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The Relationship Between Intravenous Cocaine Self-Administration and Avidity for Saccharin

BLAKE A. GOSNELL, DEAN D. KRAHN, JOSEPH M. YRACHETA AND BRIAN J. HARASHA

Neuropsychiatric Research Institute, Fargo, ND 58107

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GOSNELL, B. A., D. D. KRAHN, J. M. YRACHETA AND B. J. HARASHA. *The relationship between intravenous cocaine self-administration and avidity for saccharin*. PHARMACOL BIOCHEM BEHAV **60**(1) 229–236, 1998.—Two experiments were conducted to determine whether measures of saccharin intake could be used as a predictor of intravenous cocaine self-administration. Saccharin avidity, defined as the ratio of total daily fluid intake when saccharin and water were available to total intake when only water was available, was measured in male rats. Cocaine self-administration (0.4 mg/kg/infusion) was subsequently measured in an initial 18-h session, followed by daily 1-h sessions in which the infusion dose and the reinforcement schedule were varied. In the initial overnight session, some rats obtained the maximum or near-maximum number of infusions; this high level of cocaine intake was unrelated to saccharin avidity. In the remaining rats, there was a pattern somewhat resembling an "inverted-U," in which rats with low or high avidity self-administered less cocaine than those with intermediate avidity. This pattern reemerged later in the experiment when rats were tested at a low cocaine infusion dose combined with a FR-6 reinforcement schedule. In a second experiment, no significant relationship was observed between the self-administration of a lower cocaine dose (0.125 mg/kg/infusion) and avidity for either saccharin or the artificial sweetener SC-45647. Although these results are consistent with a previous report indicating no simple relationship between saccharin preference and the acquisition of cocaine self-administration, they do suggest that a more complex relationship may be observed under some conditions. Additional research with other drugs, as well as with caloric and noncaloric sweeteners, will be needed to determine the usefulness of taste measures in identifying or treating substance abuse. © 1998 Elsevier Science Inc.

Cocaine Taste Saccharin Avidity Dopamine Sweet Self-administration

A number of studies indicate a relationship between dietary or taste preferences and the self-administration of drugs. Several labs have found that, in rats, preference for saccharin solutions is positively related to alcohol consumption (1,18, 26,34). Furthermore, rats selectively bred for high vs. low alcohol consumption differ in intakes or preferences for saccharin and sucrose solutions (42,43). Rats selected for high saccharin intakes also self-administered more morphine intravenously than rats selected for low saccharin intake (20). Because the intravenous route minimizes the orosensory and oromotor aspects of drug intake, this result suggests that the parallels between saccharin and drug intake may not simply be the result of similarities in taste qualities or of differences in the propensity to consume any fluids available. Rather, it suggests that the processes controlling saccharin and drug intake may overlap or interact. An interaction between opioid systems and palatable fluid intake is further suggested by demonstrations that opioid agonists and antagonists cause increases and decreases, respectively, in palatable fluid intake [see (2,5,19)], and that the consumption of palatable fluids can influence the antinociceptive effects of morphine (6,28,29).

Human studies also indicate a relationship between sweet taste and drug use. Opiate addicts frequently report a high preference for sweets (44), and the daily intake of sucrose was found to be higher in addicts than in controls (31). In recovering alcoholics, the duration of a period of abstinence was associated with sugar intake (46). Kampov-Polevoy et al. (25) reported that detoxified alcoholics generally preferred higher concentrations of sucrose than control subjects. In a large epidemiological study, there was an inverse relationship between the intakes of alcohol and sugar (4).

In light of the observations that the oral infusion of saccharin causes an increase in extracellular dopamine in the nucleus accumbens (30), and that dopamine antagonists cause a reduction in the intake of sweetened fluids (32,35,47), a relationship between taste preferences and the effects or self-adminis-

Requests for reprints should be addressed to Blake A. Gosnell, Ph.D., Neuropsychiatric Research Institute, 700 First Avenue South, P.O. Box 1415, Fargo, ND 58107.

tration of psychostimulants might also be expected. Sills and Vaccarino (40) found that sucrose intake predicts the locomotor response to amphetamine: rats consuming more sucrose displayed a greater response than rats consuming less sucrose. Furthermore, DeSousa et al. (8) reported in a recent abstract that rats consuming large amounts of sucrose also self-administered more amphetamine than rats consuming less sucrose. On the other hand, Gahtan et al. (12) reported no relationship between saccharin intake and cocaine self-administration. The differences in the general conclusions one might draw from these two reports may be due to differences in the sweetener or the psychostimulant used, as well as to less obvious differences in methodological details. In this article we describe experiments intended to explore the relationship between saccharin intake and cocaine self-administration in more detail.

METHOD

Male Sprague–Dawley rats (Harlan–Sprague–Dawley, Indianapolis, IN) were used in all experiments. In all cases, they were individually housed in stainless steel cages and maintained in a temperature-controlled room with a 12 L:12 D cycle. Food and water were available ad lib in the home cages and were not available in the testing chambers (described below) unless otherwise specified.

