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The interaction of sex and route of drug administration in cocaine-induced conditioned taste aversions

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Abstract

Although taste aversion learning has been reported to be a function of a variety of factors, one that has received considerable attention is the subject's sex, wherein males generally display stronger taste aversions than females. An exception to these findings is with cocaine for which females have been shown to display greater aversions than males. Although suggestive of a Sex × Drug interaction, cocaine was administered subcutaneously (SC) in this report while others administered drug intraperitoneally (IP). Thus, there may be a Sex × Route interaction. To address the contributions of sex and route in cocaine aversions, the present study examined aversions in male and female Sprague–Dawley rats administered a range of doses of cocaine either SC or IP. At the two higher doses of cocaine tested (20 and 32 mg/kg), aversions were a function of route with animals injected SC with cocaine displaying greater aversions than those injected IP. Although there was no main effect of sex at either dose there was an interaction between sex and route at the 20 mg/kg dose. Specifically, SC-injected males displayed stronger aversions than IP-injected males. There were no differences between the two routes for females. Further, males displayed stronger aversions than females when injected SC. There was no sex difference when both groups were injected IP. This interaction was no longer evident at the highest does of cocaine (32 mg/kg). These data indicate that sex differences in aversion learning with cocaine are a function of the route of cocaine administration (and are dose specific).
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1. Introduction

It has been widely reported that rats will avoid consumption of solutions that have been paired with a number of different compounds, i.e., they will acquire a conditioned taste aversion to the drug-associated solution (Garcia and Ervin, 1968; Revusky and Garcia, 1970; Rozin and Kalat, 1971; see also Riley and Freeman, 2004a; see also www.CTAlearning.com). While robust, such learning appears to be influenced by a variety of factors (Riley and Freeman, 2004b). One factor that has received considerable attention is the sex of the subject used in the taste aversion procedure. For example, as early as 1976, Chambers and Sengstake reported that male rats displayed a more rapid acquisition of a LiCl-induced taste aversion than did female rats (see Chambers and Sengstake, 1976; see also Dacanay et al., 1984). Subsequently, Chambers and her colleagues (Chambers et al., 1981) also reported that males displayed significantly slower extinction of LiCl-induced taste aversions, even under conditions when males and females acquired aversions to similar degrees (see also Randall-Thompson and Riley, 2003). Although these differences in acquisition and extinction may be a function of different processes, specifically, a differential drug sensitivity (during acquisition) and differences in learning about the consequences of consumption (during extinction; for a review see Chambers et al., 1997), the more rapid acquisition and delayed extinction both suggest stronger aversions in males

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than females when LiCl is used as the aversion-inducing agent.

In addition to these investigations with LiCl, sex differences in aversion learning have been examined with a variety of other compounds, including toxins (Brot et al., 1992; Ingram and Corfman, 1981), hormones (Peeters et al., 1992) and recreational drugs (Caihol and Mormede, 2002; Randall-Thompson and Riley, 2003; van Haaren and Hughes, 1990). The relative sensitivity of males (compared to females) within this preparation is generally reported, although the strength of the sex difference varies across studies and is dependent upon a number of factors, e.g., strain (Caihol and Mormede, 2002; Ingram and Corfman, 1981), hormonal state (Brot et al., 1992; Chambers et al., 1981; Foy and Foy, 2003) and testing procedure (Chambers and Sengstake, 1978; Chambers et al., 1981; Sengstake and Chambers, 1979; van Haaren and Hughes, 1990).

