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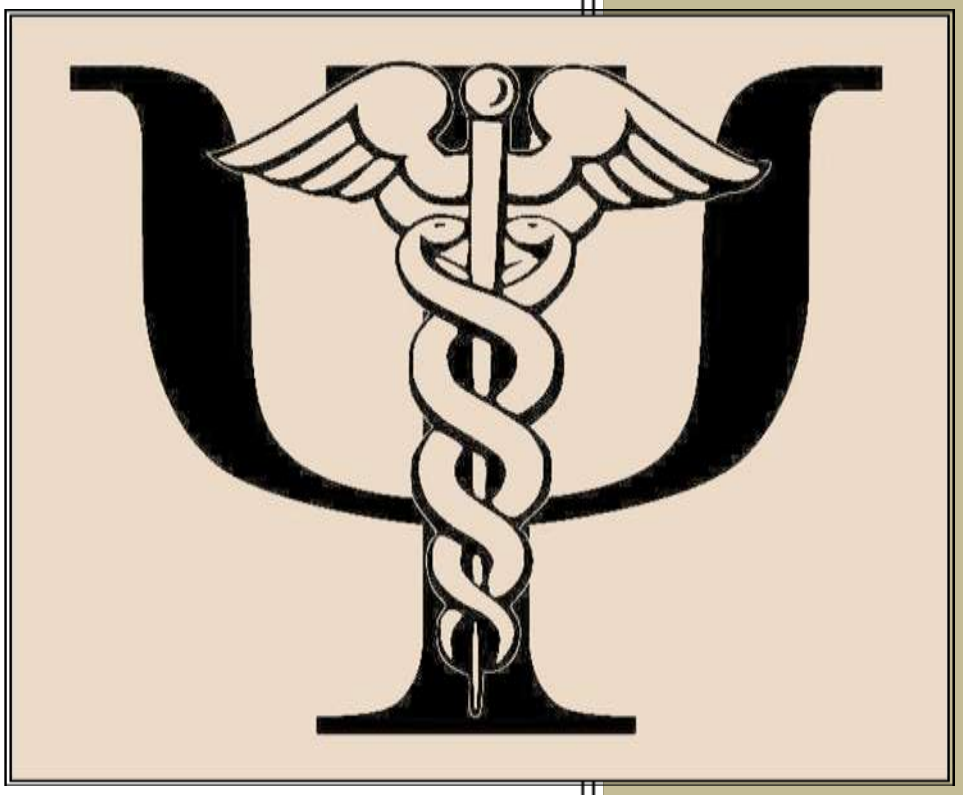

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OPPOSITE EFFECTS OF ETHANOL ON TASTE AND PLACE CONDITIONING IN RATS

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Abstract

In two experiments with rats, we tested the positive and negative motivational effects of ethanol using the taste avoidance and place conditioning procedures. In Experiment 1, rats received, on alternate days, pairings of a flavour with 1.0 g/kg ethanol (i.p.) and pairings of a different flavour with saline. During testing, the subjects showed a lower consumption of the ethanol-paired flavour. In Experiment 2, rats were tested for the rewarding effects of ethanol using the place preference procedure. They received injections of ethanol before being placed in a distinctive environment for 30 min. When later given a choice between this location and a novel environment, the rats showed a preference for the environment in which they experienced the drug effects relative to control subjects injected with saline. These results show that alcohol appeared to have both aversive and rewarding effects given that the same dose of drug was able to condition an aversion for a paired flavour but a preference for a paired spatial location.

Keywords: Ethanol; Conditioning; Taste aversion; Place preference; Rats.

