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Heroin-induced Suppression of Saccharin Intake in Water-Deprived and Water-Replete Rats

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GRIGSON, P. S., R. C. TWINING AND R. M. CARELLI. *Heroin induced suppression of saccharin intake in water-deprived and water-replete rats*. PHARMACOL BIOCHEM BEHAV **66**(3) 603–608, 2000.—Rats suppress intake of a saccharin conditioned stimulus (CS) when paired with an aversive unconditioned stimulus such as lithium chloride. This phenomenon is referred to as a conditioned taste aversion (CTA). Rats also suppress intake of a saccharin CS when paired with a rewarding sucrose solution and when paired with a drug of abuse. Although the suppressive effects of drugs of abuse have long been interpreted as CTAs, evidence suggests that rats may suppress intake of the saccharin CS following taste–drug pairings because they are anticipating the rewarding rather than the aversive properties of the drug. Oddly, however, while all other drugs of abuse tested suppress intake of a gustatory CS, the highly reinforcing drug, heroin, is reportedly ineffective. The present study reexamined this issue in both water-deprived and water-replete rats using procedures that sustain both morphine- and cocaine-induced suppression of CS intake. The results showed that heroin greatly reduced CS intake following saccharin-heroin pairings and that this effect was less variable when assessed in water-replete subjects. When taken with other reports, these data suggest that rats suppress intake of a saccharin CS in anticipation of the availability of all drugs of abuse tested. © 2000 Elsevier Science Inc.

Heroin Conditioned taste aversion CTA Reward comparison Saccharin Anticipatory contrast

RATS suppress intake of a saccharin conditioned stimulus (CS) when paired with the administration of a drug of abuse (5,6,28). Because they also suppress intake of a saccharin CS when paired with an aversive agent, such as lithium chloride (LiCl) or X-radiation (14,32,33), the suppressive effects of drugs of abuse have been interpreted as conditioned taste aversions [CTAs, (34)]. Of course, the finding that drugs of abuse induce CTAs has been viewed as highly paradoxical and has initiated a number of relatively unsuccessful attempts to resolve the paradox. Explanations have focused upon: the nature of the drug; the dose of the drug; the time course of drug action; the nature of drug action (e.g., whether the drug induces nausea, toxicity, adipsia, or suppression of appetite); the familiarity or novelty of drug action; the route of drug administration; and the active or passive nature of drug administration [(7,13,18,24,41,44); see (17) for review].

Although the solution to the paradox was not revealed by such investigations, the paradox has been somewhat untangled by data clearly showing that the suppressive effects of drugs of abuse differ from those of the aversive agent, LiCl. For example, while LiCl-induced CTAs are associated with aversive orofacial responses such as gapes and chin rubs, the reduction in CS intake induced by drugs of abuse is not accompanied by such aversive responses even when using very high doses (31,32). Instrumental performance also is differentially affected by LiCl and drugs of abuse. That is, rats will decrease both instrumental and consumatory responding for a gustatory CS that has been paired with LiCl, but will increase instrumental responding for, and decrease ingestion of, a gustatory CS that has been paired with a drug of abuse (35,46,47). Further, striking individual differences have been revealed showing that the greatest reduction in CS intake is

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associated with the fastest running speed in the runway and the most drug self-administration behavior (46,47).

Recent evidence potentially accounts for these data by suggesting that the same reinforcing properties that mediate the increase in running speed and self-administration also are responsible for the reduction in CS intake following taste–drug pairings (20,21,23). According to this alternative hypothesis, rats suppress intake of a saccharin CS following taste–drug pairings because the value of the saccharin CS pales as it comes to predict the availability of the preferred drug of abuse (20). This effect is thought to be similar to a phenomenon referred to as anticipatory contrast where intake of a saccharin CS is suppressed as it comes to predict the availability of a highly preferred sucrose reward following daily saccharin–sucrose pairings (10,11). Support for this reward comparison hypothesis is accumulating. First, while LiCl-induced CTAs occur with all CSs tested, the suppressive effects of a rewarding sucrose solution and drugs of abuse can be reduced or eliminated when using sucrose or salt, rather than saccharin, as the CS (4,12,16,20,23). Second, the suppressive effects of a rewarding sucrose unconditioned stimulus (US) and cocaine, but not LiCl, are exaggerated in the reward-preferring Lewis rat [(15,21); but see (27)]. Finally, bilateral lesions of the gustatory thalamus prevent the suppressive effects of sucrose and morphine, but have absolutely no impact upon the development of a LiCl-induced CTA (22,36,39). Taken together, these data suggest that rats suppress intake of a saccharin CS following daily pairings with a drug of abuse because they are anticipating the rewarding properties of the drug.

