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ScienceDirect
Pharmacology, Biochemistry and Behavior 88 (2008) 427–431
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

An assessment of sex differences in nicotine-induced conditioned taste aversions

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Received 12 April 2007; received in revised form 20 September 2007; accepted 24 September 2007
Available online 29 September 2007

Abstract

Sex differences in taste aversion learning have been reported for a number of different compounds. It is unknown, however, to what degree, if any, such differences exist when nicotine is the aversion-inducing agent. To address this issue, in the present experiment male and female rats were given limited access to saccharin followed by an intraperitoneal (IP) injection of either vehicle or nicotine (0.4, 0.8 or 1.2 mg/kg). Although nicotine induced significant taste aversions in both males and females, the aversions were generally weak at all doses tested. There were no sex differences in the acquisition or strength of the aversions induced by nicotine. The vulnerability to drug abuse has been suggested to be a function of the balance of the rewarding and aversive effects of a drug. Given the relatively weak aversions induced in both sexes and the absence of differences between males and females, it is unlikely that the reported sex difference in the self-administration of nicotine is a function of differences in nicotine's aversive effects. The reported difference in the self-administration of nicotine by males and females is more likely a function of differences in the sensitivity to the rewarding effects of the drug.

Keywords: Nicotine; Sex differences; Conditioned taste aversion; Abuse vulnerability; Affective properties

1. Introduction

Although conditioned taste aversions can be robustly and rapidly induced by a variety of compounds, including drugs of abuse (Goudie et al., 1978; Hunt and Amit, 1987), these aversions can be affected by a variety of factors, e.g., strain of subjects, route of administration, dose, age (see Freeman and Riley, 2005; Klosterhalfen and Klosterhalfen, 1985). One factor that has received considerable attention in this regard is the sex of the subject (Busse et al., 2005; Cailhol and Mormede, 2002; van Haaren and Hughes, 1990). Interestingly, a number of investigators have noted that male rats acquire taste aversions faster and/or extinguish aversions slower than female rats for several compounds, e.g., LiCl (Chambers et al., 1981; Dacanay et al., 1984; Randall-Thompson and Riley, 2003; Weinberg et al., 1982), cocaine (Busse et al., 2005; van Haaren and Hughes, 1990) and alcohol (Cailhol and Mormede, 2002) (see Randall-Thompson and Riley, 2003 for a report of no sex differences with morphine). The interest in sex differences in aversion learning comes, in part, from attempts to understand the vulnerability to drug use and abuse. Specifically, the use and abuse of a specific drug may be a function of the balance between its rewarding and aversive effects, as many drugs that are readily self-administered also induce taste aversions (Hunt and Amit, 1987; Simpson and Riley, 2005; Wise et al., 1976). Understanding if the rewarding or aversive effects of a drug are dependent upon sex may provide insight into how sex may affect an individual's vulnerability to use and abuse drugs.

It is interesting in this context that female rats display weaker cocaine-induced taste aversion than males (Jones et al., 2006), an effect that may contribute to the fact that females self-administer greater amounts of cocaine than males (see review by Lynch, 2006). Similar to the work reported with cocaine, the limited assessments of sex differences in the rewarding effects of nicotine indicate that female rats have a shorter latency to the first nicotine infusion (in a self-administration preparation), have faster acquisition of self-administration of nicotine and respond more than males for nicotine (Chaudhri et al., 2005; Donny et al., 2000), suggesting that females are more sensitive to nicotine's rewarding effects than males. Although sexual dimorphism is evident in the overall reinforcing effects of

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doi:10.1016/j.pbb.2007.09.016

nicotine, sex differences in nicotine-induced taste aversions have not been examined. To assess if sex differences exist in the aversive effects of nicotine (and to possibly implicate the role of these aversive effects in nicotine use), the present study examined the ability of nicotine to induce aversions to saccharin in male and female rats. Specifically, male and female subjects were given access to saccharin followed by an injection of either saline (vehicle) or one of three doses of nicotine (0.4, 0.8 and 1.2 mg/kg) previously shown to induce aversions (Iwamoto and Williamson, 1984; Pescatore et al., 2005). Because the aversions induced by nicotine in aversion conditioning are generally reported to be weak (Etscorn et al., 1986, 1987; Iwamoto and Williamson, 1984; Ossenkopp and Giugno, 1990), subjects in the present study were given repeated pairings of saccharin and nicotine to assess the acquisition and relative strength of the aversions induced by nicotine.

