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Morphine-induced place conditioning in Fischer and Lewis rats: Acquisition and dose-response in a fully biased procedure

Catherine M. Davis [a,*], Peter G. Roma [a], Juan M. Dominguez [b], Anthony L. Riley [a]

[a] *Psychopharmacology Laboratory, Department of Psychology, American University, 4400 Massachusetts Avenue, NW, Washington, DC 20016, United States*
[b] *Behavioral Neuroscience Laboratory, Department of Psychology, American University, Washington, DC, United States*

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Abstract

The Fischer (F344) and Lewis (LEW) rat strains differ on a variety of behavioral assays examining the effects of morphine, with many of the differences observed during acquisition of behavioral responses. The results of these studies and others examining endogenous physiology and the biochemical effects of morphine suggest that F344 rats are more sensitive to morphine than LEW rats. However, LEW animals have shown greater conditioned place preferences (CPP) to 4 mg/kg than F344 rats. CPP is a popular assay of drug reward in which acquisition of the preference can be measured across multiple conditioning cycles, yet this aspect of CPP has not been assessed in F344 and LEW rats. As part of an ongoing effort to fully characterize the conditioned rewarding effects of abused drugs in these strains, the present study assessed the effects of 0, 1, 4 and 10 mg/kg subcutaneous (SC) morphine in adult male F344 and LEW rats (n=12/strain/dose). A fully biased place conditioning procedure was employed where morphine's effects were paired with the initially non-preferred chamber on Day 1, saline was paired with the preferred chamber on Day 2 and drug-free access to the entire apparatus was allowed on Day 3. This conditioning and testing regimen was repeated for four consecutive cycles. The F344 animals acquired CPP at 1 mg/kg only; this effect emerged after only two conditioning cycles. LEW rats never acquired a CPP at any dose tested. Peak blood morphine levels following SC injections of 1, 4 or 10 mg/kg revealed no significant strain or dose effects. These behavioral data are consistent with the hypothesis that F344 rats are more sensitive to the rewarding effects of morphine than LEW rats. Additional implications for the Fischer–Lewis model of drug abuse and the utility of CPP acquisition procedures are discussed.

Keywords: F344; LEW; Morphine; Conditioned place preference; Apparatus bias; Behavior genetics; Reward

1. Introduction

The Fischer (F344) and Lewis (LEW) inbred rat strains differ in their behavioral responses to a variety of drugs of abuse (Kosten and Ambrosio, 2002; Riley et al., in press), and as such, have been used to explore the underlying mechanisms mediating differential sensitivities to various drug effects (Flores et al., 1998; Grabus et al., 2004; Guitart et al., 1992, 1993; Herradón et al., 2003a,b; Selley et al., 2003). Although much of the work on drug sensitivity has focused on the rewarding effects of drugs of abuse, F344 and LEW rats also reportedly differ in their responses to the aversive effects of such drugs, as assessed by the conditioned taste aversion (CTA) procedure (Glowa et al., 1994; Grigson and Freet, 2000; Kosten et al., 1994; Lancellotti et al., 2001; Pescatore et al., 2005; Roma et al., 2006, 2007). Strain-dependent differences in sensitivity to the discriminative stimulus effects of morphine and nicotine, as assessed by drug discrimination procedures, have also been reported (Morgan et al., 1999; Philibin et al., 2005).

Of particular interest to those investigating vulnerability to drug abuse are differences observed during drug self-administration procedures. Interestingly, many of the differences between F344 and LEW rats observed during self-administration studies are seen during the acquisition phase. For example, LEW animals acquire self-administration of cocaine, morphine and other opioids, and ethanol faster than F344 rats, even though comparable intake is often seen during maintenance or at the

* Corresponding author. Tel.: +1 202 885 1721; fax: +1 202 885 1081.
E-mail address: cd2994a@american.edu (C.M. Davis).

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conclusion of self-administration studies with these drugs (Ambrosio et al., 1995; Kosten et al., 1997; Martín et al., 1999, 2003; Suzuki et al., 1988a,b). Although this pattern is not always seen with cocaine (Haile and Kosten, 2001; Haile et al., 2005; Kruzich and Xi, 2006), LEW rats are usually described as being generally more sensitive to the reinforcing effects of drugs of abuse than F344 rats (Camp et al., 1994; Flores et al., 1998; Kearns et al., 2006; Martín et al., 1999).