Method for Determining Saccharin Avidity

Five days after arrival into the animal colony, all rats were provided with 23 h/day access to two bottles—one contained tap water, and one contained a 0.1% sodium saccharin solution. The intake of this concentration of saccharin has been reported to be related to alcohol or morphine self-administration in several studies (1,18,20,26,27,34,42). Water and saccharin solution intake were determined by weight each day, and the positions of the bottles were reversed daily. After the fourth day, rats were given two water bottles and daily intake was measured for 3 days. Avidity was calculated as the ratio of the average daily fluid intake (ml/kg) of the final 2 days when saccharin was available to the average daily fluid intake of the final 2 days when only water was available. Thus, an avidity score of 1.5 indicates that a rat consumed 1.5 times as much fluid in the presence of saccharin as it did when only water was available. Dess and Minor (9) have used the term "avidity" to describe the amount of fluid consumed in the presence of a flavored solution minus the amount of water consumed when only water is available, with the difference expressed as a percentage of body weight. Although intake measures in the present report are expressed as a ratio of weight-adjusted intakes rather than a difference in intakes, we will refer to the ratio as a measure of avidity. This calculation is similar to that used by Kampov-Polevoy et al. (27), who found that the percent difference between fluid intake when saccharin was available to fluid intake when only water was available was significantly correlated with ethanol intake.

Surgery

Under sodium pentobarbital anesthesia (60 mg/kg), a silastic catheter was inserted into the right external jugular vein with procedures described previously (20). At the time of surgery, rats weighted 325–402 g. After surgery and twice daily for the next 4–5 days, rats were given an intravenous (IV) injection of the broad-spectrum antibiotic Timentin (SmithKline Beecham Pharmaceuticals, Philadelphia, PA) (3.1 mg in a 0.5-ml volume). These injections were followed by an infusion of 0.1 ml of 0.9% saline containing heparin (5 U/ml) (morning injections) or heparin (30 U/ml) and streptokinase (1000 U/ml) (afternoon injections) to prevent blood coagulation in the catheters. As a precaution against infection, Timentin injections (once daily for 5 days) were reinstated approximately 2 weeks and again approximately 7 weeks after the first self-administration session. No effects of the antibiotic on behavior were noted. The daily protocol for maintaining the catheters was a modification of that described by Emmett-Oglesby and Lane (10). Briefly, the catheters were flushed prior to each test session with 0.1 ml of a saline solution containing 5 U/ml heparin and again after each session with 0.1 ml of a saline solution containing heparin (30 U/ml) and streptokinase (1000 U/ml). In addition, heparin (0.5 U/ml) was added to the cocaine solutions described below.

Experiment 1

Rats were tested in an initial overnight session that began at 1600 h and ended at 1000 h the following day. As only eight self-administration chambers were available, this required staggering the testing across 4 nights. The surgical procedures described above were therefore staggered across 4 days, such that for all rats, the initial test session occurred 6 days after surgery. Rats were placed in operant chambers, each containing two levers and stimulus lights, a house light, and a ventilation fan (Med Associates, St. Albans, VT). An infusion pump (Med Associates Model PHM-100) on top of each chamber delivered the drugs via polyethylene and/or Tygon tubing attached to a liquid swivel apparatus. Powdered chow and water were available during this session. The session began with a press of the active lever by the investigator after the infusion line was attached and the rat was released into the chamber. This lever-press initiated a single priming infusion of cocaine to clear the heparin–saline solution from the catheter and to facilitate responding. This infusion was of the same volume and duration as those self-administered during the remainder of the session (described below). The total catheter volume was approximately 10–15 μl, such that roughly 65–85% of the initial priming infusion was actually delivered into the animal. During each session, pressing the right lever activated an infusion pump to deliver cocaine hydrochloride at a dose of 0.4 mg/kg/infusion over a period of approximately 2.5–4.5 s in a volume of 0.125 ml/kg. A 30-s time-out period followed the start of each infusion; during this time, the stimulus light above the lever was turned on, and lever presses were counted but did not activate the infusion pumps. Presses of the left lever were counted only.

Three to 4 days after the end of the initial overnight session, rats were tested in daily 1 h sessions for 13–15 consecutive days at a dose of 0.4 mg/kg/infusion in a manner similar to that described above. Rats were then tested 5 days per week for 37 additional days, during which the infusion dose and reinforcement schedule were varied every 3–5 days. Due to the limited number of test chambers, it was necessary to conduct four sessions of six to eight rats per session each day; the two morning sessions began approximately 2 and 3 h after the onset of the light period (0800 h), and the early afternoon sessions began roughly 4.5 and 6 h after light onset. The dose–schedule combinations were tested in the following order, with the number preceding the parentheses referring to the infusion dose (mg/kg/infusion): 0.4 (FR-1), 1.0 (FR-1), 0.4 (FR-1), 0.125 (FR-1), 0.125 (FR-3), 0.125 (FR-6), 0.4 (FR-6), 0.4 (FR-1), 0.4 (FR-3), 0.4 (FR-6), and 0.125 (FR-6).