Although males generally display greater aversions than females (in terms of a faster acquisition and/or a delayed extinction, see above), there is an exception. Specifically, van Haaren and Hughes (1990) reported that female Wistar rats acquired a stronger taste aversion than male Wistar rats when a saccharin solution was paired with 20 mg/kg cocaine (lower doses did not induce an aversion in either sex). Such a finding suggests that the effects of sex in taste aversion learning may be drug dependent (see also Peeters et al., 1992), i.e., there may be a Sex × Drug interaction. Thus, it is possible that the general sensitivity in males reported to occur in the literature does not extend to aversion learning with cocaine (see also Foltin and Schuster, 1982). Although possible, it should be noted that in their assessment of sex differences in taste aversion learning with cocaine, van Haaren and Hughes administered the drug subcutaneously (SC). In other work reporting stronger aversions in males relative to females, the various drugs have been administered intraperitoneally (IP; see also Peeters et al., 1992). As such, it is possible that the increased sensitivity that females display to cocaine's aversive effect, as reported by van Haaren and Hughes, may be, in part, an effect of the route of drug administration (i.e., a Sex × Route interaction). It is important to note that the relative strength of cocaine-induced taste aversions varies with route of administration (when route assessments are made within any specific sex and strain), indicating that route can affect such aversion learning (Ferrari et al., 1991; Mayer and Parker, 1993; see Riley and Freeman, 2004b). In fact, when assessing cocaine-induced aversions in Long Evans rats, Ferrari et al. (1991) reported aversions only when cocaine was administered subcutaneously. Intraperitoneally administered cocaine produced no measurable effect. Thus, the discrepancy between the van Haaren and Hughes report and those generally reporting greater aversion learning in males (see above) may, in part, be a function of route of drug administration.

To address the possible interaction of sex and route in cocaine-induced taste aversions, the present study examined taste aversions in male and female rats administered cocaine either SC or IP. Specifically, Sprague–Dawley rats of both sexes were given access to saccharin and injected either SC or IP with various doses of cocaine to assess differences in cocaine-induced taste aversions. Given that drug use and abuse is a function of the balance between the reinforcing and aversive effects of drugs (Cunningham and Henderson, 2000; Gaiardi et al., 1991; Gauvin et al., 2000; Grakalic and Riley, 2002; Hunt and Amit, 1987; Riley and Simpson, 2001; White et al., 1977; Wise et al., 1976), understanding the variety of factors (including sex) that impact this balance may provide some insight into the behavioral vulnerability of drug taking.

2. Method

2.1. Subjects

A total of 80 male and 77 female Sprague–Dawley rats, weighing between 270–450 g (males, 325–450 g; females, 270–350 g) at the start of the experiment, were housed in separate hanging wire-mesh cages in a room maintained on a 12:12 light–dark cycle (lights on at 0800 h) and at an ambient temperature of 23 °C. Food and water (except where noted) were available ad libitum. Animals were handled daily beginning 2 weeks prior to the start of the experiment in order to limit any effects of handling stress during conditioning and testing. All conditioning and testing were carried out between 0900 h and 1400 h. 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. Drugs and solutions

Cocaine hydrochloride (generously provided by the National Institute on Drug Abuse) was prepared as a 10 mg/ml solution in distilled water. Doses of cocaine refer to weight of the salt. Saccharin (0.1% sodium saccharin, Sigma Chemical Co., St. Louis, MO) was prepared as a 1 g/l solution in tap water.

2.3. Procedure

Phase I Habituation. Following 23-h water deprivation, subjects were given 20-min access to water (presented in graduated 50-ml Nalgene tubes). This procedure was repeated daily until all subjects were approaching and drinking from the tube within 2 s of its presentation.

Phase II Conditioning. On Day 1 of this phase, all subjects were given 20-min access to a novel saccharin solution (presented in a single 50-ml Nalgene

tube). Immediately following saccharin access, subjects from both sexes were randomly assigned to receive cocaine either IP or SC. This assignment yielded four groups of subjects, i.e., Group M-IP (male, intraperitoneal cocaine; $n=41$), M-SC (male, subcutaneous cocaine; $n=39$), F-IP (female, intraperitoneal cocaine; $n=38$) and F-SC (female, subcutaneous cocaine, $n=39$). Within each Sex × Route group, subjects were ranked on initial saccharin consumption and assigned to five subgroups to receive one of five different doses of cocaine [0 (vehicle matched in volume to highest cocaine dose), 5, 10, 20 and 32 mg/kg; the number of subjects varied from six to nine animals per group]. All animals were then given an injection of cocaine (or vehicle) based on their respective dose and route of cocaine administration. All injections were given within 10 min of removal of the saccharin bottles.