As with other hypotheses, however, the usefulness of this reward comparison account depends not only upon its accuracy, but also upon its generality. In this regard, it is relevant to note that intake of a saccharin CS is reduced following pairings with a range of drugs of abuse including morphine, cocaine, amphetamine, alcohol, amobarbital, chlordiazepoxide, flurazepam, and nicotine [(5,6,8,19,28,40,44); for a review, see (37)]. Furthermore, manipulations that influence the suppressive effects of one drug of abuse often exert a similar impact upon the suppressive effects of another. As eluded to, use of a salt rather than a saccharin CS prevents the suppressive effects of both morphine and cocaine in water-deprived rats (4,20). Use of a caloric sucrose CS can reduce or eliminate the suppressive effects of morphine in water-deprived rats and the suppressive effects of morphine and cocaine in food-deprived rats (16,23). Finally, food deprivation has been found to attenuate the suppressive effects of morphine, cocaine, amphetamine, and chlordiazepoxide when using a saccharin CS (2,45).

Despite these similarities, one glaring exception remains. That is, although rats suppress intake of a saccharin CS when paired with a range of drugs of abuse, they fail to do so when paired with a 0.5, 1, 2, 4, 8, or 12 mg/kg dose of heroin (42). This finding poses a challenge for the reward comparison hypothesis. First, the hypothesis suggests that the reinforcing, rather than the aversive, properties of the drugs are responsible for suppressing intake of a saccharin CS following taste–drug pairings, and heroin is known to be a highly potent reinforcer (3,25). Second, morphine readily suppresses intake of a saccharin CS (20) and, while heroin is known to exhibit unique receptor binding characteristics, it is quickly converted into morphine following injection (26). Given the importance of these data to the reward-comparison hypothesis, the following experiment was designed to revisit this issue by testing whether heroin will suppress intake of a saccharin CS using procedures that are known to sustain clear morphine- and cocaine-induced suppression of saccharin intake (20). Moreover, because recent data indicate that the suppressive effects of both morphine and cocaine are most robust when evaluated in rats that have free access to both food and water (45), heroin-induced suppression of saccharin intake was tested in both water-deprived and water-replete subjects. Finally, in an effort to maximize our changes of obtaining heroin-induced suppression, we selected one of the higher doses (i.e., 8 mg/kg) from the dose–response function evaluated by Switzman et al. (42). Clearly, a single instance of heroin-induced suppression of saccharin intake will prove that heroin, like all other drugs of abuse tested, reduces intake of a saccharin CS following taste–drug pairings.

METHOD

Subjects

The subjects were 32 naive, male Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA) weighing between 275 and 300 g at the start of the experiment. All rats were individually housed in stainless steel cages in a colony room where temperature (21°C), humidity, and lighting (12L:12D cycle) were controlled automatically. All experimental manipulations began 2 h into the light phase of the cycle.

Apparatus

The experiment was conducted using inverted Nalgene-graduated cylinders with silicone stoppers and stainless steel spouts affixed to the front of each home cage with springs. Fluid intake was recorded to the nearest 0.5 ml.