The ability to withdraw blood from the catheter either before or after the daily sessions was taken as evidence of catheter patency and proper placement. With the exception of two rats that developed infections and were subsequently removed from the study, all rats showed evidence of patency and proper placement on the final four test days and on at least 92% of all test days.

Experiment 2

Separate groups of rats were used to determine the relationship between preferences for sweet fluids and the overnight self-administration of a lower dose of cocaine. One group ($n = 17$) was tested with procedures similar to those described above, with a few exceptions. Water intake was measured for 4 days, followed by the measurement of saccharin and water intake (available concurrently) for 4 days. The final 2 days of each period were used to calculate saccharin avidity. At the time of surgery, rats weighed 325–406 g. During the overnight self-administration session (12 days postsurgery), the infusion dose was 0.125 mg/kg/infusion, with a cutoff at 640 infusions (80 mg/kg total). The infusion volume was 36–44 μl (0.1 ml/kg), and was delivered over approximately 1 s.

A second group of rats was also tested at the 0.125 mg/kg infusion dose. Prior to surgery, these rats were tested for avidity for saccharin and for the artificial sweetener SC-45647 (1.7 mg/100 ml) (21,33,45). Fluid intake was measured in four consecutive periods of 4 days each. In the first and third periods, only water was available. During periods 2 and 4, water and one of the sweeteners were available concurrently. All rats were tested with both sweeteners in counterbalanced order, and avidity was calculated as the ratio of total fluid intake in the final 2 days when a sweetener was available to total water intake in the 2 days prior to presentation of the sweetener. In contrast to the other groups, surgery was performed under ketamine/xylamine anesthesia (40/10 mg/kg, IP), with supplementation with smaller amounts of this combination or with sodium pentobarbital as needed (approximately 6–12 mg, IV). Rats weighed 371–488 g at the time of surgery and were tested for cocaine self-administration 6–9 days postsurgery. Data from all rats tested at this dose were pooled. These rats were not available for the more extensive testing described in Experiment 1.

The ability to withdraw blood from the catheter either before or after the daily sessions was taken as evidence of catheter patency and proper placement. Rats that did not meet this criteria ($n = 5$) were later tested for signs of ataxia after the IV infusion of sodium pentobarbital (0.1–0.3 ml of a 60-mg/ml solution). A catheter was judged to be patent if the rat showed clear signs of ataxia within seconds of the infusion.

Statistics

Correlations (Pearson) were calculated between the avidity measures described above and the number of self-administered cocaine infusions during the initial 18-h session. For the various combinations of infusion dose and reinforcement schedule, the number of infusions obtained on the final 2 days of each condition were averaged. The rats were then divided into low, intermediate, and high avidity groups, based on a rank ordering of avidity scores. The mean number of infusions on the final 2 days of each dose–schedule combination were compared across groups with an analysis of variance. Tukey's test was used for post hoc comparisons.

RESULTS

In Experiment 1, a total of 34 rats were tested for saccharin avidity, and cocaine data were subsequently collected on 32 of these. The range of water intakes over the last 2 days of access to water only was 109–153 ml/kg/day; the range of total fluid intakes for the final 2 days when saccharin was also available was 116–323 ml/kg/day. Avidity in these rats ranged from 0.99–2.37. When both fluids were present, saccharin preference (daily saccharin intake as a percentage of total fluid intake) ranged from 8–98%. Most rats showed a strong preference for saccharin over water, even if total fluid intake was similar to intake when only water was available. Only 3 out of 32 rats had saccharin preference scores less than 80%, and 28 of 32 had scores greater than 90%; the mean saccharin preference score (±SEM) was 89 ± 4%. Thus, it was possible for two rats to have similarly strong saccharin preferences yet differ greatly in saccharin avidity.

Figure 1 represents avidity scores and cocaine self-administration in the initial 18-h session when the infusion dose was 0.4 mg/kg. Across the entire avidity range, some rats obtained the maximum number of infusions permitted (200). The overall correlation between avidity and the number of infusions was not significant. A closer inspection of the data, however, suggests the possibility of a more complex relationship between avidity and cocaine self-administration in a subset of rats. If those rats that obtained 75% or more of the maximum number of infusions are excluded, those with intermediate avidity generally self-administered more cocaine than those with lower or higher avidity scores. Two types of analyses support this observation. When those rats that obtained greater than 150 infusions are excluded, a regression analysis indicated a significant second-order polynomial equation describing the relationship between avidity and cocaine self-administration, $F(2, 20) = 7.92$, $p < 0.02$. Further, if the remaining

