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Pharmacology, Biochemistry and Behavior 69 (2001) 117–123

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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The suppressive effects of intraperitoneal cocaine are augmented when evaluated in nondeprived rats

Patricia Sue Grigson*, Kimbrin Cornelius, Daniel S. Wheeler

Department of Behavioral Science, Pennsylvania State College of Medicine, Hershey, PA 17033, USA

Received 15 September 2000; received in revised form 22 December 2000; accepted 22 January 2001

Abstract

Rats suppress intake of a saccharin conditioned stimulus (CS) when paired with all drugs of abuse tested including morphine, cocaine, heroin, amphetamine, and ethanol. Although most of these drugs suppress intake when administered via a range of routes, the efficacy of cocaine is an exception. Specifically, cocaine-induced suppression of saccharin intake is much greater when administered subcutaneously than when administered intraperitoneally. The subcutaneous route of administration of cocaine, however, is somewhat problematic because, unless diluted, can cause stark necrosis. The present study, then, reexamined the effectiveness of intraperitoneal cocaine using less restrictive deprivation regimens that are known to facilitate the expression of the phenomenon. The results showed that, while only a 10- and 20-mg/kg dose of cocaine suppressed intake of the saccharin CS when evaluated in moderately water-deprived rats, all doses tested (i.e., 5, 10, and 20 mg/kg) significantly reduced CS intake when saccharin–cocaine pairings were evaluated in rats maintained on food and water ad libitum. Taken together, these data show that rats will readily avoid intake of a saccharin cue when paired with the intraperitoneal administration of cocaine and that the magnitude of the effect is augmented when examined in a need-free state.

Keywords: Conditioned taste aversion; Cocaine; Deprivation state; Reward comparison; Intraperitoneal injection; Water-deprived; Free-feeding

1. Introduction

Intake of a saccharin conditioned stimulus (CS) is suppressed following pairing with a range of drugs of abuse including cocaine, morphine, alcohol, amphetamine, and heroin (Berger, 1972; Cappell et al., 1973; D'Mello et al., 1981; Ferrari et al., 1991; Goudie et al., 1978; Grigson, 1997; Grigson et al., 2000b; Le Magnen, 1969). Although the suppressive effects of these drugs have long been thought to reflect conditioned taste aversion (CTA) learning (Nachman et al., 1970), recent evidence suggests that intake of the saccharin CS may be suppressed by anticipation of the rewarding, rather than the aversive, properties of the drugs of abuse (Grigson, 1997, 2000). In accordance, rats also avoid intake of the same saccharin CS when it is paired with a highly rewarding sucrose solution (Flaherty and Checke, 1982; Flaherty and Grigson, 1988). Moreover, as with the suppressive effects of the drugs of abuse, the suppressive effects of a rewarding sucrose solution, but not LiCl, are greater in reward-preferring Lewis rats, are exaggerated by chronic treatment with morphine pellets, and are eliminated by bilateral lesions of the gustatory thalamus (Glowa et al., 1994; Grigson and Freet, 2000; Grigson et al., 2000a, in press; Kosten et al., 1994; Reilly and Pritchard, 1996; Scalera et al., 1997).

Although rats will avoid intake of a saccharin CS when paired with all of the drugs of abuse tested, the degree of suppression depends upon factors such as the nature of the gustatory CS (Bevins et al., 1996; Grigson, 1997), the dose of the drug (Farber et al., 1976; Parker, 1991), the route of administration (Ferrari et al., 1991), and the deprivation state of the animal (Bell et al., 1998; Grigson et al., 1999). Of these factors, the route of administration is one of the most critical parameters for cocaine-induced suppression of saccharin intake. That is, while cocaine readily suppresses intake of a saccharin CS when administered subcutaneously, it is far less effective when administered intraperitoneally. Ferrari et al. (1991) found that a 32- and a 50-mg/kg dose of cocaine exerted a greater suppressive effect when adminis-

* Corresponding author. Tel.: +1-717-531-5772; fax: +1-717-531-6916.

E-mail address: psg6@psu.edu (P.S. Grigson).

0091-3057/01/$ – see front matter
PII: S0091-3057(01)00501-9

tered subcutaneously than when administered intraperitoneally. An 18-mg/kg dose of cocaine was equally effective whether administered intraperitoneally or subcutaneously, but the suppressive effects were weak. Similarly, Foltin and Schuster (1982) reported that neither a 24- nor a 36-mg/kg dose of cocaine was very effective in suppressing intake of a saccharin CS when administered intraperitoneally, and Mayer and Parker (1993) found that a 20-mg/kg dose of cocaine failed to suppress intake of a gustatory CS when administered intraperitoneally rather than subcutaneously.