Procedure

The protocol was approved by the Institutional Review Committee for the use of animal subjects, and is in compliance with the National Institutes of Health Guide for the Care and Use of laboratory Animals (Publication No. 85-23, revised 1985). The animals were given approximately 2 weeks to adapt to the colony room, and then were handled for 3 days. Access to water was then restricted to 5 min in the morning and 1 h in the afternoon to encourage drinking at the front of the home cage. Once intake stabilized (9 days), the subjects were divided into two groups. Half of the rats ($n = 16$) continued on the water-deprived condition described above, and were given free access to food. The other half of the animals ($n = 16$) were given free access to food and water. The water was always provided at the back of the home cage for these subjects. Morning (5 min) and afternoon (1 h) dH_2O intake continued to be recorded at the front of the home cage for 4 additional days for both the water-deprived and the water-replete subjects. The animals were then matched on the basis of mean 5 min dH_2O intake during the final 2 days of baseline, and were assigned to one of two US conditions: saline ($n = 8$/cell) or 8.0 mg/kg heroin ($n = 8$/cell). During testing, all animals were weighed and given 5-min access to a 0.15% saccharin solution. After a 5-min interstimulus interval they were injected intraperitoneally (IP) with either saline or heroin. One such CS–US pairing occurred every other day for a total of seven trials, followed by one CS-only test. Sodium saccharin was obtained from Sigma Chemical Co., St. Louis, MO, and was presented at room temperature. Heroin was provided by the National Institute on Drug Abuse, and was prepared immediately before testing.

RESULTS

Mean CS Intake

The data were analyzed using 2 × 2 × 8 repeated-measures analysis of variance (ANOVA) varying drug (saline or heroin), deprivation state (water-replete or water-deprived), and trials [1–8]. The results revealed a significant main effect of drug, $F(1, 28) = 48.63$, $p < 0.0001$, indicating that the rats injected with heroin consumed less saccharin than the saline injected controls overall (see Fig. 1).

The main effect of deprivation state was significant, $F(1, 28) = 33.45$, $p < 0.0001$. This finding showed that, as a group, the water-replete subjects consumed significantly less saccharin than the water-deprived subjects. The drug × trials interaction also was significant, $F(7, 196) = 20.51$, $p < 0.0001$. Post hoc Newman–Keuls tests revealed that, relative to the saline injected controls, heroin suppressed intake of the saccharin CS following a single CS–US pairing and intake remained suppressed throughout, ps < 0.05. Finally, the drug × deprivation state × trials interaction was not significant, $F < 1$, confirming that the 8-mg/kg dose of heroin suppressed intake of the saccharin CS, and that the magnitude of this effect did not differ significantly as a function of deprivation state.

Five-minute dH_2O Intake

A 2 × 8 ANOVA varying drug (saline or heroin) and day [1–8] was conducted on the 5-min dH_2O data for the water-deprived rats on the days between injections. Neither the main effect of drug, $F < 1$, nor day, $F < 1$, attained statistical significance. Thus, morning dH_2O intake was not significantly affected by the injection of heroin overall and the function for dH_2O intake was flat across days. The drug × day interaction, however, did approach statistical significance, $F(7, 98) = 2.09$, $p < 0.052$. This finding reflects a nonsignificant tendency for the heroin treated rats to consume less dH_2O than the saline treated controls across the mornings between injections (data not shown).

One-hour dH_2O Intake

A 2 × 15 ANOVA was performed on 1 h afternoon dH_2O intake for the water-deprived animals varying drug (saline or heroin) and days [1–15]. The results of the analysis revealed that, while the main effect of drug was not statistically significant, $F < 1$, there was a significant main effect of day, $F(14, 196) = 8.14$, $p < 0.0001$, and drug × day interaction, $F(14, 196) = 3.45$, $p < 0.0001$. Post hoc analysis of the drug × day