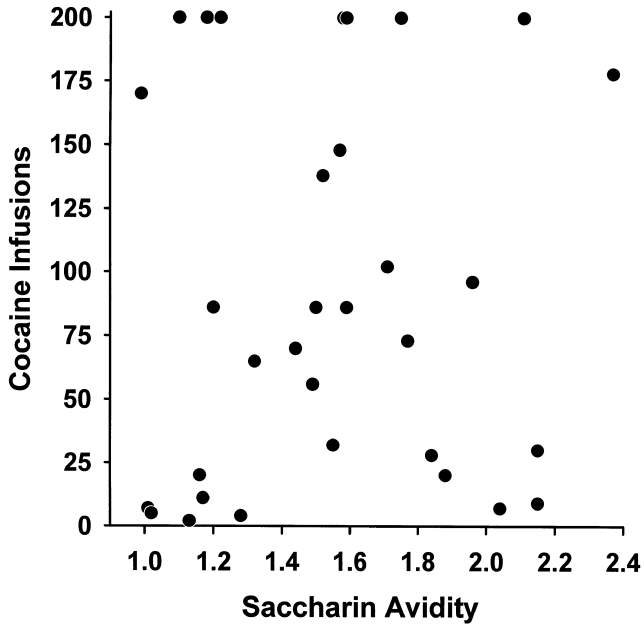

FIG. 1. Cocaine self-administration as a function of saccharin avidity. Rats ($n = 32$) with no prior self-administration experience were tested in a single 18-h session in which cocaine was available on a FR-1 schedule of reinforcement at a dose of 0.4 mg/kg/infusion.

rats are divided into groups of low, intermediate, and high avidity (n = 8, 7, and 8, respectively), an analysis of variance indicated a significant group effect, $F(2, 20) = 5.37$, $p < 0.02$. The means (±SEM) for these groups were 25 ± 11, 88 ± 16, and 46 ± 14 infusions, respectively; post hoc tests (Tukey) indicated that self-administration by the intermediate group was significantly greater than that of the low avidity group ($p < 0.05$).

Because cocaine self-administration did not appear to be linearly related to saccharin avidity, rats were divided into groups of low, intermediate, and high avidity to assess the relationship between these two measures when the infusion dose and reinforcement schedule were varied. Only those rats whose catheters remained patent for the entire series of 1-h sessions were included (n = 30). Thus, the rats were rank ordered for saccharin avidity and divided into three groups of 10 rats each. Mean avidity ratios for the low, intermediate, and high groups were 1.14 ± 0.03, 1.52 ± 0.03, and 1.99 ± 0.07, respectively. As indicated in Fig. 2, there was an inverse relationship between infusion dose and the number of infusions obtained on a FR1 reinforcement schedule. The groups did not significantly differ in the number of infusions obtained at any of the tested doses, $F(2, 27) = 0.43$, 0.22, and 1.39 for the 0.125, 0.4, and 1.0 mg/kg/infusion doses, respectively (all ps > 0.05).

The effects of varying the reinforcement schedule are shown in Fig. 3. At 0.125 mg/kg/infusion, increases in the fixed-ratio size led to a decrease in the number of infusions obtained. At FR-1 and FR-3, the three avidity groups did not significantly differ. AT FR-6, however, rats in the intermediate avidity group self-administered significantly more cocaine than the low and high avidity groups (Tukey's test, $p < 0.05$).

The effects of fixed-ratio size on self-administration of a higher dose (0.4 mg/kg/infusion) are also shown in Fig. 3. There was a slight overall decrease in the number of infusions obtained in the FR-6 condition when compared to the FR-1 and FR-3 conditions. There were, however, no significant differences among the avidity groups at any of the schedules tested at this dose. When, as a final test,the infusion dose was lowered again to 0.125 mg/kg, the pattern observed previously reemerged: rats in the intermediate avidity group obtained more infusions than rats in the low or high avidity groups. The differences, however, were not significant. Compared to the earlier trial under these conditions, mean number of infusions and the within-group variability increased in the low and high avidity groups.

An inspection of the data indicated the possibility that self-administration by rats tested in the early afternoon differed from that of rats tested in the morning. The data were, therefore, reanalyzed with a two-factor ANOVA that treated time of testing (a.m. vs. p.m.) as an independent factor along with avidity (low, middle, or high). Tukey's test was used for post hoc comparisons. These analyses indicated that while the morning and afternoon subgroups of the low and high avidity groups did not differ, there were significant differences within the middle avidity group. Generally, rats with intermediate avidity tested in the morning obtained more infusions than the comparable group tested in the afternoon. This difference was significant for most of the conditions tested in the latter half of the study. Among the morning-tested groups, rats with intermediate avidity self-administered significantly more cocaine than rats with low avidity in all conditions tested at 0.125 mg/kg/infusion (FR-1, -3, and -6). This intermediate subgroup significantly differed from the high avidity subgroup only when this dose was tested at FR-6. In afternoon-tested rats, the number of cocaine infusions obtained by rats with intermediate avidity was generally lower than that of the low and high avidity subgroups throughout the study, but was significantly lower than that of the low avidity subgroup only when the 0.4 mg/kg/infusion dose was tested at FR-6.

