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Cocaine-Induced Taste Aversions: Effect of Route of Administration

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FERRARI, C M , D A O'CONNOR AND A L RILEY *Cocaine-induced taste aversions Effect of route of administration* PHARMACOL BIOCHEM BEHAV **38**(2) 267–271, 1991 —Female Long-Evans rats were given 20-min access to saccharin followed by either intraperitoneal (IP) or subcutaneous (SC) cocaine (18, 32 or 50 mg/kg) or vehicle Aversions induced by IP-administered cocaine were relatively weak, with subjects at all doses decreasing consumption by only 35% after four conditioning trials On the other hand, aversions induced by SC-administered cocaine were robust, with subjects at the two highest doses (32 and 50 mg/kg) decreasing saccharin consumption by 95 and 98%, respectively, on the final aversion test Although several possibilities exist for the differential ability of IP and SC cocaine to induce taste aversions (e g , longer duration of action with SC cocaine and the convulsant property of IP cocaine), the basis for this difference remains unknown A secondary finding was the effect of route of administration on body weight While all subjects receiving IP cocaine maintained or increased in body weight, subjects receiving the two highest doses of SC cocaine decreased in body weight by 3 and 5%, respectively The differential effect of IP and SC cocaine on body weight may be due to cocaine's action on drinking and feeding or cocaine's leptogenic property Independent of the mechanism underlying the differential ability of IP and SC administration to induce taste aversions and affect body weight, it is clear that route of administration may play an important role in the effects of cocaine

Conditioned taste aversion Route of administration Cocaine Rat

ALTHOUGH conditioned taste aversions can be reliably and robustly induced by a wide variety of agents (25), aversions induced by cocaine hydrochloride are generally reported to be weak. For example, as early as 1977 Cappell and LeBlanc (7) reported that rats injected intraperitoneally (IP) with 18 mg/kg cocaine following the consumption of saccharin *increased* consumption of saccharin by 30% on a subsequent exposure to the solution. Such an effect is in marked contrast to the dramatic one-trial *aversions* reported with LiCl (26), alcohol (19), apomorphine (28) and amphetamine (27). When higher doses and repeated trials are administered, aversions are induced by cocaine, but even here they are weak relative to other compounds. For example, Goudie and his colleagues (15) administered repeated pairings of saccharin and cocaine (36 mg/kg) and noted that consumption decreased only 60% after the fifth trial [see also (4)] Under similar conditions with LiCl or alcohol, consumption is generally totally suppressed (19). Aversions to cocaine have even been reported to be weak when the relatively sensitive two-bottle testing procedure has been used (11), a procedure that detects aversions to compounds that are often without effect in a one-bottle assessment (29).

In each of the above-mentioned assessments of cocaine-induced taste aversions, animals were given cocaine IP. In the single paper in which cocaine was administered by a different route, i.e , subcutaneously (SC), robust aversions were rapidly acquired (12). The acquisition of strong aversions via SC cocaine compared to the relative weak aversions by the IP route is consistent with other work in taste-aversion learning demonstrating an influence of route of administration (1, 5, 24, 26). Although Gale's (12) work suggests that route may be an important factor in cocaine-induced taste aversions, the concentration (400 mg/ml) and the dose (140 mg/kg) of cocaine administered in her report differed from earlier assessments of taste aversions with cocaine. Each of these parameters is high in relation to the other work on cocaine, and it remains unknown if similar concentrations and doses of IP cocaine also would induce robust aversions. In a direct assessment of the importance of route of administration in the efficacy of cocaine to induce an aversion, animals in the present study were given a novel solution to drink followed by either IP or SC cocaine. The concentration and doses of cocaine examined were held constant across the two routes of administration.

