F(3,234)=32.2$; $P<0.001$). Animals with access to a sweetened morphine solution gradually increased their consumption and preference ratios whereas animals exposed to a solution of morphine dissolved in tap water showed a progressive decline of consumption and preference ratios. The great avidity for sucrose was reflected by the high average total fluid consumption (183±8 ml/kg/day versus 65±1 ml/kg/day for the non-sweetened condition).

The consumption of morphine, diluted in tap water at the 50 mg/l concentration, was compared between rats selected as high- and low-novelty seekers (Fig. 3, left panel). Statistical analysis (ANOVA two-way for repeated measures; factors group and period) revealed that HNS and LNS did not differ in morphine intake or morphine ratio ($F(1,117)=0.2$ and $F(1,117)=0.0$, respectively) (Fig. 3, left panel).

The consumption of morphine prepared in a sweetened solution is presented for HNS and LNS rats in Fig. 3 (right panel). ANOVA revealed that a greater degree of novelty preference was associated with a higher morphine ratio ($F(1,111)=4,4$; $P<0.05$). Indeed, morphine ratio gradually increased with time in HNS on contrary to LNS (interaction group × period, $F(3,111)=3.1$; $P<0.05$) (Fig. 4, lower right panel). A similar trend was observed with regard to morphine intake ($F(3,111)=2.41$; $P=0.07$) (Fig. 3, upper right panel).

3.3. Oral quinine consumption

Other rats selected as HNS and LNS were tested for their consumption of quinine solutions (Table 1). The progressive increase in the concentration of the quinine solution (1.6 to 50 mg/l) led to a decrease in consumption ($F(5,205)=170$; $P<0.001$). Post-hoc analysis revealed that the lower concentrations (1.6 to 6.4 mg/l) did not alter consumption. Quinine consumption decreased from the 12.5 mg/l concentration (6.4 mg/l versus 12.5 mg/l: $P<0.001$). HNS and LNS did not differ in sensitivity to the bitter taste of quinine solutions (factor group: $F(1,205)=0.3$; no interaction group × concentration: $F(5,205)=0.6$).

Table 1
Average±S.E.M. of quinine ratio, defined as the quinine oral consumption as a percentage of total fluid consumption, for quinine solutions at concentrations ranging from 1.6 to 50 mg/l, in animals selected as high-novelty seekers (HNS) or low-novelty seekers (LNS)

Quinine concentration (mg/l)	Quinine ratio (%)	
	LNS	HNS
	$N=21$	$N=22$
1.6	53±1	49±1
3.2	52±1	52±1
6.4	50±1	48±2
12.5	39±2	38±3
25	23±3	24±3
50	16±3	16±2

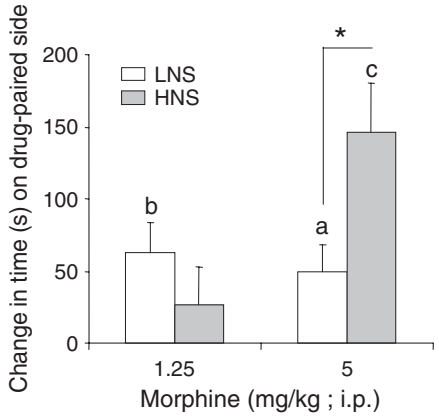

Fig. 4. Conditioned place preference induced by morphine (1.25 and 5 mg/kg) in rats selected as high-novelty seekers (HNS) or low-novelty seekers (LNS). The scores of conditioned place preference represent the difference in time (s) spent in the drug-paired side after and before conditioning. Average scores (±S.E.M.) after 3 conditioning sessions with morphine; $N=18$–21 animals per group. Rats spent more time on the drug-paired side after conditioning than before conditioning: (a) $p<0.05$; (b) $p<0.01$; (c) $p<0.001$ (paired Student's t-test). Difference between HNS and LNS groups: $*p<0.05$ (Fisher's LSD test).

3.4. Influence of novelty preference on morphine-induced place preference

Morphine-induced place preference was determined in other rats selected according to their preference for novelty (Fig. 4). ANOVA indicated no main effect of the dose ($F(1,72)=3.74$, $P=0.057$) or novelty preference level ($F(1,72)=1.18$) on the conditioned place preference scores, but HNS and LNS groups differed when the dose was increased (interaction group × dose $F(1,72)=5.89$; $P=0.018$). The 1.25 mg/kg dose of morphine produced a significant conditioned place preference only in LNS rats. However, both groups showed a conditioned place preference at the 5 mg/kg dose. Post hoc analysis revealed that HNS showed a greater conditioned place preference induced by the highest tested dose of morphine as compared to LNS ($P=0.014$). A trend for a lower score was observed in HNS compared to LNS at the 1.25 mg/kg dose.

4. Discussion

The results from the present study show that novelty preference is positively correlated with morphine consumption of a low, but not a high concentrated solution. Furthermore, our data indicate that high novelty preference is associated with a greater morphine-induced conditioned place preference at 5 mg/kg but not at 1.25 mg/kg.