Resumen

En este estudio con ratas se examinaron las propiedades motivacionales del alcohol con los procedimientos conductuales de aversión condicionada al sabor y de preferencia de lugar. El Experimento 1 se realizó con el procedimiento de aversión al sabor. Las ratas recibieron durante el condicionamiento, en días alternos, emparejamientos de una solución gustativa con una inyección de etanol (1.0 g/kg) y de un sabor diferente con una inyección de salino. En una prueba posterior los animales consumieron menos la solución gustativa asociada con el alcohol durante el condicionamiento. En el Experimento 2 se empleó el procedimiento de preferencia condicionada de lugar. Las ratas eran inyectadas con alcohol o con salino antes de introducirlas durante 30 minutos en uno de los lados de una cámara de condicionamiento con dos compartimentos. En la prueba se medía el tiempo que pasaban los animales en cada una de los lados de la cámara de condicionamiento. Los sujetos inyectados con alcohol mostraron una preferencia por el lado del aparato en el que habían experimentado los efectos fisiológicos del alcohol. Los resultados indican que la dosis de alcohol administrada en este estudio puede tener tanto efectos motivacionales positivos como negativos en el organismo.

Palabras clave: **A**lcohol, Condicionamiento, Aversión al sabor, Preferencia de lugar, Ratas.

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Introduction

There is considerable evidence from the animal learning research to indicate that drugs of abuse, such as morphine, heroine, cocaine, and amphetamine, have both rewarding and aversive properties (for reviews, see Hunt & Amit, 1987; Tzschentke, 2007). It has been shown that these drugs have a positive motivational effect in some behavioural paradigms, such as self-administration (oral and operant methods) and place conditioning procedures, but an aversive effect when drug is tested with the taste avoidance paradigm. For example, when exposures to a flavoured solution and a distinctive environment are simultaneously paired with amphetamine (Reicher & Holman, 1977; Sherman, Roberts, Roskam, & Holman, 1980) or morphine (Sherman, Pickman, Rice, Liebeskind, & Holman, 1980), the rats later show an aversion to the flavour paired with the drug but a preference for the spatial location. It is important to note, however, that the ability of the drugs of abuse to promote flavour aversion or place conditioning may vary depending on pharmacological, procedural and organismic factors (reviewed in Riley & Simpson, 2001). For example, it has been reported that amphetamine produces opposite effects (avoidance *versus* preference) in the place conditioning procedure depending on dosage and individual susceptibility (Cabib, Puglisi-Allegra, Simon, Le Moal, & Piazza, 1996); that morphine pretreatment enhances morphine-induced place preference and attenuates morphine taste aversion (Simpson & Riley, 2005), and that there are genetic differences in the sensitivity to the positive and negative properties of drugs of abuse (Lancelloti, Bayer, Glowa, Houghtling, & Riley, 2001; Orsini, Bonito-Oliva, Conversi, & Cabib, 2005).

Since opiate and psychostimulant drugs produce taste avoidance and place preference over a range of experimental conditions, ethanol may do so as well. In taste conditioning studies, ethanol (often given by injection) is typically paired with ingestion of a novel flavoured fluid, and the effects of taste-ethanol pairings are evaluated by measuring subsequent consumption of the fluid in the absence of the drug. The most of these studies have obtained conditioned aversion to taste solutions that have been paired with moderate to high doses of ethanol in both rats and mice (see Broadbent, Muccino, & Cunningham, 2002; Cunningham, Fidler, & Hill, 2000). However, studies of the effects of ethanol in the place conditioning procedure have generated inconsistent results (for reviews, see Green & Grahame, 2008; Pautassi, Nizhnikov, & Spear, 2009).

The most commonly used method to study place conditioning in rodents has been the two-compartment conditioning apparatus (see Bardo & Bevins, 2000; Tzschentke, 1998). In this procedure, the animals experience the effects of the ethanol (usually administered by intraperitoneal injection) in one of the compartments, while the other one is associated with vehicle injections. Subsequent approach (place preference) or avoidance (place aversion) behaviour directed toward or away from that drug-paired compartment, usually under a drug-free state, indicates that the animal has come associate either positive or aversive aspects of the ethanol with the environment in which it was experienced. The general finding has been either no effects (at doses lower than 1.0 g/kg) or place aversion (usually at doses of 1.0 g/kg or higher), indicated by the avoidance of the ethanol-paired environment. However, a number of factors including route of administration, species and strain of rats employed, ethanol experience before conditioning, the number of conditioning trials, and temporal variables, can determine the rewarding and aversive effects ethanol in this paradigm (see Risinger, Cunningham, Bevins, & Holloway, 2002).