2. Method

2.1. Subjects

The subjects were 42 male and 42 female, experimentally naïve, Long Evans rats (purchased from Harlan Sprague Dawley, Indianapolis, IN), approximately 90 days of age at the start of the experiment. Body weights averaged 333.3 g (males) and 252.5 g (females) at the start of the experiment. All animals were maintained on a 12:12 light–dark cycle (lights on at 0800 h) and at an ambient temperature of 23 °C. Except where noted, food and water were available *ad libitum*. Animals were handled approximately two weeks prior to conditioning to limit the effects of handling stress during conditioning and testing. Procedures recommended by the Guide for the Care and Use of Laboratory Animals (1996), the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (2003) and the Institutional Animal Care and Use Committee at American University were followed at all times.

2.2. Apparatus

Subjects were individually housed in hanging stainless steel, wire-mesh cages. Graduated 50-mL Nalgene centrifuge tubes were used to provide fluid access during habituation and conditioning (see below).

2.3. Drugs

(−)-Nicotine hydrogen tartrate (Sigma Aldrich Co., St. Louis, MO) was prepared as a 0.5 mg/mL solution dissolved in 0.9% saline. All doses of nicotine are expressed as the salt. Saccharin (sodium saccharin, Sigma) was prepared as a 0.1% (1 g/L) solution in tap water.

2.4. Procedure

2.4.1. Phase 1: Habituation

Following 24-h water deprivation, all subjects were given 20-min access to tap water daily. Water was presented in graduated 50-mL Nalgene tubes between 1400 and 1600 h. This procedure was repeated until consumption stabilized, i.e., water consumption was within 2 mL of the previous day for a minimum of 4 consecutive days. Consumption was measured by the difference between the pre- and post-consumption volume in the tubes.

2.4.2. Phase 2: Conditioning

Once water consumption stabilized, all subjects were given 20-min access to a novel saccharin solution (day 1). Immediately following this initial presentation, male and female rats were independently rank ordered on saccharin consumption and then assigned to a treatment group (vehicle, 0.4 mg/kg, 0.8 mg/kg or 1.2 mg/kg nicotine) such that overall consumption was comparable among groups within each sex. Subjects received an intraperitoneal (IP) injection of either saline or their respective dose of nicotine approximately 20 min after access to the saccharin solution. The three days following this initial saccharin presentation were water-recovery days, during which animals were given 20-min access to tap water followed by no injections. This alternating procedure of saccharin-drug/water-recovery was repeated for a total of three complete cycles. Following the third cycle, an aversion test was given in which all subjects had 20-min access to saccharin.

2.5. Statistical analyses

Given that consumption of saccharin at the outset of conditioning (Trial 1) was significantly greater in males (15.429+0.405 mL) than in females (10.429+0.426 mL) ($t=8.509$, $p<0.001$), absolute saccharin consumption data for each group were transformed to a percentage of their respective controls in order to make direct comparisons between males and females. To determine this percentage of controls, consumption for each nicotine-injected animal on each trial was divided by the control group average and multiplied by 100. The average of the percentage of controls was then determined for each experimental group. After the data were transformed, a $2\times3\times4$ Repeated Measures ANOVA was performed with between-subjects factors of Sex and Dose and a repeated measures factor of Trial. Additionally, a 2×4 ANOVA was performed to assess the differences in the strength of the nicotine-induced aversions between males and females on the aversion test alone.