In Experiment 2, a total of 50 rats were tested for saccharin avidity; 33 of these were also tested for SC-45647 avidity. For all rats, the range of water intakes over the last 2 days of ac-

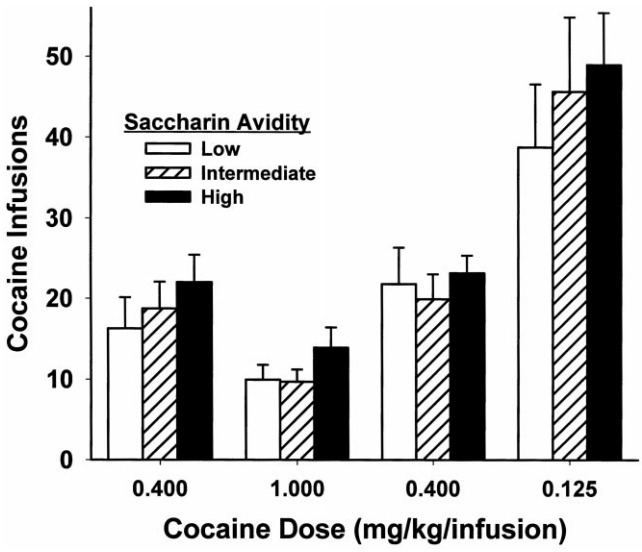

FIG. 2. Cocaine self-administration as a function of infusion dose in rats with low, intermediate or high saccharin avidity (n = 10 per group). Each bar represents the group mean (+SEM) for the final two sessions tested at each dose. Doses were tested in the order represented on the x-axis.

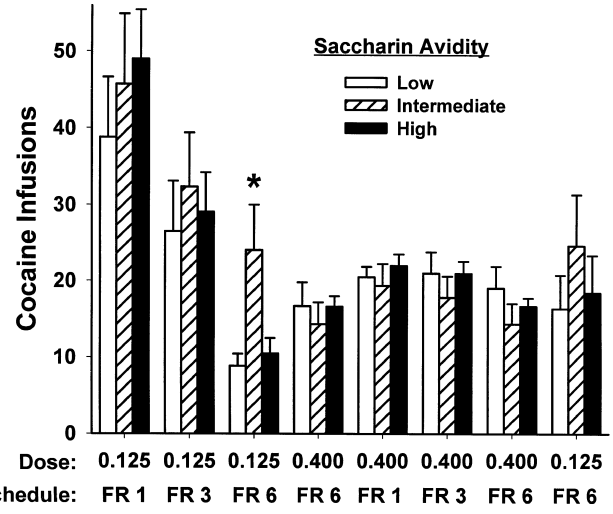

FIG. 3. Cocaine self-administration as a function of dose and reinforcement schedule. Each bar represents the group mean (+SEM) for the final two sessions tested at each dose/schedule combination. Doses were tested in the order represented on the x-axis. Results from the trials at FR 1 (0.125 mg/kg/infusion) are also shown in Fig. 2 and are included here for comparison to the other conditions. Asterisk indicates a significant difference from the low and high avidity groups ($p < 0.05$, Tukey's test).

cess to water only was 90–167 ml/kg/day; the range of total fluid intakes for the final 2 days when saccharin was also available was 99–486 mg/kg/day. Of the rats from which cocaine self-administration was obtained (n = 40), the range of intakes was 90–167 ml/kg/day with only water present and 106–406 ml/kg/day when saccharin and water were available. Avidity in these rats ranged from 0.94–3.36, with most rats scoring in the 1.0–2.0 range. When both fluids were present, saccharin preference ranged from 12–99%. As in the first experiment, most rats showed a strong preference for saccharin over water. Only 4 of the 40 cocaine-tested rats had saccharin preference scores less than 80%, and 33 of 40 had scores greater than 90%; the mean saccharin preference score (±SEM) was 91 ± 3%.

Of the 33 rats tested for SC-45647 avidity, cocaine self-administration data were obtained from 25 rats. The range of total fluid intakes over the final 2 days by these 25 rats was 99–146 ml/kg/day when only water was present and 86–294 ml/kg/day when SC-45647 was available along with water. The range of avidity scores was 0.63–2.40. As with saccharin, preference for SC-45647 over water when both were available was high, with only 2 of 25 rats exhibiting a preference for this sweetener below 80% (mean = 91 ± 3%). For saccharin tests in this group of rats only, water intake ranged from 90–145 ml/kg/day, while saccharin + water intakes ranged from 106–486 mg/kg/day. The avidity scores ranged from 0.96–3.36. When data from all rats tested with both sweeteners (n = 33) were considered, avidity for saccharin was significantly correlated with avidity for SC-45647 (Fig. 4C).

The relationships between self-administration of a lower dose of cocaine and avidity for saccharin and SC-45647 are shown in Fig. 4. In regression analyses, neither the first-order nor the second-order polynomials were significant between the avidity for either sweetener and cocaine self-administration. An inspection of the scatter plots suggested that two subjects were outliers. As an exploratory analysis that might indicate directions for future studies, the data were reanalyzed after excluding the data from these two subjects. For saccharin, excluding these data points did not change the outcome of the regression analyses. For SC-45647, the correlation between avidity and cocaine self-administration was significant when these two subjects were excluded (r = 0.61, $p < 0.002$).