With regard to the route of administration, a common outcome has been place aversion when ethanol was consumed orally (Stewart & Grupp, 1986), or administered by intraperitoneal (Cunningham, 1981), intravenous (Van der Kooy, O´Shaughnessy, Mucha, & Kalant, 1983) or intragastric routes (Fidler, Bakner, & Cunningham, 2004) at doses above 1.0 g/kg in drug naive rats. Relative to time effects on ethanol-induced place conditioning, it has been shown in mice that the direction of place conditioning depends critically on the time interval between exposure to the environment and administration of the drug. In particular, in a study by Cunningham, Okorn, & Howard (1997; see also Cunningham & Henderson, 2000; Cunningham, Smith, & McMullin, 2003), place preference was observed when ethanol was given immediately or 30 min before placing animals into the conditioning context, whereas place aversion was observed when the drug administration occurs after context exposure. However, in contrast to findings with mice, the ethanol´s motivational influence on place conditioning does not appear to be related to interval variables in rats (see Bormann & Cunningham, 1998; Cunningham, Niehus, & Noble, 1993). As above mentioned, the literature supports the conclusion that ethanol induces conditioned place aversion in rats.

Nevertheless, there have been some exceptions to the general finding of ethanol-induced place aversions in rats. Conditioned place preferences have been observed in

adult rats after extensive alcohol pre-exposure or multiple conditioning trials. For example, Reid Hunter, Beaman, and Hubbell (1985) reported a place preference for an environment paired with injections of ethanol. However, such a result emerged only in rats that had previously consumed a solution of 6% ethanol on each of 26 consecutive days under conditions of fluid deprivation. Most relevant for the objectives of the present experiments is the effect of the number of conditioning trials. Of particular interest is the study by Bozarth (1990) that suggests a development of sensitization to the rewarding effects of ethanol after prolonged administration. In this study, a conditioned place preference was produced in rats after receiving a total of 15 conditioning trials under 1.0 g/kg ethanol, but not in rats conditioned with 0.5 g/kg ethanol. In contrast, Bienkowski, Kuca, Piasecki, and Kostowski (1996) reported place preference in rats that received 20 injections of ethanol (0.5 g/kg), while 15 conditioning trials with 1.0 g/kg dose of ethanol did not result in a significant change in place preference. Jointly, these studies suggest that repeated exposure to ethanol may be the critical factor in producing place preference in rats.

Given this background, we were concerned with two issues. The first was whether we could replicate the finding by Bozarth (1990) that ethanol-induced place preference occurs in rats after many conditioning trials. Secondly, we were concerned with whether the same ethanol dose can produce conditioned place preference and conditioned taste aversion. Consequently, the purpose of the Experiment 1 was to examine the aversive motivational effects of ethanol using the taste aversion procedure, while the aim of the Experiment 2 was provide evidence for the rewarding effects of ethanol in the place conditioning method. We used the same ethanol dose (1.0 g/kg, i.p.) employed by Bozarth (1990). Using the taste aversion procedure and Wistar rats as subjects, we have shown in a previous experiment from our laboratory that five conditioning sessions with 1.0 g/kg ethanol resulted in a significant conditioned taste aversion (but not with 0.5 g/kg).

