

Effect of Morphine Preequposure on Morphine-Induced Conditioned Taste Aversions and Place Preferences in the Fischer (F344) and Lewis (LEW) Inbred Rat Strains.



Preferences in the Fischer (F344) and Lewis (LEW) Inbred Rat Strains.

Catherine M. Davis, Jorge Valderama and Anthony L. Riley

Psychopharmacology Laboratory, Department of Psychology American University, Washington, DC 20016, USA



Introduction

It is well documented that the reinforcing and aversive effects of a variety of drugs change with drug history. For example, in 1975 Cappell and colleagues reported that preexposure to morphine attenuated the drug's ability to condition a taste aversion (CTA), an index of the aversive properties of drugs (Cappell et al., 1975; for a review see Riley and Simpson, 2001). The rewarding effects of drugs are also affected by drug preexposure, as measured by the ability of subthreshold doses to support drug self-administration and the enhancement of conditioned place preference (CPP) (Valadez & Schenk, 1994; Lett, 1989; Simpson and Riley, 2005, respectively). Although it is not clear whether these respective changes in the affective properties of abused drugs reflect common or different mechanisms, it is clear that drug preexposure impacts the subsequent rewarding/reinforcing and aversive effects of these drugs. Taken together, this shift in affective properties could possibly lead to further use of the drug, increasing the chance the drug will be abused.

Although the effects of drug history are well documented, most of these reports employ outbred animals. Given the importance of genetic factors in drug addiction, it is of interest to study these effects in inbred rat strains that may differ in their sensitivity to many drugs of abuse. Two such strains are the Fischer (F344) and Lewis (LEW) rats. For example, F344 acquire strong taste aversions to morphine, while LEW do not acquire a morphine-induced CTA at any dose tested (Lancellotti et al., 2001). In the CPP preparation, LEW rats have shown a greater degree of morphine-conditioned preference for the drug-paired side when compared to F344 rats (Guitart et al., 1992).

Accordingly, the present study assessed the effects of morphine preexposure on conditioned taste aversions and conditioned place preferences in LEW and F344 rats using the combined CTA/CPP design (Martin et al., 1988; Simpson and Riley, 2005). By determining what effect prior experience with morphine has on its subsequent affective properties in genetic models of drug addiction, further insights might be made as to the consequences of the interaction of genes and prior substance use.

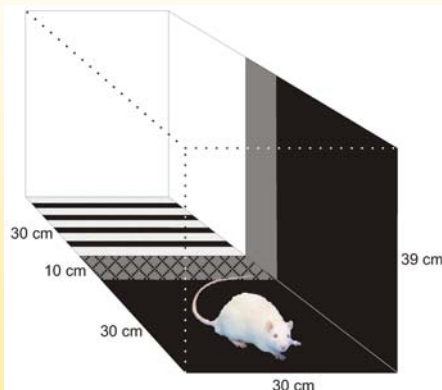


Figure 1. Place conditioning apparatus

Subjects

Twenty-three F344/N and 26 LEW/N male rats, approximately 6 months of age and weighing 300-400 g at the beginning of the experiment were used. Guidelines established by the Institutional Animal Care and Use Committee at American University were followed at all times.

Apparatus

Animals were individually housed in stainless-steel wire mesh cages with *ad-lib* access to food. Animals were maintained on a 12:12 light dark cycle, with lights on at 0800h and at an ambient temperature of 23°C for the duration of the experiment.

CTA: Graduated 50 ml Nalgene bottles were attached to the front of each cage for the presentation of either water or saccharin during the 20-min fluid access period.

CPP: Six separate boxes, each with three distinct chambers separated by two removable dividers served as the CPP apparatus. The left side compartment was black, with a smooth floor; the right side compartment was white with a textured floor; the middle compartment was gray in color and had a wire-mesh floor. The CPP room was illuminated with a red light, 1.52 m above the place conditioning apparatus (see Figure 1).

Drugs & Solutions

Morphine sulfate (generously supplied by NIDA) was prepared as a 5 mg/ml solution in physiological saline (drug vehicle). Saccharin (0.1 % sodium saccharin, Sigma) was prepared as a 1 g/l solution in tap water.