DISCUSSION

Studies by our lab and others indicate a relationship between sweet taste preferences and the self-administration of alcohol and morphine. This article reports experiments designed to determine whether cocaine self-administration might also be related to the intake or preference for sweet-tasting solutions. Gahtan et al. (12) reported no differences in rate of acquisition of cocaine self-administration or in cocaine consumption by rats with high or low saccharin intake. At first glance, our results support this conclusion, inasmuch as no monotonic relationship was observed between saccharin avidity and cocaine self-administration under a variety of conditions. However, by testing rats representing the entire range of saccharin avidity, rather than those representing the "tails" of the saccharin preference distribution, we were able to ex-

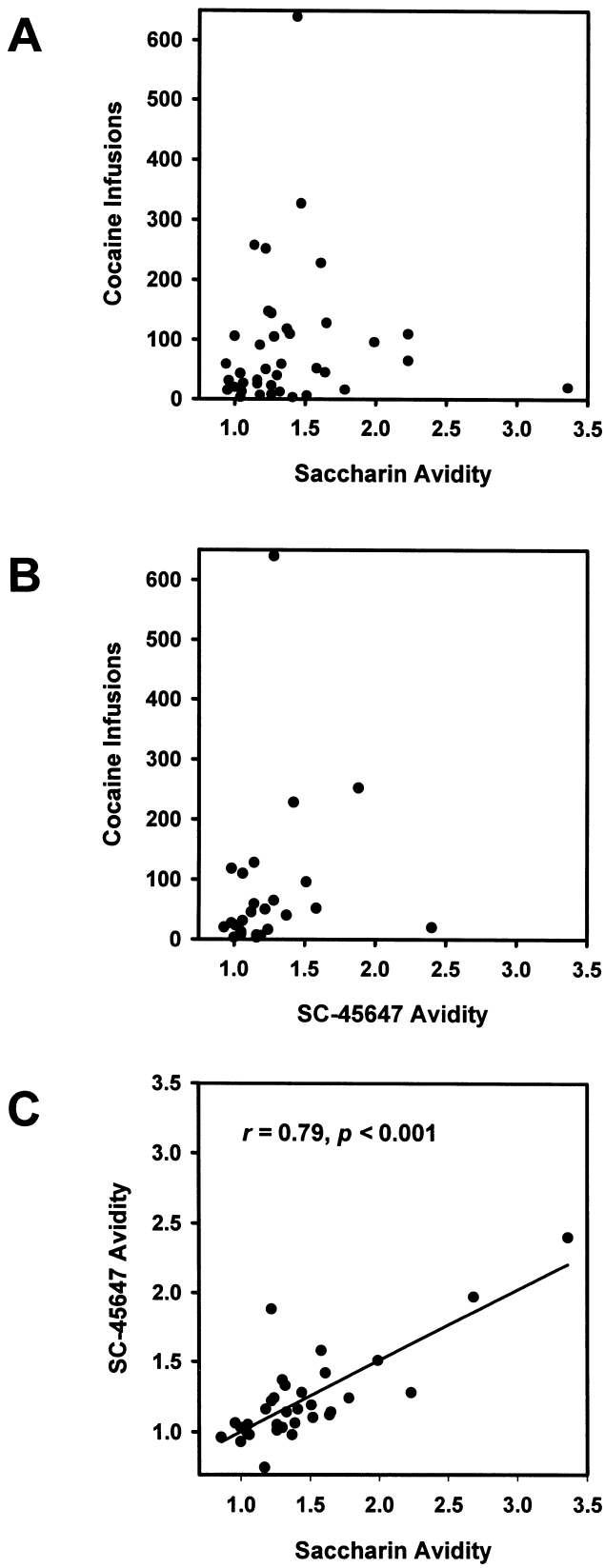

FIG. 4. The relationship between avidity for (A) saccharin (n = 40) or (B) the artificial sweetener SC-45647 (n = 25) and cocaine self-administration when the infusion dose was 0.125 mg/kg/infusion. C represents the relationship between saccharin avidity and avidity for SC-45647 (n = 33). The two measures were significantly correlated. Self-administration data were obtained from 25 of these rats and are included in A and B.

amine the relationship between saccharin intake and cocaine self-administration in more detail. The results suggest the possibility of a more complex relationship that may only be apparent under certain conditions. In the initial overnight session of Experiment 1, some rats obtained the maximum, or near-maximum number of infusions allowed. Saccharin avidity appeared to be unrelated to the self-administration of these large amounts of cocaine. In the remaining rats, there was a pattern somewhat resembling an "inverted-U," in which rats with low or high avidity self-administered less cocaine than those with intermediate avidity. This pattern reemerged later in the experiment when rats were tested at a low cocaine infusion dose combined with a FR-6 reinforcement schedule.

