Original Paper

Psychopharm

Journal of Psychopharmacology
0(0) 1–9

DOI: 10.1177/0269881110367444
jop.sagepub.com
SAGE

Strain differences in the dose–response relationship for morphine self-administration and impulsive choice between Lewis and Fischer 344 rats

Carmen García-Lecumberri, Isabel Torres, Sonsoles Martín, José A Crespo, Miguel Miguéns, Cristina Nicanor, Alejandro Higuera-Matas and Emilio Ambrosio

Abstract

Dose–response studies are thought to be a valuable tool to predict the most genetically drug-vulnerable individuals. However, dose–response curves for morphine self-administration have not yet been examined and nor strain differences might be evident. Therefore, this study aimed to define the dose–response curve for morphine self-administration (0.25, 0.5, 1 and 2 mg/kg) in Lewis (LEW) rats and their histocompatible Fischer-344 (F344) rats. In addition, impulsivity has been suggested as one of the genetic factors contributing most to the initiation of drug use. Therefore, the impulsive choice of both rat strains in the presence or absence of the same morphine doses was also analysed. LEW rats self-administered significantly more morphine whatever the dose tested and they exhibited greater basal impulsive choice compared with F344 rats. The F344 strain showed a preference for the dose of 0.5 mg/kg, while any of the doses used had a differential reinforcing effect in the LEW strain. The basal pattern of strain differences in impulsive choice was not affected by morphine administration. These data suggest that the LEW strain has a highly drug-vulnerable phenotype and they point to the strength of impulsivity as a pre-existing behavioural trait that might make this rat strain more vulnerable to the reinforcing effects of drugs and, therefore, to develop addiction.

Keywords

delayed reinforcement, impulsive choice, morphine self-administration, strain differences, vulnerability to addiction

Introduction

It is well accepted that a distinct biological vulnerability may either facilitate or inhibit the development of drug addiction in human beings. Genetic predisposition to drug addiction has been addressed from an experimental approach by using different inbred rat strains such as the Lewis (LEW) and its histocompatible control the Fischer 344 (F344) strain. It has consistently been shown that LEW rats self-administer alcohol (Suzuki et al., 1988), etonitazene (Suzuki et al., 1992), cocaine (Kosten et al., 1997) and nicotine (Brower et al., 2002) more readily than F344 rats. In addition, we found that LEW rats more rapidly acquired morphine self-administration behaviour than F344 rats under fixed and progressive ratio schedules of reinforcement (Ambrosio et al., 1995; Martín et al., 1999, 2003).

However, in most drug self-administration studies dose–response relationships have not been examined. Specifically, as far as we know, dose–response function for morphine self-administration has not yet been assessed. Likewise, it remains unclear whether different strains might display distinct dose–response functions for morphine self-administration, as has been reported for other drugs of abuse such as ethanol (Suzuki et al., 1988), nicotine (Brower et al., 2002) and cocaine (Kosten et al., 1997). In addition, dose–response relationships have been suggested to be a useful tool to predict drug-vulnerable and drug-resistant phenotypes (Piazza et al., 2000). Therefore, one of the main purposes of the present work has been to assess dose–response function for morphine self-administration in LEW and F344 rats. To address this issue, both rat strains were allowed to self-administer different doses of morphine (0.25, 0.5, 1 and 2 mg/kg) under a progressive ratio schedule of reinforcement, a regime that is considered to provide more information about the magnitude of reinforcing efficacy (i.e. motivational

Psychobiology Department, School of Psychology, UNED, Madrid, Spain.

Corresponding author:
Carmen García-Lecumberri, Psychobiology Department, School of Psychology, UNED, Madrid, Spain
Email: cglecumberri@psi.uned.es

properties) of a particular drug than the FR1 schedule, which best determines whether or not a drug is reinforcing (Hodos, 1961; Arnold and Roberts, 1997). Since the response requirements are higher in the PR than in the FR1 schedules, animals have to work harder to obtain the drug and, consequently, PR schedules could better reveal whether the motivational properties of addictive drugs are really altered depending on the dose.