Method

Subjects

Thirty-two male Wistar rats from the breeding colony of the University of Oviedo were used in this study. Eight rats were assigned to the flavour aversion

procedure (Experiment 1) and twenty-four to the place conditioning procedure (Experiment 2). The rats were about 90 days old and weighed 453-538 g at the start of the experiments. Upon arrival, they were housed individually in opaque plastic cages (27 cm long x 27 cm wide x 19 cm high), and kept in a housing room maintained at 22ºC on a 12:12 h light:dark cycle (lights on at 08:00 h). All experimental manipulations occurred at the same time each day during the light portion of the cycle. Throughout the experiments, animals were on a water deprivation schedule (see procedure), receiving 1-h access to water in their home cages at the end of each daily session. Food was always available in the home cages. All experimental manipulations were in accordance with guidelines for the care and use of laboratory animals of the European Council Directive (86/609/EEC).

Drugs and solutions

Ethanol was prepared every day by diluting ethyl alcohol in a 15% (v/v) solution with saline (0.9%) and was administered intraperitoneally (i.p.) at a dose of 1.0 g/kg (8.4 ml/kg of the ethanol solution). A 0.9% saline solution was used as control injections (10 ml/kg).The fluids employed in the flavour aversion study were a 8% sucrose solution and a 1% sodium chloride solution.

Apparatus

The opaque plastic cages located in the housing room were used for the flavour aversion procedure (Experiment 1). The roof of these cages was made of wire mesh. Inverted 50-ml centrifuge tubes equipped with stainless steel, ball-bearing spouts were used to present the fluids. The location of the tubes in either the left part or the right part of the roof of the cages was counterbalanced. Fluid consumption was measured by weighing the tubes before and after fluid presentation and recording to the nearest 0.1 g.

The apparatus used for measuring place conditioning (Experiment 2) consisted of two adjoining wooden chambers that were each 40 cm long x 30 cm wide x 57 cm high. This apparatus was located in a separate room of the laboratory that was dimly illuminated by a 40-W white bulb and contained a speaker delivering a background noise with an intensity of 75 dB. The front wall of the chambers was made from transparent plastic. The chambers were made distinctive by the tactile stimuli of the interchangeable floor halves placed below each chamber. One of the floors was made from wire mesh, and the other floor consisted of a tray covered with commercially

obtained cat litter. These two environments are known to be discriminative from each other because they were used in our previous studies on contextual conditioning in rats. During training sessions, a thin wooden barrier was inserted in the apparatus to restrict the rats to the appropriate box only. The position of the floors on each side of the apparatus was counterbalanced within groups. During habituation and testing sessions, time spent on each side of the apparatus was recorded using a video camera. The inside of the apparatus and floors were cleaned with water, and the cat litter changed after each animal.

Design and procedure

Experiment 1. Taste conditioning.

A within-subjects design was employed to contrast consumption of a flavour (A) repeatedly paired with ethanol to consumption of a second flavour (B) paired with an injection of saline. The rats were gradually adapted to a water-deprivation schedule over a period of 7 days. During that period, they received access to water in the drinking tubes for 30 min per day in their home cages. By the end of this phase, the rats had achieved a steady baseline of water consumption. Following this phase came the conditioning phase of the experiment, which consisted of six cycles of alternating ethanol and saline injections. On ethanol days, the rats received access to 10 ml of flavour A for 30 min in the home cages, which was followed 10 min later by an injection (i.p.) of ethanol. On saline days, the rats were allowed to drink 10 ml of flavour B for 30 min followed 10 min later for an injection of saline. The flavours were counterbalanced such that, for half of the subjects, the sucrose solution served as flavour A and the sodium chloride as flavour B; for the remaining animals, the assignment was reversed. After two recovery days, in which the subjects were given access to water for 60 min in the home cages, the test session began. In this test, the rats received non-reinforced presentations of the flavours, first of the flavour A and then of the flavour B on alternative days. On each, the rats received access to 30 ml of the appropriate solution for 30 min.

Experiment 2. Place conditioning.