Procedure

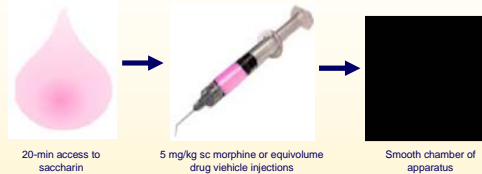
Habituation: After 23-h of water deprivation, all rats were given 20-min access to water daily, until they were approaching and drinking from the tube within 2 s of its presentation.

Preexposure: Once the drinking criterion was reached, animals were ranked by water consumption and assigned to a preexposure condition by strain (Groups MF and ML, morphine preexposed; Groups VF and VL, vehicle preexposed). All animals in Groups MF and ML were given a 5 mg/kg sc injection of morphine every other day for five exposures. Animals in Group VF and VL were given sc injections of saline equivalent volume to morphine (5 mg/kg) according to the schedule noted above. Fluid intake was monitored throughout the preexposure phase.

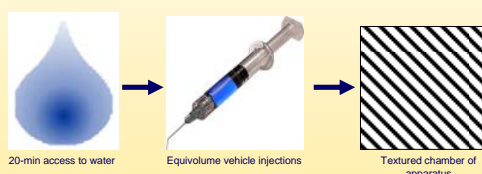
CPP Pretest: All animals were pretested in the place conditioning apparatus to determine the subjects' natural bias. The majority of animals preferred the textured side [$F(1, 47) = 73.743, p < .05$]. Therefore, a biased procedure was performed and the smooth (black) chamber was termed the 'drug-paired' side.

Conditioning: Days 1A and 2A constitute one conditioning cycle; a total of 4 cycles were run.

Day 1A:



Day 2A:

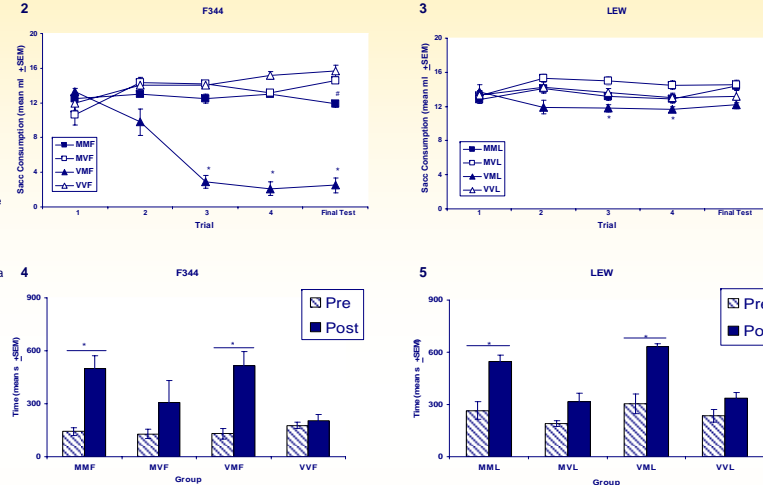


CPP Posttest: On day after the last conditioning day (i.e., Day 4B), all animals were given a posttest to determine the degree of preference for the drug-paired side. All animals were placed in the middle gray chamber, drug free, with the doors removed to allow free access to all chambers for 15 min. Animals received 20-min access to water after the posttest.

CTA Final Test: The day following the CPP posttest, all animals were given a drug-free saccharin test. During the scheduled fluid-access period, animals were given saccharin to drink without subsequent injections. Fluid intake was monitored.

Method

Results



Conclusions

✓ Vehicle-preexposed F344 rats conditioned with morphine acquired taste aversions similar to previous reports (Lancellotti et al., 2001).

✓ Morphine preexposure significantly attenuated morphine-induced taste aversions in F344 animals.

✓ LEW animals conditioned with morphine failed to acquire a taste aversion, an effect consistent with prior reports

✓ Morphine preexposure had no effect on the acquisition of taste aversions in LEW animals

✓ Morphine preexposure had no effect on morphine-conditioned place preferences in either strain; all animals conditioned with morphine, regardless of strain or preexposure group, showed a significant preference for the drug-paired side during the posttest.