METHOD

Subjects

The subjects were 56 experimentally naive, female rats of Long-Evans descent, approximately 100 days of age at the beginning of the experiment

Apparatus

Subjects were individually housed in stainless-steel wire-mesh cages on the front of which graduated Nalgene tubes could be placed for the presentation of either water or saccharin Subjects were maintained on a 12-h light/12-h dark cycle and at an ambi-

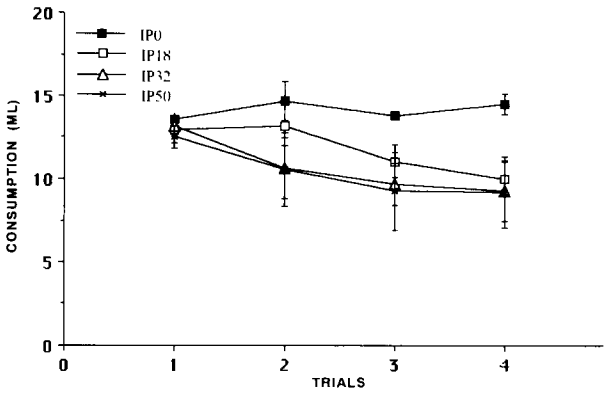

FIG 1 Mean saccharin consumption for subjects in Groups IP0, IP18, IP32 and IP50 on each of the four conditioning trials Bars above and below each point represent S E M

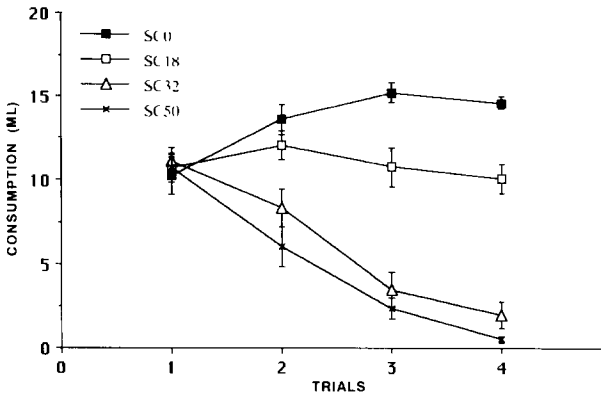

FIG 2 Mean saccharin consumption for subjects in Groups SC0, SC18, SC32 and SC50 on each of the four conditioning trials Bars above and below each point represent S E M

ent temperature of 28° for the duration of the experiment. Food was available ad lib.

Drugs and Solutions

Cocaine hydrochloride (NIDA) was prepared as a 50 mg/ml solution in distilled water. Saccharin (0 1% sodium saccharin, Sigma) was prepared as a 1 g/l solution in tap water.

Procedure

Phase 1 Habituation. Following 23-h water deprivation, all subjects were given 20-min access to water This procedure was repeated until all subjects were approaching and drinking from the tube within 2 s of its presentation (between 18 and 20 days).

Phase 2· Conditioning On Day 1 of this phase, subjects in Group IP (n = 28) were given 20-min access to a novel saccharin solution during their scheduled 20-min fluid-access period. Immediately following this exposure, subjects were matched on saccharin consumption and assigned to four groups (n = 7 per group) Subjects in Groups IP0, IP18, IP32 and IP50 were given an IP injection of 0 (distilled water), 18, 32 and 50 mg/kg cocaine hydrochloride, respectively. Subjects in Group SC (n = 28) were also given 20-min access to saccharin on Day 1 of this phase Immediately following this exposure, these subjects were matched on saccharin consumption and assigned to four groups (n = 7 per group) Subjects in Groups SC0, SC18, SC32 and SC50 were then given a SC injection of 0, 18, 32 and 50 mg/kg cocaine hydrochloride, respectively. On the following three days, all subjects were given 20-min access to water This alternating procedure of conditioning/water recovery was continued until all subjects had received three complete cycles On the day following the final water recovery session of the third cycle, all subjects were given 20-min access to saccharin in a final one-bottle test of the aversion to saccharin No injections were given following this test.