Several studies in humans and animals have suggested that impulsivity is an important behavioural trait involved in drug dependence (see Evenden, 1999; Ho et al., 1999; Dalley et al., 2008, for reviewing the varieties of impulsive behaviours and the different methodological procedures to assess them). Indeed, increased impulsive behaviour has been reported in alcohol (Vuchinich and Simpson, 1998), heroin (Madden et al., 1997; Kirby et al., 1999), nicotine (Bickel et al., 1999; Mitchell, 1999) and cocaine abusers (Coffey et al., 2003). Accordingly, impulsive behaviour has also been found to be closely related to elevated alcohol consumption (Logue et al., 1998; Poulos et al., 1995), as well as increased nicotine (Diergaarde et al., 2008), amphetamine (Klebaur et al., 2001; Stoffel and Cunningham, 2008) and cocaine self-administration (Perry et al., 2005; Dalley et al., 2007) in rodents. In addition, differences in impulsive behaviour have been reported among strains. For instance, LEW rats make more impulsive choices than F344 rats (Anderson and Woolverton, 2005); that is, they prefer a smaller food intake (one pellet) with immediate reinforcement rather than delayed larger intake (three pellets) under a delayed reinforcement protocol (Logue, 1988, 1995).

Impulsive choices have been explained in terms of the delay discounting theory (Mazur, 1987; Rachlin, 2006). The discounting hypothesis of impulsivity proposes that the degree to which an individual disregards delayed rewards is a measure of impulsivity (i.e. as the value of the delayed reward decreases, impulsivity increases). In this model, the value assigned to each reinforcer is a function of delay and magnitude of both reinforcers, and the sensitivity to either feature. Interestingly, higher rates of delay discounting (i.e. increased impulsivity) have been consistently found in drug abusers by using several assessment methods (see Reynolds, 2006 for a review). However, it is not clear whether this increment in impulsivity reflects a pre-existing trait, the effects of exposure to drugs of abuse, or both (Moeller and Dougherty, 2003). Therefore, we were also interested in assessing whether impulsivity might be a behavioural trait associated with the differences in morphine self-administration found between LEW and F344 rats. To this end, basal impulsive choice behaviour of both inbred rat strains was assessed under an operant delayed reinforcement procedure in order to verify whether impulsive behaviour in the LEW strain was persistently exhibited even with greater delayed reinforcement. Thus, in the present study a higher small-immediate:large-delayed reinforcer ratio of 1 : 5 was established (Anderson and Woolverton, 2005). In addition, the same doses of morphine used in the self-administration study were tested to examine whether impulsive choice in both rat strains was affected by morphine treatment.

Materials and methods

Animals

Male LEW and F344 inbred rats weighing 200–250 g (Harlan Iberia, Spain) at the beginning of the experiments were used in this study. All animals were experimentally naïve and they were housed individually in a temperature-controlled room (23°C) with a 12-h light–dark cycle (08:00–20:00 lights on). The rats had free access to Purina laboratory chow and tap water prior to initiation of the experiments. Animals used in this study were maintained in facilities that complied with European Union Laboratory Animal Care Rules (86/609/EEC Directive).

Apparatus

Twelve operant chambers (Coulburn Instruments, USA) were used for impulsive and morphine self-administration behaviour studies. Two levers designed to register a response when 3.0 g of force was applied were placed 14 cm apart on the front wall of the chamber. Operant data were acquired and stored on IBM computers (Med Associates, USA).

Experimental procedure

Dose–response curve for morphine-self administration. Four separate groups of each inbred rat strain were randomly assigned to self-administer 0.25 (LEW: $n=9$, F344: $n=8$), 0.5 (LEW: $n=8$, F344: $n=9$), 1 (LEW: $n=9$, F344: $n=6$) or 2 (LEW: $n=7$, F344: $n=7$) mg/kg of morphine. The animals were surgically prepared by implanting a chronic intravenous catheter into the jugular vein as reported previously (Ambrosio et al., 1995; Martín et al., 1999, 2003). Morphine-reinforced behaviour was studied under a progressive ratio (PR) schedule of reinforcement for 15 days, as in our previous works (Martín et al., 1999, 2003). Briefly, animals were firstly submitted to an autoshaping fixed ratio 1 (FR1) schedule of food reinforcement in which a single press of the left lever of the chamber turned on a stimulus light above the lever that signalled pellet delivery (45 mg; Noyes Pellets, USA). A food pellet was also randomly delivered every 60 sec on average. Under the FR1 schedule, pressing the right lever had no consequences. Food-reinforced behaviour was acquired over 30 min for 5 days and a 30-sec time out period in which responses had no consequences followed each pellet delivery (FR1:TO 30 sec). Subsequently, animals were submitted to a PR schedule of reinforcement, in which the number of lever presses required to obtain reinforcement increased for successive reinforcers until the animal failed to meet the demands of the schedule. That point is denominated the 'breaking point' (Hodos, 1961) and it was defined as the ordinal value of the final ratio reached prior to a 60 min period of non-response sufficient to obtain an injection. In this study the lever responses required to obtain a pellet increased according to the series: 3,5,7,9,12,15,18,23,28,33 .... etc. When the animal completed the successive demands of the PR schedule the stimulus light was turned on over the lever that signalled drug delivery, resulting in the administration of a dose of 0.25, 0.5, 1 or 2 mg/kg morphine sulphate. The drug was delivered in a 90–115-µl volume during a 15-second interval dependent

upon the weight of the animal. Animals were given access to the drug 12 h/day during the dark cycle and they did not receive a priming injection prior to the initiation of the session.