A between-subjects design was used to examine the effect of pairing a distinctive environment with ethanol on expression of preference or aversion for that

context. The rats were randomly divided into two groups (n = 12). One group Ehanol received injections (i.p.) of ethanol, and the other group (Saline) received saline injections. The experiment involved three phases: habituation, place conditioning, and testing. The habituation phase (2 sessions) served to habituate rats to handling associated with the procedure and the specific features of the apparatus. The second day of this phase (pre-test) served as a measure of initial preference of each rat for the tactile stimuli provided by the left and right sides of the place conditioning apparatus. In the habituation sessions, the rats had access to the entire apparatus for 15 min.

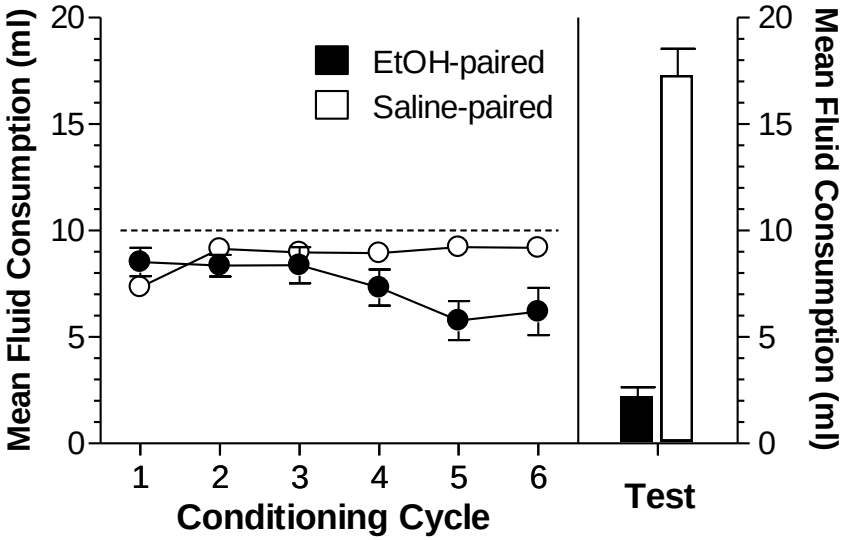
The place conditioning phase lasted 21 days (3 cycles of 7 days). In the first five days of each cycle, the rats in group Ethanol were injected (i.p.) with ethanol, while those in group Saline received control injections of saline. After each daily injection, all rats were placed on their non-preferred side of the place conditioning apparatus for 30 min (i.e., a biased stimulus assignment procedure was employed). The last two days of each cycle were non-treatment days. The rats were given free access to water in their home cages for 60 min at the end of each daily session. Preference testing (2 sessions) began on the day after the last conditioning cycle. In these test sessions, the rats had access to the entire apparatus for 15 min. Drug or saline injections were not given during testing sessions.

Data analysis

In Experiment 1, intakes of flavour A and flavour B across conditioning cycles was analyzed by analysis of variance (ANOVA) with two within-subject factors (flavour and cycle). The difference in flavour consumptions during testing was evaluated with a paired t test. In Experiment 2, the dependent variable was the amount of time spent on each side of the place conditioning apparatus. As before mentioned, we used a biased design such that the rats show an unconditioned preference for one of the sides of the conditioning apparatus during the pre-test, being the ethanol paired with the non-preferred side during conditioning phase. To simplify presentation and interpretation of results, the data were analyzed by subtracting each rat's pre-test score (second day of habituation) from the amount of time spent on the side paired with the ethanol following the 15 conditioning trials (preference testing). A difference score of zero indicates no change in place preference following conditioning, while positive and negative scores indicate place preference and place aversion, respectively. The change in place preference following injections of ethanol or saline was evaluated with a t test.

Values are expressed as mean (± SEM), and $p < .05$ was considered significant in the present experiments.

Figure 1.Mean intakes of the ethanol-paired flavour and the saline-paired flavour over the conditioning cycles (left-hand panel), and mean amounts of fluid consumed during the test session (right-hand panel). Error bars represent the standard errors of mean.