RESULTS

All determinations of statistical significance are based on $p<0.05$, one-tailed Friedman two-way analysis of variance and a one-tailed Kruskal Wallis one-way analysis of variance

Saccharin Consumption

Intraperitoneal administration. Figure 1 illustrates the mean consumption of saccharin for subjects in Groups IP0, IP18, IP32 and IP50 over repeated conditioning trials and on the final aversion test. On the first exposure to saccharin, there were no significant differences in saccharin consumption with all subjects drinking approximately 12 ml of saccharin. On the second exposure to saccharin (i.e., the first exposure following conditioning), subjects in Groups IP0 and IP18 slightly, but not significantly, increased saccharin consumption above the amount consumed on the initial trial. Subjects in Groups IP32 and IP50 slightly, but not significantly, decreased saccharin consumption on this day On this first aversion test, subjects in Group IP0 drank significantly more saccharin than subjects in Group IP50, H(3) = 4 474 No other comparisons were significant

With repeated conditioning trials, subjects in Group IP0 continued to consume high levels of saccharin, drinking approximately 15 ml on the final aversion test. Consumption on this day was not significantly different from the amount consumed on the first trial Although subjects in Group IP18 initially increased consumption of saccharin following conditioning, with repeated trials these subjects slightly decreased saccharin consumption, consuming approximately 10 ml on the final aversion test. Consumption for these subjects was not significantly different from consumption on the first trial. Subjects in Groups IP32 and IP50 decreased saccharin consumption slightly over repeated conditioning trials, drinking approximately 9 ml on the final test On this day, consumption for neither group was significantly different from the amount consumed on the first trial. On the final aversion test, subjects in Group IP0 drank significantly more saccharin than subjects in Groups IP18, IP32 and IP50, H(3) = 10.142. No other comparisons were significant

Subcutaneous administration Figure 2 illustrates the mean saccharin consumption for subjects in Groups SC0, SC18, SC32 and SC50 over repeated conditioning trials and on the final aversion test As illustrated, on the first exposure to saccharin there were no significant differences in saccharin consumption among groups with all subjects drinking approximately 11 ml On the second exposure to saccharin, subjects in Groups SC0 and SC18 slightly, but not significantly, increased saccharin consumption above the amount consumed on the initial conditioning trial. Subjects in Groups SC32 and SC50 significantly decreased saccharin consumption below the amount consumed on the initial conditioning trial, F(3) = 18 943 and 19 279, respectively. On this first aversion test, subjects in Groups SC0 and SC18 drank significantly more than subjects in Groups SC32 and SC50, H(3) =

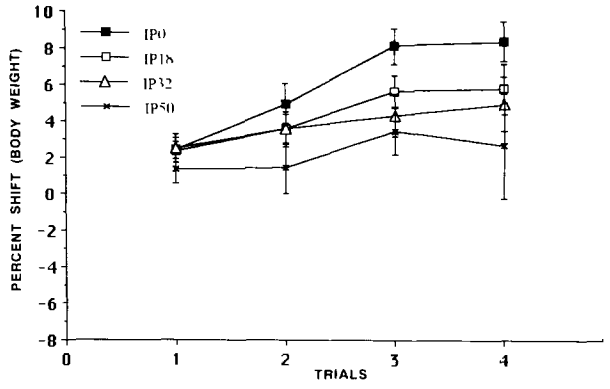

FIG 3 Percent shift in body weight for subjects in Groups IP0, IP18, IP32 and IP50 on each of the four conditioning trials The percent shift on each conditioning trial reflects changes from baseline weights [(B − C)/B, see text] Bars above and below each point represent S E M

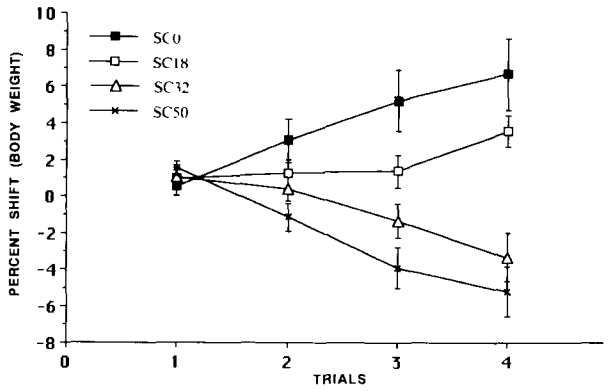

FIG 4 Percent shift in body weight for subjects in Groups SC0, SC18, SC32 and SC50 on each of the four conditioning trials The percent shift on each conditioning trial reflects changes from baseline weights [(B − C)/B, see text] Bars above and below each point represent S E M