Basal impulsive behaviour. An impulsive choice study was carried out on four separate groups of naïve rats from each inbred strain. Before the start of the training, the body weight of animals was reduced to 90%–95% of original body weight. This body weight reduction was held constant throughout the entire experiment. Initially, F344 and LEW rats were habituated to the chamber components with an autoshaping-fixed ratio 1 (FR1) schedule of reinforcement. After stable responses were reached, animals were trained to earn food pellets alternately using both levers, so that each lever press resulted in the delivery of one pellet, regardless of which lever was chosen. Subsequently, the rats were submitted to a delayed reinforcement procedure in which both levers were simultaneously activated and animals had to choose between a single food pellet (small reinforcer) delivered immediately or five food pellets (large reinforcer) delivered after programmed delays (Evenden and Ryan, 1999). At the start of the session there was no delay between the response and the delivery of the large reinforcer, but this delivery increased stepwise during the session to delays of 5, 10, 20 and 30 sec. The sessions were divided into five sets of 12 trials. During the first set of trials the delay between the lever pressing response and the delivery of the large reinforcer was 0 sec (i.e. no programmed delay), during the second set the delay was 5 sec, during the third 10 sec, during the fourth 20 sec, and during the last set the delay of reinforcement was 30 sec. A randomly determined inter-trial interval (30, 40, 50 sec) was established throughout the sessions and no signal was given to indicate the increase in the delay. Finally, the animals were immediately submitted to a similar delayed reinforcement procedure with increased delays of 10, 20, 40 and 60 sec over eight consecutive days. The length of each session was 70 min. Once the impulsive choice of animals was stable, data from the last three sessions were averaged to perform the statistical analysis.

Dose–response effects of i.v. morphine on basal impulsive behaviour. When impulsive food choice was established under the delayed procedure described above, a catheter was surgically implanted in the jugular vein of the animals as reported previously (Ambrosio et al., 1995; Martín et al., 1999, 2003). Intravenous administration of morphine was chosen so as to maintain the same conditions as in the self-administration study. After a recovery period of 8 days, animals were submitted to the same delayed reinforcement procedure described in the basal impulsive choice study, and they were infused twice with i.v. 0, 0.25, 0.5, 1 and 2 mg/kg of morphine sulphate in the operant chamber through a spring tether system (Alice King Chatham, USA) mounted to the skull of the rats with dental cement, both at the start (0 min) and in the middle (35 min) of the sessions. Each dose of morphine was tested in the same animals on different days following a counterbalanced design. A washout period of 48 h was established to assure disappearance of morphine before the administration of the following drug dose. In the middle of this washout period, the animals received an i.v. injection of saline solution.

Data analysis

In the morphine self-administration study, the average injection number (equal to the ordinal value of breaking points) of i.v. self-administered morphine (0.25, 0.5, 1 and 2 mg/kg) across the 15 sessions was the variable analysed. The Kruskal–Wallis non-parametric test was run to test whether there were significant differences among groups, given that the requirements of analysis of variance were not accomplished. Subsequent comparisons between pairs of means were made through the Mann–Whitney *U*-test.

In the basal impulsive behaviour study, the percentage of response in choosing a delayed large reinforcer obtained by averaging the last three sessions was the dependent variable. The non-parametric Mann–Whitney *U*-test was used to determine strain differences at the delay intervals used for food reinforcement (0, 10, 20, 40 and 60 sec) in the presence or absence of i.v. morphine. Within each rat strain, the differences in the percentage response in choosing a delayed reinforcer among the five delay intervals used in the drug-free conditions were tested with the non-parametric Friedman test for multiple related samples. Subsequent comparisons between pairs of means were made using the Wilcoxon signed-ranks test. The Friedman and Wilcoxon signed-ranks procedures were also used to test the effect of the different doses of i.v. morphine (0, 0.25, 0.5, 1 and 2 mg/kg) on operant impulsive choice within each rat strain. In all cases, differences were considered significant if the probability of error was less than 5%, and the calculations were made using the SPSS statistical package 12.0 version.