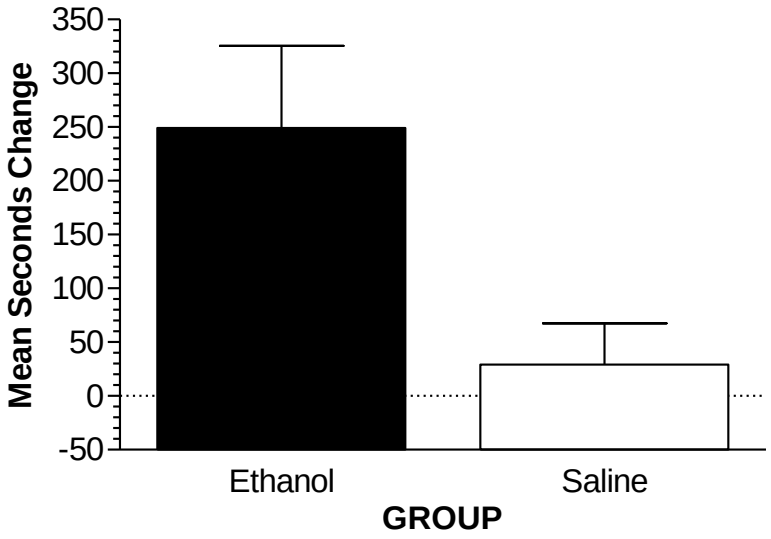
Results

Experiment 1. Taste conditioning

The left side of Figure 1 shows flavour consumptions over the course of the conditioning cycles. It may be seen that intake of the ethanol-paired flavour declined over the cycles, whereas intake of the flavour paired with saline remained high across the days. The ANOVA carried out on consumption with flavour and cycle as factors revealed significant effects of cycle, $F(5, 35) = 1.98$; $p < .05$; $\eta^2 = .45$, and flavour, $F(1, 7) = 5.81$; $p < .01$; $\eta^2 = .64$, and a significant interaction between these factors, $F(5, 35) = 7.12$; $p < .01$; $\eta^2 = .84$. In addition, paired *t* tests demonstrated that there was a significant difference between flavour intakes in cycles 5-6, ts(7) > 3.14; ps < .01; ds > 0.76. The right side of Figure 1 depicts the mean consumptions during the test session.

Subjects consumed significantly less the solution associated with ethanol than the saline-paired solution, $t(7) = 11.75$; $p < .001$; $d = 0.97$.

Figure 2. The figure depicts the mean changes in place preference following conditioning with ethanol or saline. Positive scores indicate a place preference. Error bars represent the standard errors of mean.



Experiment 2. Place conditioning

A *t* test conducted on the pre-test data showed that the groups did not differ in their initial bias, i.e., the amount of time spent on the non-preferred side of the conditioning apparatus, $t(22) = 0.51$; $p > .05$; $d = 0.21$. Figure 2 shows mean changes in place preference following conditioning trials in the two treatment groups (positive scores indicate conditioned place preference). A *t* test conducted on the test data indicated that the difference between the two groups was significant, $t(22) = 2.41$; $p < .01$; $d = 1.02$. Thus, repeated injections of ethanol produced an increase in time spent in the drug-paired environment (group Ethanol) while no changes in place preference were observed following saline injections (group Saline).

Discussion

The present experiments examined the aversive and rewarding effects of ethanol as indexed by flavour aversion and place preference conditioning paradigms. The data

from the first experiment indicated that ethanol administered at a dose of 1.0 g/kg (i.p.) produced a conditioned taste aversion to a novel fluid paired with the drug effects. In the second experiment, repeated pairings of environmental cues with the same dose of ethanol resulted in conditioned place preference for that environment. Thus, using a dose of 1.0 g/kg (i.p.), the rats showed conditioned taste aversion to the flavour paired with ethanol (Exp. 1) and conditioned preference for the place in which the drug was administered (Exp. 2). Based on data collected thus far, we think that ethanol (at dose above 1.0 g/kg), as other abused drugs, appeared to have both positive and negative motivational effects.