On the following three water-recovery days, all subjects were given 20-min access to water. No injections were given following water access on these days. These four day blocks of conditioning/water recovery were repeated until all subjects received four complete cycles, resulting in four saccharin–cocaine pairings.

3. Statistical analyses

Given significant differences between males and females in saccharin consumption on the initial saccharin exposure [males consumed more of the saccharin solution than females at the outset of conditioning, i.e., on Conditioning Trial 1 ($p<0.05$)], data for each group within each sex were transformed to a percent difference in saccharin consumption of its respective vehicle control for subsequent analyses. That is, for each trial the absolute amount of saccharin consumption for each treatment group within each sex was divided by the amount consumed by its respective control group on that trial. The percent scores on the final conditioning trial (Trial 4) were then compared separately for each dose of cocaine (i.e., 5, 10, 20 and 32 mg/kg) using a 2×2 ANOVA with the between group factors of Sex

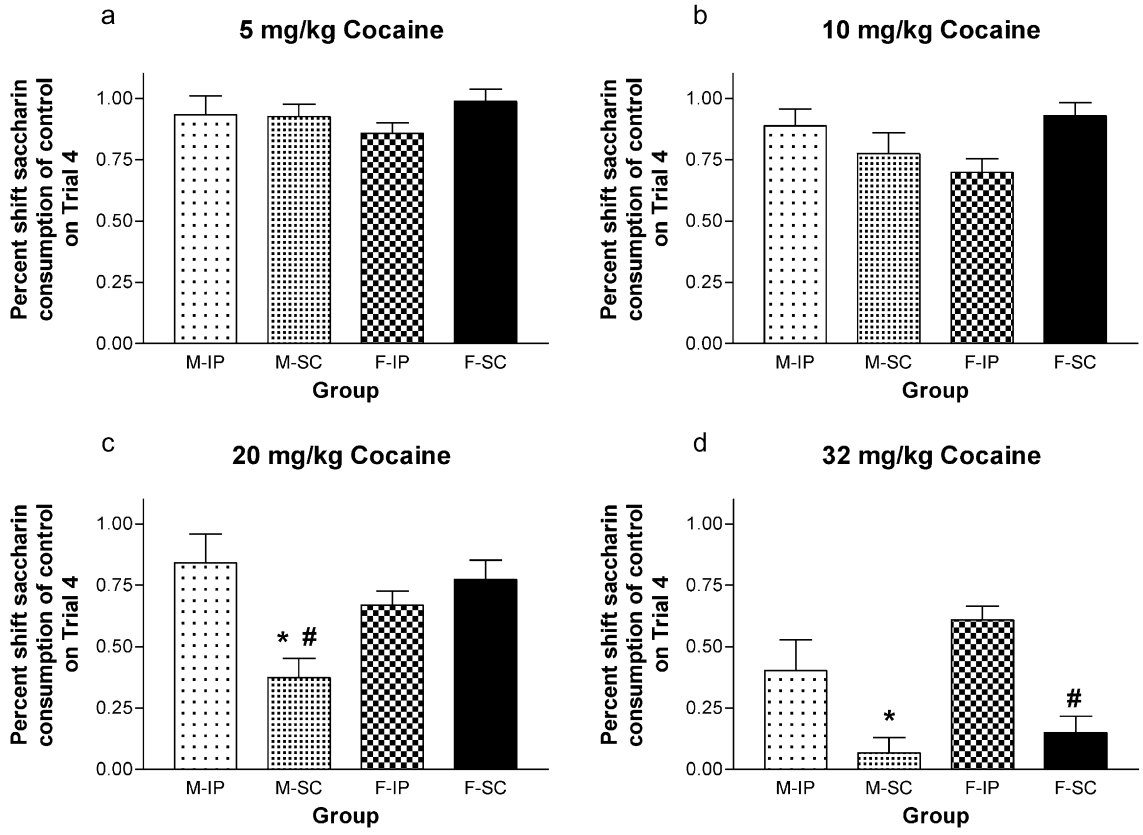

Fig. 1. Percent shift in saccharin consumption of controls on Trial 4 as a function of Sex and Route for 5 (top, left panel), 10 (top, right panel), 20 (bottom, left panel) and 32 (bottom, right panel) mg/kg cocaine. At 20 mg/kg cocaine, * indicates a greater reduction in saccharin consumption in males injected subcutaneously (M-SC) as compared to males injected intraperitonealy (M-IP; $p<0.05$). # indicates a significant a greater reduction in saccharin consumption in males injected subcutaneously (M-SC) as compared to females injected subcutaneously (F-SC; $p<0.05$). At 32 mg/kg cocaine, * indicates a greater reduction in saccharin consumption in males injected subcutaneously (M-SC) as compared to males injected intraperitonealy (M-IP; $p<.05$). # indicates a significant a greater reduction in saccharin consumption in females injected subcutaneously (F-SC) as compared to females injected intraperitonealy (F-IP; $p<0.05$).

(Male or Female) and Route (SC or IP). Trial 4 was used in group comparisons given that aversions to cocaine appeared asymptotic by this trial. All determinations of statistical significance were made at $p < .05$.

4. Results