Results

The dose–response relationship for morphine self-administration is presented in Figure 1. Panels A and B show the number of morphine injections (0.25, 0.5, 1 and 2 mg/kg) self-administered by LEW and F344 rats, respectively, under a PR schedule of reinforcement throughout the sessions. The average number of self-administered injections over the 15 sessions for the four morphine doses tested is also shown (Panel C). Statistically significant differences were found among groups in terms of the average morphine injections during the study (Kruskal–Wallis test: $\chi^2 = 31.66$, d.f. = 7, $p < 0.001$). Indeed, strain differences were revealed by Mann–Whitney *U*-test at all the doses of morphine tested (0.25 mg/kg: $U = 5$, $p = 0.003$; 0.5 mg/kg: $U = 11.5$, $p < 0.018$; 1 mg/kg: $U = 2$, $p = 0.003$; 2 mg/kg: $U = 9.5$, $p = 0.05$). As evident in Panel C, LEW rats self-administered more morphine injections on average throughout the sessions (i.e. they reached higher breaking points) than F344 rats, whatever the dose of morphine tested. The F344 rats self-administered more injections at a dose of 0.5 mg/kg, a figure that was statistically different from that observed with 0.25 mg/kg ($U = 9$, $p < 0.01$) and 1 mg/kg ($U = 10$, $p < 0.05$) doses. However, the LEW strain showed similar higher self-administration rates regardless of the dose of morphine tested.

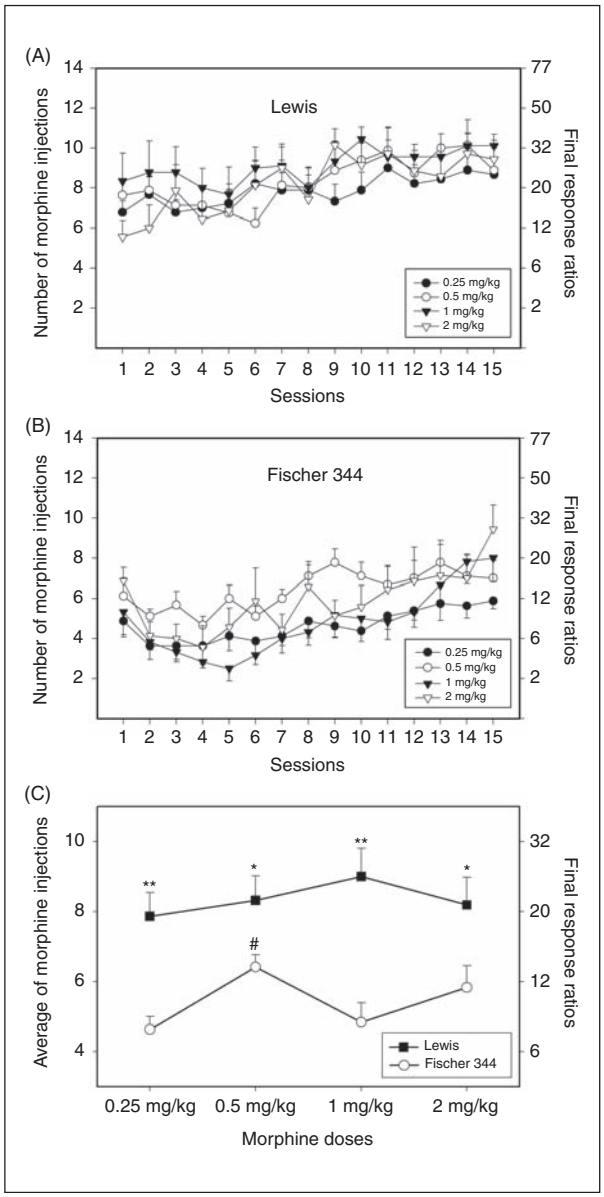

Figure 1. Dose–response relationship for morphine self-administration in Lewis and F344 rats. Number of injections of i.v. self-administered morphine (0.25, 0.5, 1 and 2 mg/kg) by LEW (Panel A) and F344 rats (Panel B) under a PR schedule of reinforcement across the sessions. Panel C represents the average number of i.v. self-administered morphine injections during the 15 sessions presented in Panels A and B. The data are presented as the mean ± SEM and the groups were: LEW rats: 0.25 mg/kg ($n = 9$), 0.5 mg/kg ($n = 8$), 1 mg/kg ($n = 9$) and 2 mg/kg ($n = 7$); F344 rats: 0.25 mg/kg ($n = 8$), 0.5 mg/kg ($n = 9$), 1 mg/kg ($n = 6$) and 2 mg/kg ($n = 7$). Strain differences: $^{*}p < 0.05$, $^{**}p < 0.01$; differences within each rat strain: #$p < 0.05$ with respect to 1 mg/kg and $p < 0.01$ with respect to 0.25 mg/kg of morphine (Mann–Whitney *U*-test).