✓ It is possible that **acquisition** of the place preferences were affected by preexposure to morphine. However, CPP acquisition was not measured in the present study.

✓ A ceiling effect could explain the CPP results. The 5 mg/kg dose of morphine used in the study could represent the dose that conditions a maximum place preference in both strains, causing all animals to exhibit the same degree of preference for the drug-paired side.

✓ Given the attenuation of morphine-induced taste aversions in the F344 strain, it seems possible that a genetic vulnerability to the aversive consequences of abused drugs can be altered by prior exposure. Attenuation of the aversive consequences of drug use could lead to subsequent abuse of these compounds, even without enhancement of the rewarding effects of the drug.

Subjects were given morphine or vehicle during preexposure and injected with either morphine or vehicle during conditioning, yielding Groups MM, MV, VM and VV. The first letter refers to the preexposure injection; the second letter refers to the conditioning injection; the third letter refers to the strain (F or L)

Figure 2. Mean (\pm SEM) saccharin consumption for F344 rats. Group VMF differed from all other groups on Trials 3 and 4 and the test ($* p < .05$). Group MMF differed on the Final Test from Group VVF ($\# p < .05$).

Figure 3. Mean (\pm SEM) saccharin consumption for LEW animals. Group VML differed from group MVL on Trials 3 and 4 ($* p < .05$); however, Group VML never differed from its control, Group VVL, on any of the trials or the Final Aversion Test.

Figure 4. Mean (\pm SEM) number of seconds spent by F344 animals in the smooth chamber during the pretest and posttest. The preference conditioned after four drug-smooth chamber pairings was not affected by the preexposure manipulation ($* p < .05$ for difference in time from pretest to posttest).

Figure 5. Mean (\pm SEM) number of seconds spent by LEW animals in the smooth chamber during the pretest and posttest. The preference conditioned after four drug-smooth chamber pairings was not affected by the preexposure manipulation ($* p < .05$ for difference in time from pretest to posttest).

References

Cappell, H., LeBlanc, A. E., and Herling, S. 1975. Modification of punishing effects of psychoactive drugs in rats by previous drug experience. *Journal of Comparative and Physiological Psychology*, 89: 347-356.

Guitart, X., Beiter-Johnson, D., Marby, D. W., Kosten, T. A., and Nestler, E. J. 1992. Fischer and Lewis rat strains differ in basal levels of neurofilament proteins and their regulation by chronic morphine in the mesolimbic dopamine system. *Synapse*, 12: 242-253.

Lancellotti, D., Bayer, B. M., Glowa, J. R., Houghtling, R. A., and Riley, A. L. 2001. Morphine-induced conditioned taste aversions in the LEW/N and F344/N rat strains. *Pharmacology, Biochemistry, and Behavior*, 68: 603-610.

Lett, B. T. 1989. Repeated exposures intensify rather than diminish the rewarding effects of amphetamine, morphine, and cocaine. *Psychopharmacology*, 98: 357-362.

Martin, G. M., Bechara, A., and van der Kooy, D. 1988. Morphine preexposure attenuates the aversive properties of opiates without preexposure to the aversive properties. *Pharmacology, Biochemistry, and Behavior*, 30: 687-692.

Riley, A. L. and Simpson, G. R. 2001. The attenuating effects of drug preexposure on taste aversion conditioning: generality, experimental parameters, underlying mechanisms and implications for drug use and abuse. In: Mowrer, R. R. and Klein, S. B., editors. *Contemporary learning theory*, 2nd ed. Hillsdale, New Jersey: Lawrence Erlbaum Associates; 2001. p. 505-559.

Simpson, G. R. and Riley, A. L. 2005. Morphine preexposure facilitates morphine place preference and attenuates morphine taste aversion. *Pharmacology, Biochemistry, and Behavior*, 80: 471-479.

Valadez, A. and Schenk, S. 1994. Persistence of the ability of amphetamine preexposure to facilitate acquisition of cocaine self-administration. *Pharmacology, Biochemistry, and Behavior*, 47(1): 203-205.