Fig. 1 illustrates the mean percent in saccharin consumption of vehicle controls on Trial 4 for both males and females injected IP and SC with cocaine. For subjects injected with 5 mg/kg cocaine (see Fig. 1a), a 2×2 ANOVA indicated that there was no significant main effect for Sex or Route [$F(1, 28) = 0.007$, $p = 0.9326$; $F(1, 28) = 1.103$, $p = 0.3025$, respectively] nor a significant Sex × Route interaction [$F(1, 28) = 1.342$, $p = 0.2564$]. For subjects injected with 10 mg/kg cocaine, the 2×2 ANOVA also indicated that there was no main effect for Sex or Route [$F(1, 28) = 0.067$, $p = 0.7979$; $F(1, 28) = 0.720$, $p = 0.4034$, respectively; see Fig. 1b]. Interestingly, there was a significant Sex × Route interaction [$F(1, 28) = 6.267$, $p = 0.0184$], although subsequent Tukey's HSD post-hoc analyses failed to detect any significant differences among groups (p's > 0.05).

For subjects injected with 20 mg/kg cocaine (see Fig. 1c), there was no main effect of Sex [$F(1, 28) = 1.756$, $p = 0.1958$]. There was, however, a significant main effect for Route [$F(1, 28) = 4.513$, $p = 0.0426$]. Post-hoc analyses revealed that subjects injected subcutaneously displayed a significantly greater reduction in saccharin consumption than those injected intraperitoneally ($p < 0.05$). In addition, there was a significant Sex × Route interaction [$F(1, 28) = 11.021$, $p = 0.0025$]. Specifically, males injected subcutaneously displayed significantly greater reductions in saccharin consumption than males injected intraperitoneally ($p < 0.05$). Further, males injected subcutaneously displayed greater reductions than similarly injected females ($p < 0.05$). Thus, at 20 mg/kg the route of cocaine administration was a significant factor in mediating the relative strength of cocaine-induced aversions in males, while it failed to affect aversions in females.

For subjects injected with 32 mg/kg cocaine, the 2×2 ANOVA indicated a main effect for Route [$F(1, 29) = 21.529$, $p < 0.0001$, see Fig. 1d]. Post-hoc analyses revealed that subjects injected subcutaneously displayed significantly greater reductions in saccharin consumption than those injected intraperitoneally ($p < 0.05$). There was no main effect for Sex nor a significant Sex × Route interaction [$F(1, 29) = 2.808$, $p = 0.1045$; $F(1, 29) = 0.530$, $p = 0.4722$, respectively].