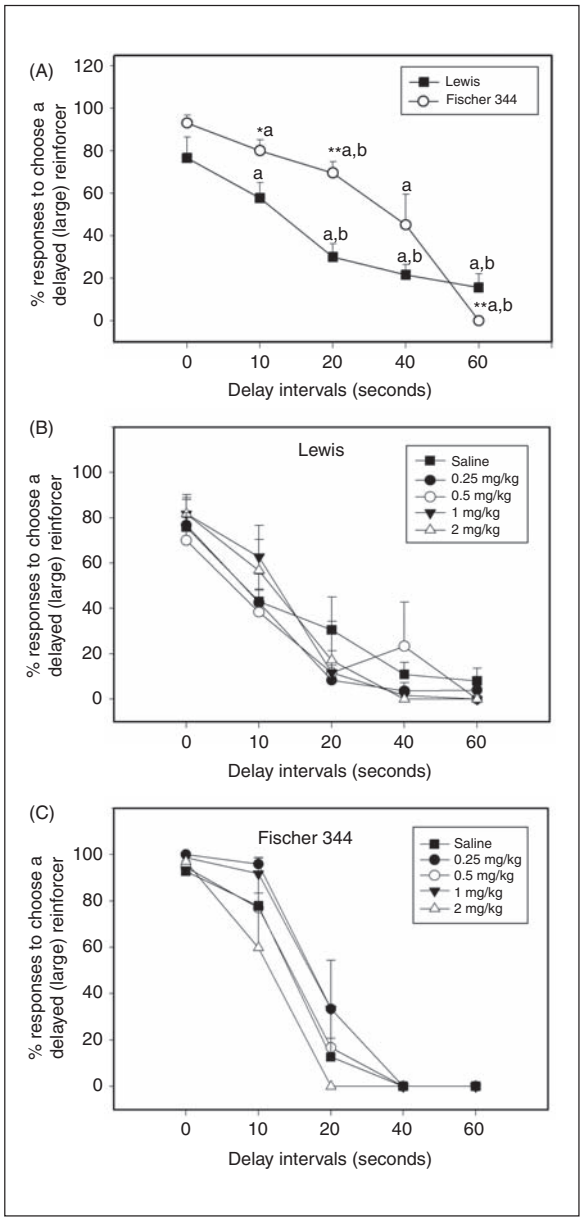

Figure 2. Impulsive choice in Lewis and F344 rats under basal conditions (Panel A) and after i.v. morphine administration (0, 0.25, 0.5, 1 and 2 mg/kg) (Panel B and Panel C, respectively). The percentage response to choose a delayed (large) reinforcer in both rat strains is represented at different delayed periods. The data are presented as the mean ± SEM of the last three sessions at each delay interval. Basal conditions: LEW rats ($n = 6$), F344 rats ($n = 6$); after morphine treatment: LEW ($n = 5$), F344 rats ($n = 6$). Strain differences shown by Mann–Whitney *U*-test: $^{*}p < 0.05$, $^{**}p < 0.01$. Differences within each rat strain were examined with the Wilcoxon signed-ranks test: $^{a}p < 0.05$ with respect to 0-sec interval; $^{b}p < 0.05$ with respect to 10-sec interval.

The choice of the delayed large reinforcer was assessed in LEW and F344 strains at the delay intervals used for food pellets (0, 10, 20, 40 and 60 sec) both under basal conditions (Figure 2, Panel A) and after morphine treatment (0, 0.25, 0.5, 1 and 2 mg/kg) (Panels B and C). As expected, both rat strains differed significantly in their basal pattern of delayed reinforcer preference. Generally, LEW rats displayed smaller percentage choice for the delayed reward over the immediate one than F344 rats, although statistically significant differences were only reached in 10 ($U = 4$; $p = 0.043$) and 20