The pattern in which rats with intermediate saccharin avidity self-administered more cocaine than rats with lower or higher avidity resembles to some extent the findings of Glick et al. (16), who measured levels of dopamine and its metabolites in the nucleus accumbens, striatum, and prefrontal cortex prior to measurements of cocaine self-administration. They found that rats with intermediate baseline levels of dopamine in the nucleus accumbens self-administered more cocaine than rats with lower or higher baseline levels. This relationship was observed when either initial or asymptotic rates of self-administration were considered. In contrast, morphine self-administration was not correlated with basal dopamine levels (15). However, these authors did observe a positive, linear relationship between dopamine metabolites in the nucleus accumbens and morphine self-administration. The present results, along with our previous finding of a positive relationship between saccharin preference and morphine self-administration (20), suggest that saccharin preference/intake may be related to drug self-administration in a manner similar to that of baseline mesolimbic dopaminergic activity reported by Glick and colleagues. It should be noted, however, that the relationship observed in the cocaine study by Glick et al. (16) differs from that suggested by studies on the predisposition to self-administer another psychostimulant, amphetamine. Piazza et al. (36) have found that rats with a high locomotor response to being placed in a novel environment (HR rats) are more prone to self-administer amphetamine than rats with a low response to novelty (LR rats). Further, this group has reported a positive relationship between the locomotor response to novelty and levels of the dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) in the nucleus accumbens (37). Similarly, Hooks et al. (23) reported that HR rats had greater basal and cocaine-stimulated dopamine levels in the nucleus accumbens than did LR rats. These studies imply a positive, monotonic relationship between dopaminergic activity in the nucleus accumbens and amphetamine self-administration, in contrast to the curvilinear relationship reported for cocaine self-administration (16). Differences in the nature of the relationship may be related to differences in cocaine vs. amphetamine self-administration or to differences in the conditions under which drug self-administration was measured.

It must be emphasized that the "inverted-U" distribution observed in Experiment 1 was apparent only after the elimination of those rats that self-administered a large amount of cocaine. Clearly, any conclusion that is subsequent to a selective elimination of data must be regarded as tentative and will require further examination. By eliminating a different subset of data points, one could perhaps interpret the relationship in a different way. An inspection of the plotted data, however, suggested that it might be useful to separate the subjects into those that self-administered near-maximal amounts of cocaine from those that self-administered less of the drug. The possibility of a nonmonotonic relationship was of particular interest in light of the cocaine results of Glick et al. (16) and of the results of subsequent test sessions with a lower infusion dose and an increased response requirement. Although the overall results indicate that saccharin avidity is not a major factor in identifying rats with a predisposition to cocaine self-administration, this secondary analysis suggests that it may have some predictive value in a subset of rats.

Deminière et al. (7) have suggested that individual differences in vulnerability to drug abuse may be more apparent when lower doses of a stimulant are used than when higher doses are used. Horger et al. (24) reported that acquisition of cocaine self-administration was more gradual with lower infusion doses than with higher doses. Similarly, low doses of amphetamine produced more diverse ingestive responses than did higher doses (41). In the present study, this differential effect of low vs. high doses appears to have interacted with the schedule of reinforcement, as group differences were observed with the lowest infusion dose (0.125 mg/kg) at FR-6 that were not observed with other dose–schedule combinations. In Experiment 2, however, testing at a lower dose during the 18-h overnight session did not permit a clearer identification of the relationship that was hinted at in Experiment 1. Nevertheless, as in the first experiment, there appeared to be more diversity in cocaine self-administration in rats with saccharin avidities in the middle range than in rats in the lower and higher ranges. For SC-45647 avidity, a linear relationship to cocaine self-administration was observed after the elimination of two "outliers." However, fewer subjects were tested for SC-45647 avidity, and there were relatively fewer rats that displayed an avidity greater than 1.5.

The inability to demonstrate a clear relationship between measures of saccharin preference and cocaine self-administration in the present study and in that by Gahtan et al. (12) contrasts with results obtained by DeSousa et al. (8) with another psychostimulant, amphetamine. These authors reported that rats classified as high sugar feeders self-administered more amphetamine than rats classified as low sugar feeders. The dose–response function for low sugar feeders was also blunted compared to high sugar feeders. After amphetamine injections, the locomotor response and the increase in extracellular dopamine were also greater in high sugar feeders than in low sugar feeders (39,40). Although the reinforcing effects of both cocaine and amphetamine are thought to involve the mesolimbic dopaminergic system, and both drugs cause an increase in extracellular dopamine in the nucleus accumbens, the two drugs differ in their mechanism of action (11). Cocaine and amphetamine self-administration also differ in their sensitivity to food deprivation and to drugs acting on serotonin systems (14,38). Furthermore, amphetamine appears to be more readily self-administered directly into the nucleus accumbens (3,17,22). The relationship to preferences for sweet tastes may represent yet another difference between the drugs.