17.264 No other comparisons were significant.

With repeated conditioning, subjects in Group SC0 increased their consumption of saccharin, consuming approximately 15 ml on the final aversion test. Consumption on this day was significantly different from the amount consumed on the first trial, $F(3) = 10\ 086$. Subjects in Group SC18 displayed no significant changes from their saccharin baseline over conditioning trials, drinking approximately 11 ml on the final exposure to saccharin. Subjects in Groups SC32 and SC50 continued to decrease saccharin consumption over repeated conditioning trials, drinking approximately 2 and 0.5 ml on the final test. Consumption for both groups on the final aversion test was significantly different from that consumed on the first trial, $F(3) = 18\ 943$ and 19.279, respectively On the final aversion test, subjects in Groups SC0 drank significantly more saccharin than subjects in Groups SC18, SC32 and SC50, $H(3) = 22.311$. Subjects in Groups SC18 drank significantly more saccharin than subjects in Groups SC32 and SC50, $H(3) = 22.311$. No other comparisons were significant.

Body Weight

Intraperitoneal administration Figure 3 illustrates the percent shift in body weight from baseline for subjects in Groups IP0, IP18, IP32 and IP50 over repeated conditioning trials and on the final aversion test. To calculate the percent shift for any individual subject, mean body weights were determined for the final three days of habituation and body weights on each of the four conditioning trials (C) were compared to this baseline weight (B) [B − C/B]. On the first conditioning trial, body weights for subjects in Groups IP0, IP18 and IP32 were significantly different from their initial baselines, $F(4) = 27.014$, 24.551 and 21.452, respectively. On this first trial, there was no significant difference among groups with all subjects increasing in body weight approximately 2 percent. Over conditioning trials, subjects in Groups IP0, IP18, IP32 and IP50 continued to increase in body weight, displaying increases of 8 34, 5 76, 4.94 and 2 61 percent, respectively, on the final aversion trial These increases were significantly different from baseline for subjects in Groups IP0, IP18 and IP32, $F(4) = 27.014$, 24.511 and 21.452, respectively. On the final conditioning trial, there were significant differences in percent shift in body weight between subjects in Group IP0 and subjects in Groups IP32 and IP50, $H(3) = 5.831$ No other comparisons were significant

Subcutaneous administration Figure 4 illustrates the percent shift in body weight from baseline for subjects in Groups SC0, SC18, SC32 and SC50 over repeated conditioning trials and on the final aversion test On the first conditioning trial, body weights for subjects in Groups SC18 and SC50 were significantly different from their initial baseline weight, $F(4) = 16\ 544$ and 24 905, respectively. On this trial, there were no significant differences among groups with all subjects increasing in body weight approximately 1 percent. With repeated conditioning, subjects in Groups SC0 and SC18 continued to increase in body weight, displaying increases of 6.67 and 3.55 percent, respectively, on the final aversion test. These increases were significantly different from baseline, $F(4) = 18.018$ and 16.544, respectively. Subjects in Groups SC32 and SC50 continued to decrease in body weight over conditioning, displaying decreases of 3.32 and 5.18 percent, respectively, on the final aversion trial. These decreases were significantly different from baseline, $F(4) = 8\ 296$ and 24.905, respectively There were significant differences in percent shifts in body weight between subjects in Groups SC0 and SC18 and subjects in Groups SC32 and SC50 on the final aversion trial, $H(3) = 18\ 617$. No other comparisons were significant.