($U = 5$; $p = 0.008$) sec delay intervals (Panel A). Within the LEW strain, the percentage choice for delayed reinforcers differed among the delay periods applied (Friedman test: $\chi^2 = 16.9$, d.f. $= 4$, $p = 0.002$). A continuous decrease in the percentage of choice was observed in this rat strain in the first three delay intervals, while this decreased response was maintained in the last two intervals. In F344 rats, the percentage choice for delayed reinforcers was also statistically different across the delay periods used (Friedman test: $\chi^2 = 20.20$, d.f. $= 4$, $p < 0.001$). F344 rats showed a decreasing percentage choice throughout all the delay periods with no response at the 60-sec interval. In addition, as can be observed in Panels B and C, none of the morphine doses affected the percentage response to choose a delayed reinforcer exhibited by LEW and F344 rats at the delay intervals applied, since no statistically significant differences were found between saline and morphine conditions. It should be noted, however, that in this case both strains showed a more pronounced decrease in response as the delay interval increased when compared with that observed in basal conditions.

Discussion

In this work we have examined whether strain differences in the dose–response relationship for morphine self-administration (0.25, 0.5, 1 and 2 mg/kg) might be evident between LEW and F344 rats under an operant reinforcement paradigm with a strong response requirement (progressive ratio). We found that LEW rats self-administered more morphine injections, reaching higher breaking points than the F344 rats across the sessions. By contrast, F344 rats achieved lower breaking points during most experimental sessions, only recording higher values in the last ones. We previously reported similar patterns of morphine self-administration in LEW (higher and consistent breaking points from the beginning of the study) and F344 rats (lower breaking points across the majority of the sessions reaching a plateau in the last experimental sessions) (Martín et al., 1999, 2003). In addition, when the average number of self-administered morphine injections across the 15 sessions was compared per dose between both rat strains, LEW rats consistently self-administered more injections than F344 rats irrespective of the morphine dose used. It might be expected that animals will modify their self-administration pattern as the amount of morphine received decreases or increases (Piazza et al., 2000). Indeed, F344 rats displayed greater self-administration with the dose of 0.5 mg/kg of morphine, suggesting that this dose has a greater reinforcing effect in this rat strain. By contrast, morphine self-administration did not change in LEW rats even though they received very different amounts of morphine (i.e. with the lowest dose of 0.25 mg/kg: 1.96 ± 0.17; with the highest dose of 2 mg/kg: 16.41 ± 1.56). Therefore, neither dose of morphine seemed to show a different reinforcing efficacy in LEW rats.

It has been suggested that an upward shift in the dose–response function for drug self-administration, as is the case here, is associated with a lower threshold dose for acquiring this behaviour, possibly indicating an increase in the efficiency of the neural substrates to translate the effects of the drug (Piazza et al., 2000). Based on the dose–response relationship for morphine self-administration presented here, the LEW strain appears to have a phenotype that is more vulnerable to develop drug dependence. Indeed, the LEW rats display higher rates of drug self-administration irrespective of the amount consumed, even though they have to work harder to obtain the drug (as in PR reinforcement schedules). Furthermore, since the LEW rats consume more of the drug, they are more likely to suffer from the drug-induced neuroadaptation that may underlie drug addiction. Our results are similar to those obtained in dose–response function for other drugs of abuse such as ethanol (Suzuki et al., 1988), nicotine (Brower et al., 2002) and cocaine (Kosten et al., 1997). In these studies, the LEW strain consistently shows higher response rates than the F344 or Holtzman strain, especially when response requirement of the schedule increases. As far as we are aware, our study is the first to establish dose–response curves for morphine self-administration, as well as identifying strain differences in this dose–response relationship between LEW and F344 rats.

In order to test whether impulsive choice might be a persistent behavioural trait involved in the vulnerability to self-administered morphine shown by LEW rats, we also studied differences in impulsive behaviour between both rat strains through a delayed operant procedure, in the presence or absence of the same doses of morphine as in the self-administration study. We found different basal patterns of impulsive choice in the two inbred rat strains, LEW rats showing a consistently lower preference for delayed reinforcement than F344 rats (i.e. LEW rats were more impulsive). Although both rat strains exhibited a decreased response to delayed reinforcement as the delay interval increased, as expected (Evenden and Ryan, 1996; Kieres et al., 2004; Anderson and Woolverton, 2005), F344 rats were more capable of waiting for delayed reinforcement when the delay was longer. These results suggest that the LEW strain is less tolerant to delays in reward than F344 rats, as these animals appear to be compelled to emit responses that provoke immediate reinforcement, which might explain the higher response exhibited by the LEW strain in operant tasks (Martín et al., 2003).