The results obtained in Experiment 1 are consistent with previous findings in studies of ethanol-induced taste aversion using many different rat and mouse strains (Broadbent et al., 2002; Kulkosky, Sickel, & Riley, 1980; Pautassi et al., 2009; Risinger & Cunningham, 1998), supporting the view that flavour aversion produced by alcohol is mediated by the drug aversive properties. Perhaps more important, was the finding in Experiment 2 of ethanol-induced place preference in drug-naive rats. As before mentioned, conditioned place preference have been observed in rats only after extensive pre-exposure to ethanol (Bienkowski, Kuca, & Kostowski, 1995; Reid et.al., 1985). Typically, the studies with alcohol-naive rats have yielded either place aversions or no effect of alcohol (see Fidler et al., 2004). The place preference effect shown here is similar to that previously reported by Bozarth (1990) after multiple conditioning trials and with the same dose of ethanol. The main contribution of the present study is that ethanol, being administered at a dose of 1.0 g/kg (i.p.), can produce conditioned place preference and conditioned taste aversion in drug-naive Wistar rats. It is important to indicate that different susceptibility to the positive and aversive effects of alcohol exists across multiple strains of rats. For example, a recent study by Roma, Flint, Higley, and Riley (2006) has reported that Fischer and Lewis rats differ in their sensitivity to the ethanol aversive effects. Specifically, the Fischer rats showed stronger and more dose-sensitive conditioned taste aversions than the Lewis rats; however, neither place preferences nor place aversions for alcohol-paired environments were apparent in either strain. These results suggest genetic vulnerability to motivational properties of ethanol.

The present results indicate, as tested with other abuse drugs, that repeated injections of ethanol enhance the drug-induced rewarding effect as measured by place preference. As mentioned in the introduction, it has been shown that repeated exposures intensify the rewarding effects of amphetamine, morphine, and cocaine (Lett, 1989;

Cabib et al., 1996), although the same drug pre-treatment attenuates the production of a taste aversion (see Simpson & Riley, 2005). This argument, i.e., sensitization to the rewarding effects of ethanol, is supported by data showing increased ethanol-induced place preference in rats after a prolonged exposure to ethanol, but not in ethanol-naive rats (Ciccocioppo, Panocka, Froldi, Quitadamo, & Massi, 1999; Reid et al, 1985). However, our findings are also consistent with other mechanisms which argue for a decreasing of the aversive effects of ethanol that result from repeated exposure, an effect that would be manifested in the observed place preference. Recent studies with mice (see Cunningham & Gremel, 2006; Cunningham, Tull, Rindal, & Meyer, 2002) offer evidence for the view that ethanol pre-exposure produces tolerance to its aversive effects, rather than sensitization to its rewarding effects. These studies examined the effects of repeated ethanol injections given in the home cages on subsequent development of ethanol-induced place preference or place aversion. The results showed that ethanol pre-exposure reduced the strength of the place aversion when ethanol was administered before exposure to the context during conditioning trials, but had no effect on place preference. In contrast, the ethanol pre-exposure eliminated the conditioned place aversion normally produced when ethanol is given immediately after exposure to context during place conditioning. These data suggest that repeated exposure to ethanol reduces its aversive effects.

In summary, these experiments provided evidence that ethanol produces taste aversion and place preference in adult Wistar rats. Although we did not use a concurrent measure of both aversive and rewarding effects of ethanol, our data suggest that repeated exposure to ethanol determines its affective properties. The identification of factors which may either intensify the positive motivational effects of ethanol or attenuate its aversive effects can enhance our knowledge of how alcohol acts as a reward and may ultimately suggest new approaches to the treatment of alcohol abuse in humans. Thus, experimental assessment of taste aversion and place conditioning should be considered as a potentially useful tool to understanding the determinants of the progression from moderate consumption to the compulsive pattern of alcohol-seeking behaviour observed in alcohol dependence.

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