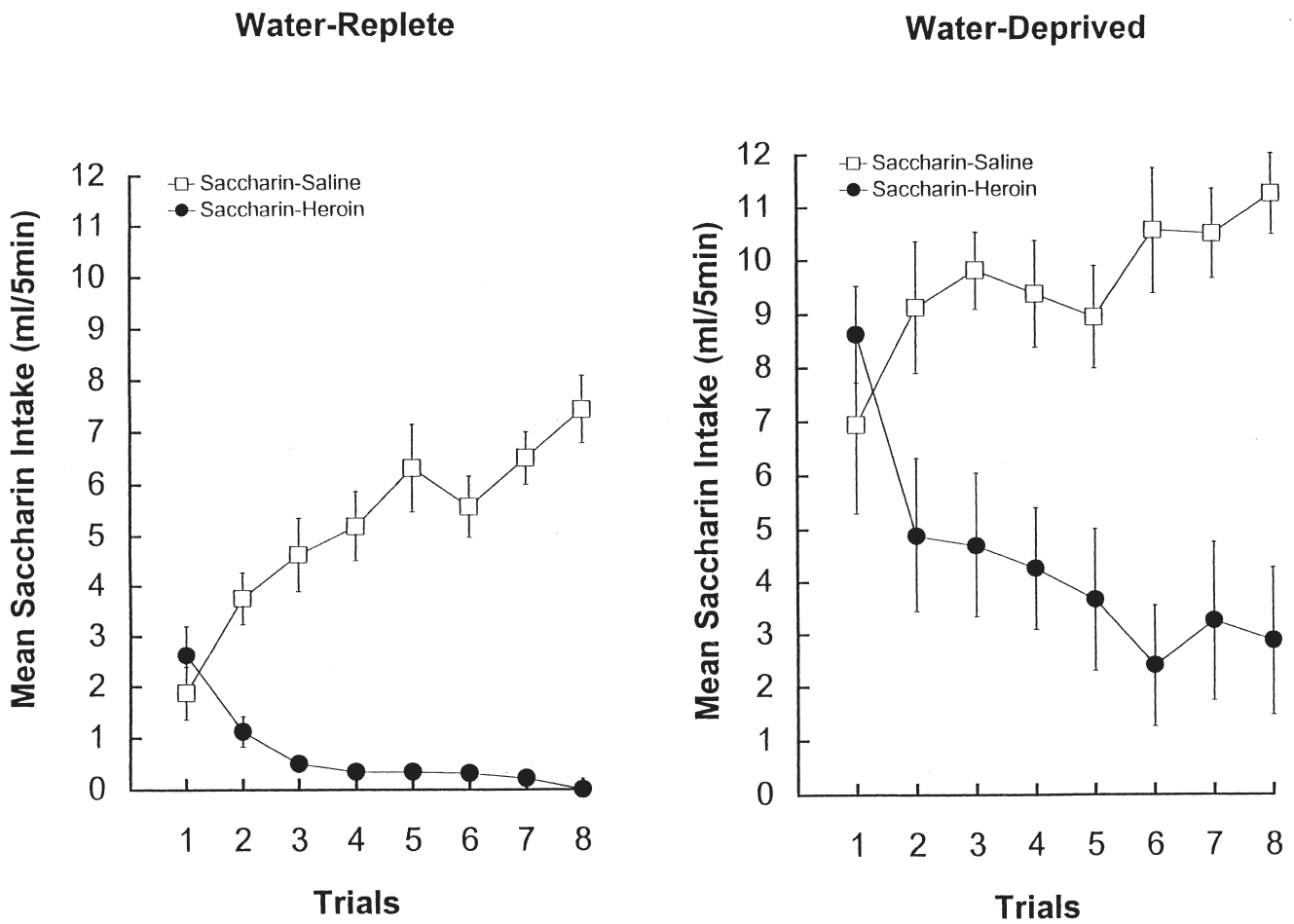

FIG. 1. Mean (±SEM) intake of 0.15% saccharin (ml/5 min) in water-replete (left) and water-deprived (right) rats following seven saccharin–saline or saccharin–heroin (8 mg/kg IP) pairings followed by one saccharin only test. Taste–drug pairings occurred at 48-h intervals.

interaction revealed a biphasic or "saw-toothed" pattern of intake for the heroin treated rats (see Fig. 2).