Differences in the sweetener tested, as well as in the methods of measuring intake or preference, may also account for the apparent discrepancies between the present findings with saccharin and those linking sucrose feeding with the effects or the self-administration of amphetamine. In the present report and in that by Gahtan et al. (12) saccharin was presented in a solution; in the reports by Sills and colleagues (39–41) and DeSousa et al. (8), sucrose was presented in granulated form. Unlike sucrose, saccharin is noncaloric, and its intake is less likely to be controlled by factors regulating energy balance. Saccharin has a complex taste, and Giza et al. (13) have pre-

sented evidence that saccharin-preferring and nonpreferring rats may differ in the degree to which saccharin taste resembles a sugar taste. It is therefore possible that saccharin intake, or the factors controlling its intake, are less closely related to the systems thought to mediate psychostimulant reward than those factors that affect sucrose intake. On this point, it is interesting to note that avidity for SC-45647 was correlated with cocaine self-administration, albeit only after exclusion of two subjects representing the highest values for avidity or self-administration. SC-45647 is an artificial sweetener which is thought to have a taste similar to sucrose in rats (21). A relationship between avidity for this sweetener and cocaine self-administration, however, is difficult to reconcile with the observations that SC-45647 and saccharin avidities were correlated and that saccharin avidity was not linearly related to cocaine self-administration. Additional work with both caloric and noncaloric sweeteners may clarify the issue.

In the present article, avidity reflects the degree to which the presence of saccharin (or SC-45647) promotes fluid intake. As mentioned in the Results section, it is possible for two rats to differ in avidity scores yet have similar saccharin preference scores. Similarly, Dess and Minor (9) have reported on two lines of rats that differ in sucrose avidity but not sucrose preference (although, as mentioned above, these authors used a slightly different method for calculating avidity). That avidity and preference are dissociable suggests that the two measures could differ in their relationship to drug intake. In the present study, in which preference and avidity were determined from intakes over 2 days, a large majority of all rats tested had preference scores greater than 90%. This limited range of scores did not permit a meaningful analysis of the relationship of saccharin preference to cocaine self-administration. Preference testing with sessions of shorter duration and/or different saccharin concentrations should yield a greater diversity of preference scores. Saccharin intake in 1-h sessions, for example, has been used as a basis for forming groups that differed in morphine self-administration (20).

In addition to the use of different psychostimulants and sweeteners, there are at least two procedural differences that may account for the apparent differences between cocaine and amphetamine self-administration in relation to sweet taste preferences. First, the amphetamine self-administration sessions reported by DeSousa et al. (8) were only 30 min in duration. The finding that HR rats self-administer more amphetamine than LR rats was also obtained in 30-min sessions (36). In contrast, sessions in the current study were 18 h in duration, and Gahtan et al. (12) used 6-h sessions. It is possible that individual differences related to a variable such as sweet taste preference are lessened in longer compared to shorter test sessions. A second procedural difference concerns the method of categorizing subjects according to their intake of saccharin or sucrose. In the present study and that by Gahtan et al. (12), saccharin intake was measured in the absence of any other manipulation. In contrast, rats in the DeSousa et al. (8) study were divided into high- and low-sugar feeders based on their intake following a saline injection. The studies by Sills and Crawley (39) and Sills and Vaccarino (40), which showed that high- and low-sugar feeders differed in their responses to amphetamine, were also based on sucrose intake after a saline injection. Inasmuch as a saline injection may be considered a mild stressor, it is possible that divergence in responses to amphetamine or self-administration of amphetamine is more related to individual differences in eating in response to stress than to differences in baseline preference for sucrose. As discussed above, the locomotor response to placement in a placement in a novel environment, which is also a mild stressor, has been shown to predict amphetamine self-administration (36). However, in the reports by Sills and Crawley (39) and Sills and Vaccarino (40), groups formed on the basis of sucrose intake after a saline injection were also significantly different in the baseline sessions conducted before the saline injection. Therefore, it is not clear from these studies whether stress was an important factor in the results.

Results of the first experiment suggested that time of day may have an influence on cocaine self-administration. In a subgroup of rats (those with intermediate saccharin avidity), more cocaine was self-administered by rats tested in the morning than by those tested in the early afternoon. However, the experimental design of the present studies, as well as the limited number of subjects in each subgroup, preclude the drawing of a conclusion regarding the influence of time of testing. This factor, however, could be a potential confound when comparing results from different studies.

In summary, two experiments were performed to determine the relationship between cocaine self-administration and measures of the intake of sweetened fluids. There was no linear relationship between avidity for saccharin and cocaine intake. Under limited conditions, however, there was some indication that rats with an intermediate saccharin avidity self-administered more cocaine than rats with a lower or higher avidity. This observation is similar to the report by Glick et al. (16) that rats with intermediate levels of extracellular dopamine in the nucleus accumbens self-administered more cocaine than rats with lower or higher baseline levels. These studies highlight the potential usefulness of experimental designs that include subjects from segments other than the tails of a distribution. Additional research with other flavored solutions, as well as with other drugs, will be necessary to identify the conditions under which ingestive behaviors are related to drug self-administration. Knowledge of these relationships may be useful in efforts to prevent or reduce substance abuse.

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