5. Discussion

To assess the possible interaction of route of cocaine administration and sex on cocaine-induced taste aversions, the present study examined cocaine-induced aversions in males and females given the drug either IP or SC. As illustrated, cocaine was effective in inducing aversions. Although no direct dose comparison was made, the relative strength of aversions appeared greater as cocaine dose increased, an effect consistent with other work assessing the dose-dependent nature of cocaine-induced taste aversions (see Ferrari et al., 1991). Also consistent with prior work with cocaine and a variety of other compounds (Ferrari et al., 1991; Hunt and Amit, 1987; Mayer and Parker, 1993; Nachman and Ashe, 1973), there was a significant effect of route of cocaine administration. Specifically, at 20 and 32 mg/kg aversions induced by SC cocaine were greater than those induced by IP cocaine.

Although there was no significant effect of sex on cocaine-induced taste aversions (at any cocaine dose), there was a significant interaction of sex and route at 20 mg/kg cocaine. Specifically, males injected subcutaneously with this dose of cocaine displayed significantly greater reductions in saccharin consumption than males injected intraperitoneally. No such route difference at this dose of cocaine was evident in females. Further, males injected subcutaneously displayed greater reductions than similarly injected females. Thus, route of cocaine administration was a significant factor in mediating the expression of cocaine-induced taste aversion in male and female rats. It should be noted, however, that this interaction was limited to 20 mg/kg cocaine. That is, at 32 mg/kg cocaine the only factor that affected the expression of cocaine aversions was route of drug administration (see Chambers et al., 1997; Randall-Thompson and Riley, 2003 for a discussion of the effects of dose on sex differences).

These data demonstrate that the ability of cocaine to induce aversions in males and females is clearly a function of the specific route by which cocaine is administered. If the comparison between males and females is made with the SC route, the data reported here are consistent with prior work reporting that conditioned taste aversions are stronger in males than in females (see above). On the other hand, if the comparison is made with the IP route, there are no effects of sex in the expression of cocaine-induced aversions (see also Caihol and Mormede, 2002; Randall-Thompson and Riley, 2003). The fact that the differences between males and females in aversion learning vary with a specific parameter (in this case route) is consistent with work with other aversion-inducing agents for which the presence or absence of sex differences is dependent on a variety of parametric conditions (although route has not been specifically examined). For example, when LiCl has been used as the aversion-inducing agent, sex differences are not always reported (Chambers and Sengstake, 1976; Earley and Leonard, 1978; Green, 1969; Lucas and McMillen, 2002; Nachman, 1970). These studies differ on a range of parameters, e.g., dose of drug, number of trials, degree of deprivation (see Chambers and Sengstake, 1976; Chambers et al., 1981; Earley and Leonard, 1978; Ingram and

Corfman, 1981; Robbins, 1980; Sengstake et al., 1978), indicating that such conditions can affect the likelihood of seeing sex differences. Sex differences in aversion learning are clearly a function of a number of parametric conditions known to affect aversion learning in general (see Klosterhalfen and Klosterhalfen, 1985; Riley and Freeman, 2004b). That route may be another important factor in the display of sex differences, thus, is not surprising.

A question raised by these findings is if the Sex × Route interaction reported here provides any insight into the findings of van Haaren and Hughes (1990) in relation to other work with sex differences in taste aversion learning. The current data argue that although there was no overall sex difference with cocaine, when one factor in the route by which cocaine was administered, it is clear that males (when injected SC) displayed stronger aversions than did females (when injected SC). Thus, the present results are clearly inconsistent with the findings of van Haaren and Hughes who noted that females displayed stronger aversions than males when both were injected with cocaine SC (20 mg/kg).