3. Results

The $2\times3\times4$ Repeated Measures ANOVA performed on the transformed (percentage of controls) data for males and females revealed significant main effects of Dose [F (3,76)=8.278, $p<0.001$] and Trial [F (3, 228)=13.781, $p<0.001$], but no effect of Sex [F (1, 76)=0.048, $p=0.827$] and no interaction effects. Tukey HSD Post Hoc analyses revealed that, overall, animals injected with 0.8 and 1.2 mg/kg drank significantly less saccharin than vehicle controls ($p=0.002$ and $p<0.001$, respectively). Paired Samples t-tests revealed that saccharin consumption significantly decreased from Trial 1 to Trial 2 [t (83)=2.982, $p=0.004$] and from Trial 2 to Trial 3 [t (83)=2.515, $p=0.014$).

Fig. 1 illustrates the amount of saccharin consumed for male and female subjects as a percentage of their respective controls across conditioning trials (CT) and on the aversion test (AT) for each of the three doses of nicotine (0.4 mg/kg — top, 0.8 mg/kg — center, 1.2 mg/kg — bottom).

The 2×4 ANOVA performed on the aversion test data revealed an effect of Dose [F (3, 76)=15.190, $p<0.001$], but did not reveal an effect of Sex [F (1, 76)=2.594, $p=0.111$] or a Sex×Dose interaction. Tukey HSD Post Hoc analyses revealed that, collapsed across sexes, animals injected with all three doses of nicotine consumed significantly less saccharin than vehicle controls. Fig. 2 illustrates the amount of saccharin consumed by males and females (as a percentage of their respective controls) on the aversion test for all three doses of nicotine. Because there were no significant sex differences, the statistical differences noted in Fig. 2 are based on consumption collapsed across sexes; the consumption for each sex is shown to illustrate the lack of differences between the two.

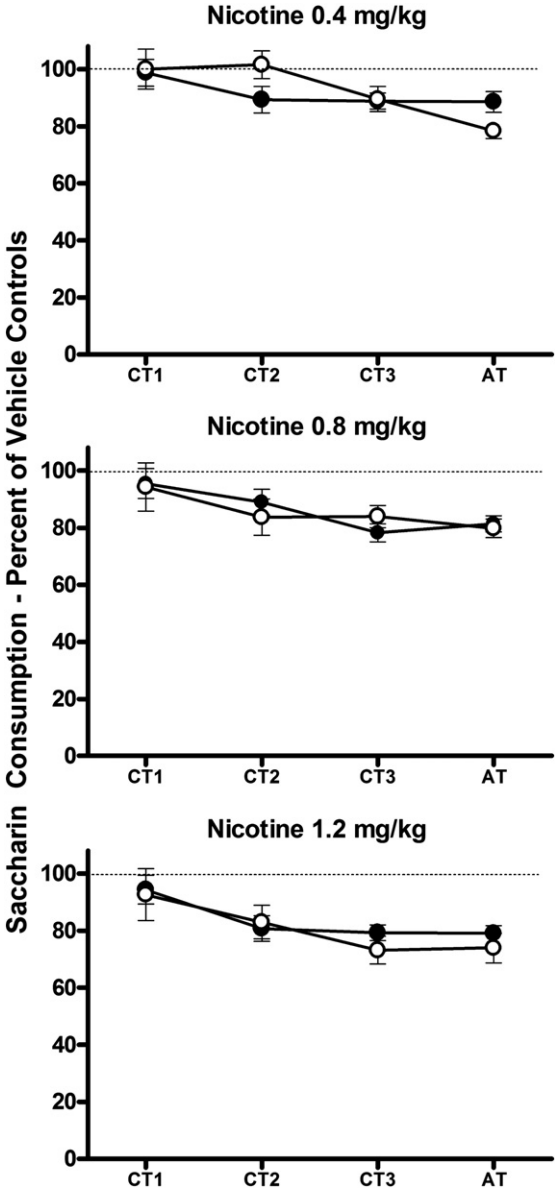

Fig. 1. Illustrates saccharin consumption as a percent of controls (±SEM) on each of the three conditioning trials (CT) and on the aversion test (AT) for the three doses of nicotine (0.4 mg/kg — top, 0.8 mg/kg — center, 1.2 mg/kg — bottom). Males are shown as ●, females are shown as ○, and vehicle controls are represented by the dashed line at 100%.