Specifically, the water-deprived heroin treated animals increased 1-h dH_2O consumption during the daily hydration periods on the day of each saccharin–heroin pairing (significant elevations occurred on days 5, 7, 9, and 13, $ps < 0.05$) and then subsequently decreased 1-h dH_2O on the days between injections (significant reductions in intake occurred on days 4, 6, 8, and 12, $ps < 0.05$). Similar increases in water intake have been obtained following saccharin–morphine pairings (23) and following the administration of morphine or heroin (29,30). Finally, rats in the saccharin–saline group did not change 1-h dH_2O intake over trials, and the intake of these subjects was neither significantly above nor below that of the heroin treated subjects, $ps > 0.05$.

Body Weight

Changes in body weight were analyzed using an ANOVA varying drug (saline or heroin), deprivation state (water-replete or water-deprived), and days [1–15]. The results of this analysis indicated that the main effects of drug, $F(1, 28) = 4.30$, $p < 0.05$, deprivation state, $F(1, 28) = 12.41$, $p < 0.002$, and days, $F(14, 392) = 45.14$, $p < 0.0001$, were significant (see Fig. 3).

Thus, rats injected with heroin weighed significantly less than rats injected with saline, water-deprived rats weighed significantly less than the water-replete rats, and all rats generally increased body weight over days. Further statistical analysis revealed a significant drug × day interaction, $F(14, 392) = 11.60$, $p < 0.0001$. Post hoc tests indicated that the heroin treated rats weighed less than the saline treated rats on days 3 and 5–15, overall, $ps < 0.05$. Finally, the drug × deprivation state × day interaction was not significant, $F < 1$, demonstrating that heroin reduced body weight gain relative to the saline-treated controls whether the animals were tested in a water-deprived or a water-replete state. A similar pattern has been obtained using the same procedures with morphine, but not with cocaine (45), suggesting that the reduction in body weight gain is related to repeated opiate treatment rather than to a simple reduction in CS intake.

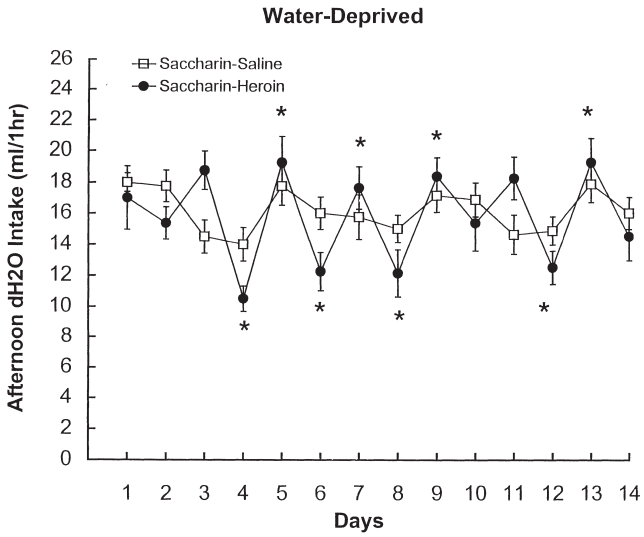

FIG. 2. Mean (±SEM) afternoon intake (ml/1 h) of distilled water (dH_2O) in water-deprived rats on the days of, and between, seven saccharin–saline or saccharin–heroin (8 mg/kg IP) pairings. Taste–drug pairings occurred on odd-numbered days, and asterisks indicate statistically significant changes in fluid consumption.

DISCUSSION

Contrary to the finding of Switzman et al. (42), an 8 mg/kg dose of heroin suppressed intake of the saccharin CS following a single taste–drug pairing in both the water-deprived and the water-replete rats. Indeed, the magnitude of the suppressive effect was comparable to, in fact slightly greater than, that found in water-deprived rats using the same testing conditions and a standard 10-mg/kg dose of cocaine or 15-mg/kg dose of morphine. Under these circumstances, intake of the saccharin CS was not reduced until the fourth and sixth CS–US pairing, respectively (20). Both drugs, however, can suppress intake following a single CS–US pairing when using higher doses (45). Thus, given the dose-dependent nature, one trial learning can no longer serve as a distinguishing feature for CTA learning. Together, these data confirm that heroin, like morphine, cocaine, amphetamine, alcohol, and nicotine, for example (5,6,8,19,28,40,44), also reduces intake of a saccharin CS following taste–drug pairings.