Our results confirm those recently reported by other authors who also found accentuated impulsive choice in LEW rats compared with the F344 strain (Anderson and Woolverton, 2005), although a small-immediate:large-delay reinforcement ratio of 1 : 3 was used, rather than the 1 : 5 ratio established here. It could be argued that differences in impulsive choice between LEW and F344 rats might be due to strain differences in discrimination of changes in delay (Acheson et al., 2006). Nevertheless, we have previously found that temporal discrimination of both inbred rat strains is very similar (Martín et al., 2003). It should not be overlooked, however, that LEW and F344 rats might exhibit differences in the precision of discrimination of the reinforcer value, as has been demonstrated by Bezzina et al. (2007) in female Wistar rats.

Taken together, these data suggest the strength of impulsive choice as a pre-existing behavioural trait in the LEW strain. However, this basal strain difference in terms of impulsive choice between LEW and F344 rats was not affected by

i.v. morphine treatment. Hence, the choice of delayed reinforcement shown by both rat strains treated with different doses of i.v. morphine was similar to that found in drug-free conditions, indicating that morphine does not interfere with the basal impulsive choice of the LEW strain when compared with F344 rats. However, it should be noted that both rat strains displayed a more pronounced decrease in the operant response when treated with saline or morphine, especially at the longest delay intervals, when compared with those observed in basal conditions. This difference could be due to the learning of the sequence of delay intervals over consecutive sessions, since i.v. saline and morphine administration was carried out in the same animals. Indeed, a decrease in the choice of delayed large reinforcement has been reported when animals are submitted to successive sessions in an operant delay procedure (Evenden and Ryan, 1996; Pitts and McKinney, 2005). The incapacity of morphine to alter the basal strain differences in terms of impulsive choice in our study is not in agreement with the earlier results (Kieres et al., 2004), where morphine administration produced a dose-dependent increase in impulsivity. However, strain differences, delay procedure, type of reinforcement, and the means and schedule of drug administration may account for such discrepancies. According to our results, other works have failed to detect consistent changes in impulsive behaviour after morphine treatment (Pitts and McKinney, 2005), as well as following heroin, cocaine or amphetamine self-administration (Dalley et al., 2005a,b).

Given that impulsive choice in LEW and F344 rats does not seem to be affected by morphine treatment, the results from this study suggest that the increased impulsive behaviour exhibited by the LEW strain may be a pre-existing behavioural trait that facilitates morphine self-administration. Thus, inherent impulsivity in LEW rats might produce a higher operant response, making this strain reach higher and consistent rates of drug self-administration from the beginning of the study, as reported previously. Accordingly, growing evidence is emerging that points out the close relationship between impulsivity and drug self-administration. Thus, impulsivity scores under a delayed reinforcement procedure are positively correlated with the magnitude of alcohol self-administration (Poulos et al., 1995). In addition, genetically selected Roman high-avoidance rats are more impulsive and drink more alcohol than low-avoidance rats (Razafimanalina et al., 1996; Aguilar et al., 2004). Also, rats with a high rate of impulsivity more rapidly acquire cocaine self-administration and they consume more cocaine at the end of the sessions than less impulsive rats (Perry et al., 2005; Dalley et al., 2007). Similarly, high-responder (HR) rats in a novel environment exhibit a higher impulsivity and amphetamine self-administration than low-responder (LR) rats (Klebaur et al., 2001; Stoffel and Cunningham, 2008). Impulsive choice has also been reported to be a predictor of reinstatement of cocaine-seeking behaviour (Perry et al., 2008). More recently, impulsivity scores have been found to predict not only nicotine self-administration, but also nicotine-seeking and vulnerability to nicotine relapse (Diergaarde et al., 2008). Similar results have been reported in mice: thus, the strains that are more able to control their behavioural responding (i.e. that are less impulsive) exhibit less voluntary ethanol consumption, while those that are more impulsive consume more ethanol (Logue et al., 1998). Also, mutant mice lacking the gene encoding the neuronal-specific gamma subtype of protein kinase C consume more ethanol and show greater impulsivity when compared with wild-type littermates (Bowers and Wehner, 2001). Taken together, these data argue in favour of impulsivity as a genetically determined behavioural trait that might alter decision-making and confer greater vulnerability to initiating drug abuse and/or facilitate the transition from controlled to compulsive drug-taking (Belin et al., 2008; Redish et al., 2008; Verdejo-García et al., 2008).