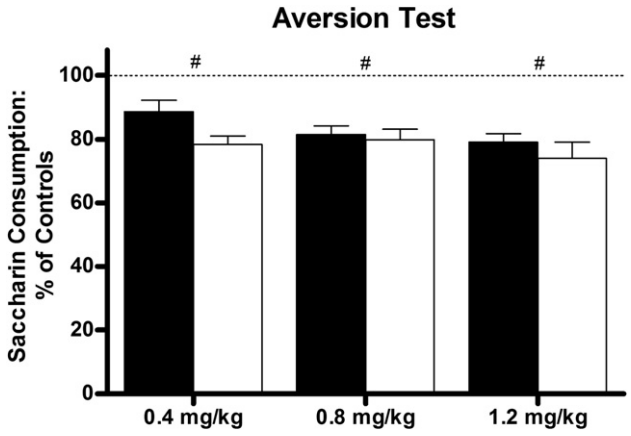

Fig. 2. Illustrates saccharin consumption as a percent of controls (+SEM) on the aversion test, for each of the three doses of nicotine (0.4, 0.8 and 1.2 mg/kg). Males are shown in black and females in white. $^{\#}(p<0.001)$ males and females (collapsed) significantly different from vehicle controls (represented by the dashed line at 100%).

4. Discussion

In the present experiment, nicotine-induced aversions were assessed in both male and female rats. As illustrated, nicotine-induced aversions were dependent upon both the dose of nicotine and the number of conditioning trials (Iwamoto and Williamson, 1984; Pescatore et al., 2005). Interestingly, aversions were comparable between the sexes, i.e., there were no sex differences in the acquisition or strength of the aversions induced by nicotine.

One possible explanation for the absence of sex differences in nicotine-induced aversions is that aversions were maximal at the specific doses examined, precluding the detection of graded differences between males and females. As described, however, saccharin consumption in the animals conditioned with nicotine was never less than 75% of respective controls. For example, on the aversion test males drank 88.6, 81.4 and 79.1% of their vehicle controls (0.4, 0.8 and 1.2 mg/kg nicotine, respectively) and females drank 78.3, 79.8 and 73.9% of their vehicle controls (0.4, 0.8 and 1.2 mg/kg, respectively). Thus, there was clearly sufficient room for differences to be revealed if they existed. The absence of sex differences in nicotine-induced aversions in the current preparation may instead be due to the fact that the aversions were too weak in general to reveal such differences consistently. As described, the aversions induced by nicotine were quite weak (and not dose-dependent) for both sexes. However, the doses of nicotine used in the current study are in the range of behaviorally active doses (see Adriani et al., 2006; Belluzzi et al., 2004; Etscorn et al., 1986; Etscorn et al., 1987; Iwamoto and Williamson, 1984; Ossenkopp and Giugno, 1990) and the effects reported are consistent with prior assessments of nicotine-induced taste aversions in males (see Etscorn et al., 1986; Iwamoto and Williamson, 1984). It is,

nonetheless, possible that because of the relative weakness of the aversions, differences between the sexes could not consistently be detected. Although possible, it should be noted that the aversions were significantly different from controls, and as such could be assayed by the design.

It is possible that under different parametric conditions, e.g., higher doses, more conditioning trials, use of two-bottle testing, non-deprived testing, or different routes of administration, sex differences may have been revealed. Varying parametric conditions have been shown to alter aversion learning with other drugs of abuse. For example, route of administration affects the strength of aversions induced by high doses (32 and 50 mg/kg) of cocaine in female rats, with SC administered cocaine inducing a stronger aversion than IP (Ferrari et al., 1991). Additionally, sex differences in aversion learning with cocaine appear to be dependent on the dose and route of administration. Specifically, Busse et al., 2005 demonstrated that at a dose of 20 mg/kg cocaine, males injected SC developed a much stronger aversion than males injected IP, whereas females injected SC at this dose failed to differ from IP-injected females. Given these parametric effects, it is possible that nicotine-induced aversions would be sex dependent under different experimental conditions. It should be noted, however, that such procedures may reveal aversions more readily but may lose the ability to detect graded differences among groups (see Freeman and Riley, 2005) as a function of their relative sensitivity.