It is evident that monitoring the acquisition of drug-induced behaviors is a useful tool when investigating genetic factors in behavioral responses to drugs of abuse. Another valuable and increasingly popular behavioral preparation in which acquisition can be assessed is the conditioned place preference procedure (CPP; Bardo and Bevins, 2000; Tzschentke, 1998; Cunningham et al., 2003). When studying acquisition in the CPP design, animals are tested for approach behavior to the cues associated with the drug after each conditioning cycle, thereby allowing investigators to determine how many drug-environment pairings are required to elicit a significant preference. It is believed that faster acquisition of CPP represents greater sensitivity to the drug's rewarding effects, as opposed to its reinforcing effects *per se* (Bardo and Bevins, 2000; Gaiardi et al., 1991; Shippenberg et al., 1996; also see Meisch and Carroll, 1987).

Place conditioning to several drugs has been examined in F344 and LEW rats (see Kosten and Ambrosio, 2002; Roma et al., 2006), but despite the important information to be gained from studying acquisition, monitoring the acquisition of drug-induced CPP over conditioning has yet to be done in these strains. Therefore, as part of a larger effort to more fully characterize the behavioral responses to the conditioned rewarding effects of drugs of abuse in F344 and LEW rats, the present study investigated the acquisition of CPPs induced by several doses of morphine. Previously, Guitart and colleagues (1992) found that both strains exhibited preferences induced by 4 mg/kg morphine, but the LEW strain had a preference double that of the F344 rats. Another recent report by Grakalic et al. (2006) assessed the effects of stress on morphine-induced CPP at doses of 1, 4 and 10 mg/kg in F344 and LEW animals; although no direct strain comparisons were reported, both strains acquired CPP at all training doses. Most relevant to the present study was the fact that acquisition was not assessed in either of the above experiments.

The current study examined the acquisition of morphine CPPs at 1, 4 and 10 mg/kg using a fully biased procedure, meaning that all animals experienced morphine's effects in the initially non-preferred conditioning chamber. Although many advocate use of an unbiased procedure where drug-paired chamber assignments are counterbalanced across the equally-preferred conditioning chambers (Carr et al., 1989; Cunningham et al., 2003; van der Kooy, 1987), the biased design has some potential advantages. Biased procedures may be more sensitive to increases from pre-conditioning to post-conditioning due to the lower amount of time spent in the initially non-preferred chamber (Schenk et al., 1985; Scoles and Siegel, 1986). Although empirical support is limited (Blander et al., 1984), it has also been argued on theoretical grounds that biased procedures may provide more room for the emergence of dose-response functions, which are somewhat rare in unbiased assessments, possibly due to "ceiling effects" (Cunningham et al., 2003; Roma and Riley, 2005). Nonetheless, monitoring acquisition of CPP allows for the detection of differences in how rapidly asymptotic preference levels are achieved, a variable absent in designs featuring a single preference test at the conclusion of multiple conditioning cycles (Simpson and Riley, 2005). If the LEW animals are indeed more sensitive to morphine's rewarding effects than F344 rats, then the assessment of place conditioning over multiple trials provides an opportunity for such differences to emerge in the form(s) of differential CPP acquisition at any of the three doses tested.

2. Method

2.1. Subjects

A total of 96 adult male rats served as subjects; 48 rats were of the Fischer strain (F344/SsNHsd), and 48 were of the Lewis strain (LEW/NH). The respective mean (±SD) weights for the two strains at the beginning of the experiment were 251±54 g and 286±56 g. All animals were housed in individual hanging wire cages (24×19×18 cm) with *ad libitum* access to food and water. Animal housing rooms operated on a 12-h light/dark schedule (lights on at 0800 h) and were maintained at an ambient temperature of 23 °C; all procedures were conducted between 0900 h and 1400 h. All procedures described in this report were in compliance with National Research Council guidelines (NRC, 1996, 2003) and were approved by the Institutional Animal Care and Use Committee at American University.

2.2. Drugs and solutions

Morphine sulfate (generously supplied by the National Institute on Drug Abuse) was prepared in a 5 mg/ml solution in saline and administered via subcutaneous (SC) injection at doses of 1, 4 or 10 mg/kg; non-drug saline injections within the drug-treated groups were also administered SC and were equivolume to morphine. Exclusively vehicle-treated control animals (0 dose) were injected with either SC saline equivolume to 4 mg/kg morphine ($n=6$) or 3 ml/kg intraperitoneal (IP) saline ($n=6$).

2.3. Place conditioning apparatus

The CPP apparatus was constructed of wood and consisted of two main conditioning chambers (30×30×39 cm each) joined by a smaller middle chamber (10×30×39 cm). One of the conditioning chambers had a smooth Plexiglas floor, the other conditioning chamber had a textured plastic floor and the smaller middle chamber had heavy steel mesh attached directly to the floor. Vertically sliding wood panels separated the chambers. Six identical apparatuses were utilized for running multiple animals simultaneously. The procedure room was illuminated only by an 85-watt red light mounted to the ceiling in the center of the room; a white noise generator was also used in the room throughout all procedures. The CPP tests were