Intergroup Comparisons

Saccharin consumption. The percent shift in saccharin consumption for all SC and IP groups was calculated individually using the first exposure to saccharin as a baseline. Consumption on subsequent conditioning trials (C) was compared to this baseline (B) [B − C/B]. The only consistent significant differences over conditioning trials were between subjects in Groups IP32 and SC32 and between subjects in Groups IP50 and SC50, all $H's(7) > 18.552$.

Body weight. The percent shift in body weight calculated previously was used to compare the subjects in the IP and SC groups. Again, the only consistent differences were between subjects in Groups IP32 and SC32 and between subjects in Groups IP50 and SC50, all $H's(7) > 10.541$

DISCUSSION

As described, subjects receiving repeated pairings of saccharin and IP cocaine displayed relatively weak taste aversions to the saccharin solution. Subjects in all groups displayed no greater

than a 35 percent decrease in saccharin consumption over repeated conditioning trials. These relatively weak aversions (even with repeated conditioning trials at high doses) are consistent with those reported by others assessing the ability of IP cocaine to induce taste aversions (see Introduction). Although subjects receiving the lowest dose of SC cocaine (18 mg/kg) did not display a significant decrease in saccharin consumption, subjects receiving SC cocaine at the two higher doses (32 and 50 mg/kg) displayed significant decreases in saccharin consumption after only a single conditioning trial and near complete suppression of saccharin consumption after four pairings of saccharin and cocaine.

The basis for the differences in the ability of IP and SC cocaine to induce taste aversions is unknown, although several possibilities exist For example, in an account of the generally weak aversions reported with IP cocaine Cappell and LeBlanc (7) suggested that cocaine's duration of action was too brief to support taste aversion learning, i.e., its action was below the minimum duration to be effective as an aversive agent to condition a taste aversion. Although it is not clear exactly what the minimum duration of action is for any specific drug [see (13) for a review of the duration of action hypothesis], the pharmacokinetics of IP cocaine are consistent with this hypothesis. For example, Benuck, Lajtha and Reith (3) have reported that in the mouse the peak values of cocaine in plasma were reached within 2.5 min after IP administration of either 10 or 25 mg/kg cocaine. The half-life of cocaine disappearance from plasma was 15 min. Thus both the time to peak value and the half-life of IP cocaine are rapid. In contrast to the IP route, the duration of action of SC cocaine appears significantly longer. For example, Misra and his colleagues (21,23) have reported that in the rat peak values of cocaine in plasma were not reached until four hours after SC administration of 20 mg/kg cocaine The half-life of cocaine disappearance from plasma for this dose was 5 hours Similar differences in plasma levels between IP and SC administrations have recently been reported in a direct comparison between these routes in the rat (10). Although the pharmacokinetics of cocaine are consistent with the duration of action hypothesis as presented by Cappell and LeBlanc (7), other data do not support this account. For example, WIN 35,428 (a long-lasting cocaine analog) was no more effective than cocaine in inducing taste aversions (8) Further, animals treated with SKF 525A (a cocaine metabolism inhibitor) prior to a conditioning trial with cocaine did not display greater aversions to the cocaine-associated taste than did subjects pretreated with the SKF 525A vehicle (14). Thus it remains unknown if and to what extent the increased effectiveness of SC cocaine to induce aversions is due to increases in its duration of action