The absence of sex differences in aversions induced by nicotine in the present experiment are in contrast to the reported clear and robust sex differences in aversion learning with other compounds, e.g., LiCl (Chambers et al., 1981; Dacanay et al., 1984; Randall-Thompson and Riley, 2003; Weinberg et al., 1982); cocaine (Busse et al., 2005; van Haaren and Hughes, 1990); alcohol (Cailhol and Mormede, 2002). This raises the question why such effects are not clearly evident with nicotine. Even though the bases for these differences remain unknown, it is important to note that even for the compounds for which sex differences have been reported such differences are not always seen and the single study examining sex differences in morphine-induced taste aversions failed to see sex differences in either acquisition or extinction (with multiple doses and with repeated conditioning trials) (Randall-Thompson and Riley, 2003). Although these studies do not currently allow a conclusion regarding the basis for the differences across drugs or experimental conditions under which the assessments are made, it is clear that sex differences in aversion learning are dependent upon a host of factors, including the specific drug examined. What is not clear is the nature of this drug dependency. The difficulty in interpretation is due in part to the fact that the nature of aversion learning is not fully understood. A host of underlying mechanisms have been proposed, including drug novelty (Gamzu, 1977), conditioned fear (Parker, 2003), sickness (Garcia and Ervin, 1968), toxicity (Riley and Tuck, 1985) and, more recently, reward itself (see Grigson, 1997). Until the nature of aversion learning is identified, the bases for the drug dependency of these sex differences remain unknown.

The fact that there were no significant sex differences in the strength or acquisition of nicotine-induced aversions suggests that males and females are equally sensitive to the aversive effects of nicotine. Given that the overall acceptability of a drug is thought to be a function of the relative contributions of both the rewarding and aversive properties of the drug (Gaiardi et al., 1991; Lynch and Carroll, 2001; Riley and Simpson, 2001; Shram et al., 2006; Stolerman and D'Mello, 1981), the immediate question from such findings is the relevance of nicotine-induced taste aversions to the reported sex differences in nicotine self-administration (see above). The failure to detect sex differences in the aversive effects of nicotine (under the specific parameters assessed) suggests that the reported sex differences in nicotine self-administration are more likely a function of sexual dimorphism in the rewarding properties of nicotine, an effect consistent with reports that female rats metabolize nicotine slower (increasing its availability) and accumulate higher brain levels of nicotine than males (Kyerematen et al., 1988; Rosecrans, 1972; Rosecrans and Schechter, 1972). It would be interesting in this context to determine if differences exist between the sexes in the relative rewarding effects of nicotine in other behavioral preparations, e.g., conditioned place preference conditioning. Although place preference conditioning with nicotine has been reported (for a review, see Le Foll and Goldberg, 2005a; Le Foll and Goldberg, 2005b), such effects are quite variable, i.e., preferences are not always reported and nicotine has, in fact, been reported to induce place aversions. Further, direct comparisons between males and females have not been examined. Thus, it remains unknown to what extent differences in the relative rewarding and/or aversive effects of nicotine mediate the reported sex differences in nicotine self-administration.

Although there were no significant sex differences in aversions induced by nicotine in the present study, it is also important to note that the current assessment was under conditions different from those in which sex differences in nicotine self-administration are reported (e.g., dose, route of administration). To better model abuse vulnerability, the relative contribution of nicotine's aversive effects to its overall acceptability needs to be assessed under conditions that more closely approximate those of the self-administration preparation. Such assessments might provide more information on the role of the aversive properties (as a potential protectant factor) in the self-administration of nicotine (Shoaib et al., 2003; Shoaib et al., 2000).

Acknowledgements

The present research was supported in part from a grant from the Mellon Foundation to Anthony L. Riley. Requests for reprints should be sent to Jennifer Rinker, Psychopharmacology Laboratory, Department of Psychology, American University, Washington, DC 20016 or jennifer.rinker@gmail.com.

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