The discrepancy between the current report and that of Switzman et al. may be attributed to a number of procedural differences. For example, Switzman et al. used Wistar rats and we used Sprague–Dawley rats. Their heroin was dissolved in Ringer's solution and ours in saline. Their animals were given a 10-, rather than a 5-min access period to a 0.1% saccharin CS, and they used a 1-, rather than a 5-min interstimulus interval. Switzman et al. also used only a single CS–US pairing and a 5-day intertrial interval. Both of these latter manipulations are likely to have contributed to the absence of conditioned suppression following saccharin–heroin pairings. Of more relevance, however, may be the fact that Switzman et al. used a very rigorous water-deprivation regimen in which the animals were restricted to 20-min access to fluid a day. It appears that this regimen often is associated with greater CS intake, presumably because the rats have only one opportunity to hydrate each day, and a failure to do so on a given day can lead to 48-h fluid deprivation. Finally, while the procedures employed by Switzman et al. may not have been conducive to heroin-induced suppression of CS intake, it must be noted that they were sufficient to sustain a significant reduction in saccharin intake following pairings with either an 8- or a 12-mg/kg dose of morphine. These effects, however, were small suggesting that the testing conditions were adequate, but not optimal.

Although fluid deprivation has been found to reduce the expression of morphine- and cocaine-induced suppression of saccharin intake at lower doses (45), heroin-induced suppression of saccharin intake occurred following a single taste–drug pairing in both the water-deprived and the water-replete rats. The similar magnitude of effectiveness of heroin in the water-deprived and the water-replete condition likely reflects the use of what now appears to be a relatively potent dose of heroin. That is, while water deprivation reduces the suppressive effects of standard doses of cocaine and morphine, it cannot offset the suppressive effects of higher doses of these drugs (45). Finally, although the 8-mg/kg dose of heroin was clearly potent, it is noteworthy that heroin-induced suppression of saccharin intake was subject to individual differences (i.e., variability), and that these effects were only evident in the water-deprived animals. Individual differences of this na-