4.1. Oral morphine consumption

During the presentation of morphine solutions, in a free choice with water, the animals decreased their consumption until a stable intake, as previously described with other drugs of abuse (Heyne, 1996, Heyne and Wolffgramm, 1998; Pelloux et al., 2004). As drugs of abuse induce both rewarding and aversive effects, a decline in consumption may occur until aversive and rewarding effects are equilibrated. It is noteworthy that rats consumed less morphine from the highest concentrated

solution compared to the lowest concentration used. These profiles suggest that consumption of morphine could be affected by its aversive pre-ingestive effects i.e. its well-known bitter taste, particularly at high concentration. Consistent with this idea, the oral consumption of quinine, a substance with bitter taste, devoid of abuse liability, decreased in a concentration-dependent manner. However, this aversive taste seemed to only influence morphine consumption at the highest concentrated solution. Indeed, the overall decline in morphine consumption at the lowest concentrated solution was progressive during the first days whereas aversive taste cues usually act very quickly.

However, the bitter taste of morphine cannot explain the initial avoidance of the morphine solution at the high concentration, as this occurred when morphine was presented in a sweetened solution. In fact, the aversion for morphine during the first days of the consumption period was even more pronounced than when the drug was diluted in tap water. This initial decrease could be due to the post-ingestive aversive effects of morphine. We observed that rats having a choice between a sucrose solution and water consumed very large amounts of sucrose as soon as the first day of the free-choice period, highlighting their high avidity for sucrose. When morphine was presented in a sweetened solution, this avidity for sucrose may produce an early rapid and high consumption of the sweetened morphine solution. This may lead to excessive intake of morphine resulting in strong post-ingestive aversive effects.

Our data show that novelty preference was positively, although weakly, correlated with consumption of a low concentrated morphine solution diluted in tap water. These results are in agreement with a previous study reporting that novelty preference is associated with greater oral amphetamine consumption from a low concentrated solution (Pelloux et al., 2004). We observed that the degree of novelty preference did not influence consumption of quinine, suggesting that difference in oral consumption of morphine between HNS and LNS is not related to differences in taste reactivity.

Interestingly, when the concentration of morphine dissolved in tap water was increased, the correlation between drug intake and novelty preference disappeared. One explanation of this finding is that as the concentration increased the aversive taste of morphine could oppose its rewarding properties and individual differences in sensitivity to morphine rewarding effect were masked. In support of this explanation, HNS consumed more morphine than LNS when the same concentration of 50 mg/l was presented in a 5% sucrose solution. It must be pointed out that novelty preference did not predict sucrose consumption in rats which had a choice between water and 5% sucrose solution.

Difference in sensitivity to morphine post-ingestive aversive effects between HNS and LNS rats may also be considered. When morphine was presented in a sweetened solution, HNS progressively increased their morphine consumption whereas LNS did not. These data suggest that tolerance to post-ingestive aversive effects may rapidly develop. Furthermore, HNS rats may become tolerant to these negative effects more easily than LNS rats during chronic morphine consumption.

The increased consumption of morphine in HNS relative to LNS rats may also reflect a difference in the reinforcing value of morphine between these groups. However, one of the difficulties in interpreting enhanced consumption of drugs is that higher intake may actually reflect an increase or a decrease in drug reward.

4.2. Morphine-induced conditioned place preference

Thus, we tested HNS and LNS rats in another paradigm that allows assessment of the motivational effects of drugs, the conditioned place preference test. We observed that high novelty preference was associated with a greater morphine-induced conditioned place preference at the dose of 5 mg/kg. This finding agrees with a previous report that the dose of 2 mg/kg induces a higher CPP in HNS rats than in LNS (Zheng et al., 2003). Whereas the previous study used a biased procedure (i.e. morphine being associated with the initial non-preferred compartment), we confirm these data with a CPP model using an unbiased procedure. In conjunction with the data from our oral consumption experiment, greater CPP score in HNS rats at the highest dose of morphine suggests that HNS consume more morphine because they experience/seek for greater rewarding effects of morphine than LNS rats. In support of this, HNS have a greater magnitude of conditioned place preference induced by amphetamine than LNS (Robinet et al., 1998), although we failed to observe such a difference between HNS and LNS (Pelloux et al., 2004).

Furthermore, the higher propensity of HNS to consume morphine from low concentrated solutions could be related to a deficit in drug sensitivity, as we previously proposed for oral consumption of amphetamine (Pelloux et al., 2004). HNS rats may need to consume more morphine in order to achieve an optimal level of stimulation of their hedonic system. In fact, in HNS and LNS rats, CPP scores varied in opposite direction as a function of morphine dose. HNS displayed a trend for a lower conditioned place preference induced by the 1.25 mg/kg dose of morphine as compared with LNS rats, suggesting a lower sensitivity of HNS rats to rewarding effects of morphine at this dose. Zuckerman (1994) postulated that the high sensation seeker would be characterized by an insensitivity to weak stimulation and a tolerance for high levels of stimulation. This idea fits well with our data showing that only high dose of morphine led to a CPP.

Drugs of abuse may be used as a self-medication to enhance mood and/or alleviate emotional distress. According to Cloninger (1987), the dimension of novelty seeking is underlain by the insufficient activity of the mesolimbic dopaminergic system which constitutes the biological substratum of the hedonic system, mediating drug reward and novelty-seeking behaviour (Koob, 1992; Robinson and Berridge, 1993; Hooks and Kalivas, 1995; Bardo et al., 1996). Chronically insufficient synaptic dopamine would lead high novelty seekers to constantly require intense stimulations in order to restore an optimum level of dopamine. Similarly, in HNS rats, activation of the mesolimbic dopaminergic transmission by consumption of either amphetamine or morphine would compensate the

deficit in dopamine, alleviating a pre-existing psychopathology (Khantzian, 1985). Although interesting, the hypothesis of reduced hedonic state in novelty-seeking subjects remains speculative at present and deserves further investigations.

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