In the present experiment, the only recorded instances of seizures (six) were with the IP route of cocaine administration [see (9) for a comparison of PO and SC route of cocaine administration]. That in the present experiment nonlethal seizures were more prevalent following IP than SC routes may offer some explanation for the weaker aversions following IP cocaine. Specifically, seizures induced by IP cocaine may have interfered with the ability of cocaine to induce an aversion Such an argument has recently been presented by Kutscher (20) in an attempt to account for the relatively weak taste aversions induced by the convulsant phenylethylamine (PEA). Kutscher (20) compared the acquisition of PEA-induced aversions in mice that either displayed or failed to display seizures when injected with PEA on the conditioning trial. Interestingly, subjects that displayed a seizure following the injection of PEA acquired significantly weaker aversions than subjects that failed to seize on the conditioning trial, supporting the position that seizures may have interfered with the acquisition of the saccharin-PEA association Although these data suggest that a convulsant might affect its own ability to function as an aversive agent in the taste aversion design, it is not clear if this is the basis for the relatively weak aversions with IP cocaine First, seizures were not evident in all of the subjects that failed to acquire robust aversions with IP cocaine. Further, even for subjects that did display seizures, these seizures were not noted following all of the conditioning trials. Thus until an independent assessment is made of cocaine's ability to disrupt a novel taste-poison association (17,20) and of the possible amnesic effects of the subconvulsant activity of cocaine (6), the role of cocaine's convulsant property in the acquisition of weak taste aversions by IP cocaine remains unknown

Although aversions induced by SC cocaine were stronger relative to those induced by IP cocaine, the basis for this difference remains unknown (see above) A related issue is why such large doses of SC cocaine were required to induce robust aversions As described, although 32 and 50 mg/kg cocaine (SC) induced taste aversions, 18 mg/kg cocaine (SC) was without effect Given that the mechanism underlying taste aversion conditioning in general is unknown [see (13)], it is difficult to speculate why specific doses of a specific drug are ineffective in inducing aversions except to indicate that the characteristic of the aversion-inducing agent which mediates aversion learning is below threshold at certain doses. Although the basis for the need to use such high doses of cocaine to induce aversions is not known, it is interesting in this context that the acute effects of 20 mg/kg cocaine (SC) on activity, stereotypies and seizures are not significantly different from control injections [see (9)] Thus the failure to find an effect of 18 mg/kg cocaine in the taste aversion design is consistent with other assessments of the acute effect of SC-administered cocaine

Although the main focus of the present experiment was on the effect of route of administration of cocaine on conditioned taste aversions, a secondary finding was the effect of route of administration on body weight. For example, over the course of the experiment subjects in Groups SC32 and SC50 decreased body weight by approximately 3 and 5 percent, respectively. Interestingly, subjects in the two highest doses of IP cocaine either maintained body weight or displayed a significant increase above their baseline It is possible that the differential effects of cocaine on body weight in the IP and SC groups simply reflect the fact that subjects in Groups SC32 and SC50 acquired a robust aversion to the cocaine-associated solution, thereby limiting their fluid consumption every fourth day, i.e., on each conditioning trial. Although this reduction in consumption likely affected body weight, it is not the sole basis for the dramatic differences between the groups. For example, there was a significant loss in body weight for subjects in Groups SC32 and SC50 on the day following the first saccharin-cocaine pairing Given that subjects in all groups drank saccharin at high levels on the first conditioning trial, any differential changes in body weight for the IP and SC groups had to be a function of the route of drug administration. Further, in unpublished work from this laboratory water-deprived subjects that were given a repeated four-day cycle of no water (Day 1) followed by 20-min access to water (Days 2–4), a procedure that resulted in a drinking pattern that paralleled that of subjects in Groups SC32 and SC50, showed only a modest loss in body weight [approximately 25% of the amount lost by subjects receiving repeated pairings of saccharin and cocaine (50 mg/kg)] over the same deprivation period. A second possibility for the differential effects of IP and SC cocaine on body weight is the well-documented anorexic effects of cocaine (18) Although cocaine has been reported to suppress food consumption, there is no clear relationship between changes in food consumption and body weight (2, 16, 22) following cocaine administration Further, there is no evidence that IP and SC cocaine affect food consumption differentially. It is possible that cocaine affects body weight directly, e.g., through its leptogenic or thinning effect (22), al-

though comparisons between IP and SC cocaine have not been made

Independent of the mechanism underlying the differential ability of IP and SC cocaine to induce taste aversions and affect body weight, it is clear that route of administration is an important variable in cocaine's effects Route of administration thus should be considered when conclusions regarding the consequences of cocaine are made (9)

ACKNOWLEDGEMENT

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