Although the bases for the differences in findings between the present results and those of van Haaren and Hughes (1990) are not known, several parametric differences exist between the two studies that may contribute to the differences. For example, in the van Haaren and Hughes report, animals were group housed and separated only for the 20-min period during which conditioning and testing occurred. In the present assessment, animals were housed individually throughout all phases of the experiment. It is possible that isolation affected cocaine-induced aversions differentially in males and females, resulting in greater aversions in males. Interestingly, Chambers and Sengstake (1978) have assessed the effects of isolation on the extinction of LiCl-induced aversions in males and females and reported that while males displayed slower extinction of aversions than females after being individually housed for only one week, this sex difference was not evident after 6 weeks of isolation. In fact, with the extended isolation, male rats displayed the more rapid extinction of aversions characteristic of females. Given that isolation housing appeared to weaken aversions in male subjects (Chambers and Sengstake, 1978), it is unlikely that the greater aversions by males than females in the present experiment (relative to that reported by van Haaren and Hughes) can be accounted for by the different housing condition of the two studies.

A second parameter that may mediate the differences between the data reported here and those of van Haaren and Hughes (1990) is the estrous cycle of the female subjects. Neither van Haaren and Hughes nor the present study assessed where in the estrous cycle the females were during training and testing. Given the role of estrogen in the display of a variety of behavioral responses to cocaine and other drugs of abuse (Carroll et al., 2004), it is possible that the differences between the present data and those of van Haaren and Hughes could reflect the fact that the females in the two assessments were in different phases of the estrous cycle (with their corresponding changes in estrogen levels). Interestingly, Chambers and her colleagues have reported that exogenously administered estradiol facilitated the extinction of LiCl-induced taste aversions in both gonadectomized male and female rats (for a review, see Chambers et al., 1997), suggesting that variations in estrogen may impact aversion learning with other compounds as well. It is also possible that in different phases of the estrous cycle, the differences reported here between males and females with cocaine might be abated (given that manipulations that affect estrous levels affect aversion learning with other aversion-inducing agents; see above).

One additional factor that varied across the van Haaren and Hughes (1990) report and the present study was the strain of the subject. Specifically, van Haaren and Hughes used Wistar rats while the present investigation used rats of Sprague–Dawley descent. Strain differences are well documented in taste aversion learning (e.g., Broadbent et al., 2002; Glowa et al., 1994; Ingram, 1982; Lancellotti et al., 2001; Orr et al., 2004). Further, there are reports that strain differences can be a function of the sex of the subject (Caihol and Mormede, 2002; Ingram and Corfman, 1981). For example, Cailhol and Mormede (2002) demonstrated a strain (Wistar Kyoto versus Wistar Kyoto Hyperactive versus Spontaneous Hypertensive) × sex interaction in the expression of ethanol-induced taste aversions. Specifically, whereas male rats of the SHR strain displayed significantly stronger ethanol-induced taste aversions than female SHR subjects, this sex difference was not evident with the WKHA or WHY strains (where males and females did not differ). Further, Ingram and Corfman (1981) reported that while male and female C57 mice displayed no differences in the extinction of a LiCl-induced taste aversion, extinction was significantly slower in male DBA mice than female DBA subjects. These significant Strain × Sex interactions suggest that the differences in strain of subject used by van Haaren and Hughes (1990) and the present experiment may have contributed to the reported differences in cocaine-induced aversions in males and females.

Although the basis for the specific Sex × Route interaction reported in the present study (or for sex differences in taste aversion learning in general; for a discussion, see Chambers et al., 1997; see also Festa et al., 2004 for a discussion on sex differences in cocaine sensitivity) is not known, the present data do suggest that comparisons between males and females in aversion learning (and in other behavioral endpoints) might consider a wide range of parametric factors before concluding that there is a general sex difference. Although the present study focused on the interaction of route and sex in cocaine-induced aversions, other variables should be considered as well, including housing conditions, hormone levels and strain of subject. Such investigations may help elucidate the mechanisms that contribute to the differences in the relative sensitivity to the aversive properties of drugs between male and female

subjects. Understanding how aversion learning is affected by such factors may provide some insight into the balance of the affective properties of drugs and the likelihood and conditions of drug use and abuse.

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