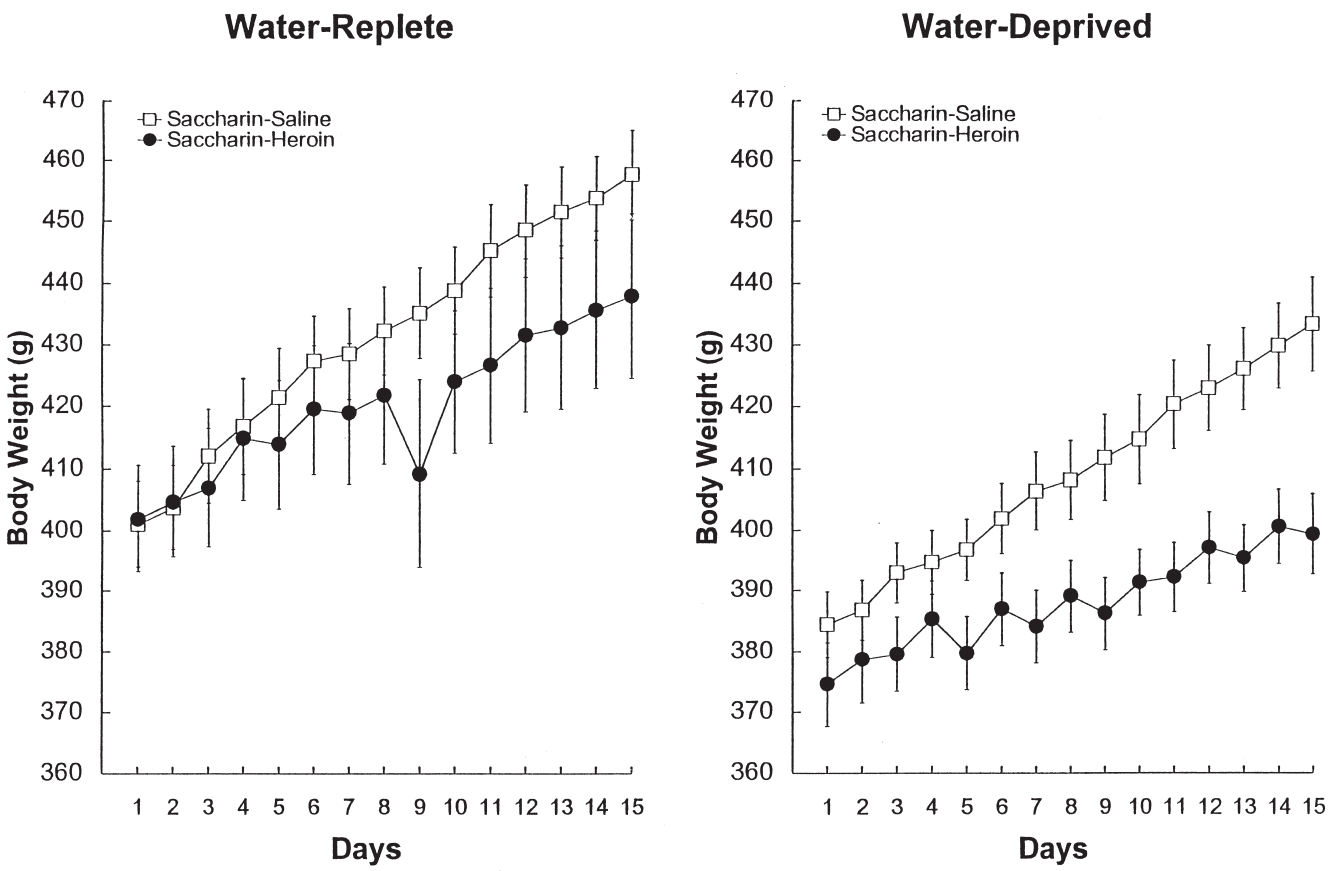

FIG. 3. Mean (±SEM) body weight (g) in water-replete (left) and water-deprived (right) rats throughout testing (days 1–15) for subjects in the saccharin–saline vs. the saccharin–heroin condition. Taste–drug pairings occurred on odd-numbered days.

ture have been reported previously in water-deprived rats when using other drugs of abuse (38,43). They have, however, never been investigated with heroin and never with rats maintained on food and water ad lib. Thus, the present account serves as the first indication that individual differences in the sensitivity to heroin (perhaps to the rewarding properties of heroin) can be exposed by investigating this phenomenon in water-deprived rats.

In sum, the results demonstrate that rats will reduce intake of a saccharin CS following pairings with all drugs of abuse tested (5,6,8,19,28,40,44). As stated, these suppressive effects have long been interpreted as CTAs and, as such, as evidence that drugs of abuse have both reinforcing and aversive properties [for a review, see (17,24)]. Although there is evidence that drugs of abuse have aversive properties (1,9), rats also will suppress intake of a saccharin CS when predicting the availability of a highly preferred sucrose solution (10,11) and the suppressive effects of drugs of abuse closely parallel those of a sucrose reward. As stated, the suppressive effects of sucrose, morphine, and cocaine, but to a lesser degree LiCl, are reduced or eliminated when using a caloric sucrose solution as the gustatory CS (12,16,23). The suppressive effects of cocaine and sucrose, but not LiCl, are greater in reward-preferring Lewis rats than in Fischer 344 rats [(15,21), but see (27)]. Finally, the suppressive effects of morphine and sucrose, but not those of LiCl, are eliminated by bilateral lesions of the gustatory thalamus (22,36). Thus, the evidence suggests that rats suppress intake of a saccharin cue following saccharin–morphine or saccharin–cocaine pairings because they are anticipating the availability of the preferred drug of abuse (20). The present data demonstrate that heroin is no exception.

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