It has been suggested that impulsivity is one of the genetic factors contributing most to the initiation of drug use and progression from recreational to regular drug usage, and less to addiction and relapse after chronic exposure to drugs (Kreek et al., 2005). Indeed, impulsivity has been proposed to be mainly involved in the progression to compulsive drug use, and an impulsivity–addiction construct has been identified (Belin et al., 2008). Several genes with one or more alleles encoding different elements of the neurotransmitter systems have been associated with impulsive and addictive behaviours in both humans and animals (Kreek et al., 2005; Pattij and Vanderschuren, 2008; Verdejo-García et al., 2008). For instance, polymorphisms have been found in genes encoding D2, D3, D4, 5HT1B and 5HT2A receptors and dopamine (DA) and noradrenaline (NA) transporters, as well as in those encoding enzymes involved in the degradation of amines, such as catechol-O-methyltransferase (COMT) and monoamine oxidase A (MAO-A). In addition, recent cumulative evidence has also highlighted the role of glutamatergic and cannabinoid systems in the regulation of impulsive behaviour (Pattij and Vanderschuren, 2008), besides their well known involvement in addictive disorders (Maldonado et al., 2006; Kalivas et al., 2008).

It is well established that F344 and LEW rat strains differ in several neurochemical parameters of the neurotransmitter systems, including dopaminergic, serotonergic, noradrenergic and glutamatergic systems (Burnet et al., 1992; Chaouloff et al., 1995; Selim and Bradberry, 1996; Flores et al., 1998; Lindley et al., 1999; Sziraki et al., 2001). In this respect, we previously found that LEW rats show higher basal N-methyl-D-aspartate (NMDA) receptor levels in several brain areas (Martín et al., 2003), as well as decreased basal μ-opioid receptor (Oliva et al., 1999; Sánchez-Cardoso et al., 2007) and proenkephalin (PENK) mRNA levels in dorsal striatum and nucleus accumbens compared with F344 rats (Martín et al., 1999). Interestingly, a diminished μ-opioid binding has been found in mice exhibiting higher impulsive behaviour (Ognibene et al., 2007) and a decreased glutamatergic activity by blockade of mGlu1 receptors has been demonstrated to reduce impulsivity (Sukhotina et al., 2008). More recently, we have found strain differences in basal levels of D2 receptors and in their modulation after acquisition and extinction of morphine self-administration, LEW rats showing a decreased D2 receptor binding compared with F344 rats in several brain regions, including nucleus accumbens (Sánchez-Cardoso et al., 2009). Accordingly, a diminished D2/D3 receptor availability has been reported in the nucleus accumbens of impulsive rats exhibiting higher rates of cocaine self-administration when compared with less impulsive rats (Dalley et al., 2007).

These findings are consistent with the widely observed reduction in striatal D2 binding reported in cocaine self-administered monkeys (Nader et al., 2006), as well as in cocaine abusers (Volkow et al., 1993). Thus, neurochemical dissimilarities found between LEW and F344 rats may be involved in the observed differences in impulsivity and drug self-administration between these rat strains, and might confer on LEW rats a higher chance of developing drug addiction.

In summary, in this study we have shown that LEW rats self-administered more morphine injections than F344 rats, whatever the morphine dose used. The F344 strain exhibited a preference for an intermediate dose of morphine (0.5 mg/kg), while the LEW strain showed similar higher self-administration rates regardless of the amount of morphine received. This result suggests that LEW rats have a highly vulnerable phenotype that makes them more prone to develop drug dependence. In addition, LEW rats exhibited a greater basal impulsive choice than F344 rats, even when a higher immediate:delayed reinforcer ratio of 1 : 5 was assessed. Therefore, the LEW strain shows a lesser tolerance to the delay of reward, which results in responses that provide immediate reinforcement. This basal pattern of strain differences in impulsive choice was not affected by morphine treatment. Taken together and in the conditions of our study, these data indicate the strength of impulsive choice as a pre-existing behavioural trait that might make the LEW strain more vulnerable to the reinforcing properties of opiates, as measured in operant self-administration paradigms.

Acknowledgements

The authors are grateful to R. Ferrado for technical assistance. This research has been supported by grants from the Ministerio de Educación y Ciencia (SAF2004-08-148; SAF2007-064890); Ministerio de Sanidad y Consumo (RD06/001/0029 of Instituto de Salud Carlos III and Plan Nacional sobre Drogas 2008–2010); Dirección General de Investigación de la Comunidad de Madrid (S-SAL/0261/2006; Consorcio I + D CANNAB-CM); and UNED (Plan de Promoción de la Investigación y Premio de Investigación 2010 sponsored by Banco de Santander). Morphine sulphate was kindly provided by Agencia Española del Medicamento (Ministerio de Sanidad y Consumo).

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