One study did find some effectiveness with cocaine when administered intraperitoneally (Goudie et al., 1978). In this case, female rats were allowed 30 min access to fluid daily. During testing they were given 30 min access to 0.1% saccharin and 10 min later, were injected intraperitoneally with saline or a 5-, 10-, 20-, or 36-mg/kg dose of cocaine. Two water days (30 min access/day) elapsed between each of four conditioning trials. The results showed that the 10-, 20-, and 36-mg/kg dose of cocaine exerted a significant suppression in saccharin intake relative to the saline-injected controls, with the 10-mg/kg dose being the least effective. Although the suppressive effects of the 10-mg/kg dose of cocaine were reportedly small in this paper, they appeared at least as large as those induced by the 18-mg/kg dose administered intraperitoneally by Ferrari et al. (1991). One of the few differences between the two experiments that may be of relevance is that the 10-mg/kg dose was evaluated using a 30-min access period, while the 18-mg/kg dose was tested using only a 20-min access period. Thus, greater fluid restriction (i.e., only 20 min access to fluid daily) may have offset the suppressive effects of the 18-mg/kg dose of cocaine, leading to a smaller reduction in CS intake. Of course, without knowing the between-trial fluid consumption across the two reports, we can only speculate about a role for fluid deprivation. Even so, it is interesting to note that a 20-mg/kg dose of cocaine also was fully ineffective in suppressing CS intake when administered intraperitoneally in the Mayer and Parker (1993) report, and in this case, the rats were restricted to only 15 min access to fluid daily.

Taken together, these findings suggest that the subcutaneous route of cocaine administration may be more effective than the intraperitoneal route and that water deprivation may contribute to a reduction in the magnitude of the suppressive effects of intraperitoneal cocaine. The subcutaneous route of cocaine administration, however, can lead to severe necrosis if the drug is not diluted (Durazzo et al., 1994). Consequently, the present set of studies was designed to reexamine the effectiveness of intraperitoneal cocaine when using a less restrictive water deprivation regimen that is known to support clear suppressive effects when a 10-mg/kg dose of cocaine is administered subcutaneously (Grigson, 1997). Moreover, because recent data in our laboratory have demonstrated that the suppressive effects drugs of abuse are robust when the animals are tested in the absence of need (i.e., when maintained on food and water ad libitum), the suppressive effects of intraperitoneal cocaine were also evaluated in rats maintained in a nondeprived state (Grigson et al., 2000b; Wheeler et al., 1999).

2. Experiment 1

There are two means by which to reduce or eliminate the disruptive effects of water deprivation on drug-induced suppression of CS intake. The first method involves the use of a two-bottle test that allows for the simultaneous availability of an alternate source of fluid (usually water). In keeping, both a LiCl-induced CTA (Grote and Brown, 1973) and the suppressive effects of subcutaneous cocaine (Van Haaren and Hughes, 1990) are reportedly greater when examined using a two-bottle, rather than a one-bottle, test. Relative to the two-bottle test, the disruptive effects of water deprivation can be fully prevented when using a second manipulation, i.e., free food and water. In support, evidence shows that the suppressive effects of intraperitoneal morphine, subcutaneous cocaine, and intraperitoneal heroin are greater when examined in rats that are maintained in a nondeprived state (Grigson et al., 2000b; Twining and Grigson, 1998; Wheeler et al., 1999). The present study, then, was designed to evaluate the effectiveness of a 10- and a 20-mg/kg dose of cocaine when administered intraperitoneally using one set of rats that were maintained on a less restrictive water deprivation regimen that allowed for a daily rehydration period and another set of rats that were maintained on food and water ad libitum.

2.1. Method

2.1.1. Subjects

The subjects were 48 naive male Sprague–Dawley rats (Charles River, Wilmington, MA) weighing between 254 and 344 g at the start of the experiment. They were housed individually in stainless steel cages in a colony room where temperature (21°C), humidity, and lighting (12:12 h light/dark cycle) were controlled automatically with lights on at 7:00 a.m. Except where noted otherwise, the rats received water and Purina rat chow (Ralston-Purina, St. Louis, MO) ad libitum.

2.1.2. Apparatus

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

2.1.3. Procedure

2.1.3.1. Water training. All rats were initially deprived of water and trained to drink distilled water (dH_2O) at the front of the cage for 5 min each morning (9:00 a.m.) and for 1 h each afternoon (3:00 p.m.). Once they were approaching the bottles and drinking (approximately 4 days), 24 of the

subjects (those in the nondeprived group) were returned to water ad libitum, matched on 5 min dH_2O intake on Days 3 and 4, and assigned to one of three drug conditions: saline ($n=8$); 10 mg/kg cocaine ($n=8$); or 20 mg/kg cocaine ($n=8$). Although water was freely available at the back of the cage for these nondeprived rats, dH_2O continued to be presented at the front of the cage during the morning and afternoon sessions for an additional 4 days of baseline. The rats in the water-deprived condition ($n=24$), on the other hand, continued to have restricted access to dH_2O (5 min a.m./1 h p.m.) for a total of 8 days of baseline. They were then matched on the basis of 5 min intake on the final 2 days of baseline and were assigned to one of three drug conditions: saline ($n=8$); 10 mg/kg cocaine ($n=8$); or 20 mg/kg cocaine ($n=8$).

2.1.3.2. Conditioning. During conditioning, all rats were given 5 min access to the CS, 0.15% saccharin. After a 5-min interval, they were injected intraperitoneally with the appropriate US (saline, 10-, or 20-mg/kg cocaine). The cocaine hydrochloride was injected as a 1.5-mg/ml stock solution adjusted for dose and body weight. All groups received seven such CS–US pairings followed by 1 test day during which the CS was presented without the US. One water day elapsed between each conditioning trial (i.e., 5 min supplemental access to dH_2O in the morning at the front of the cage for the nondeprived rats and 5 min access to dH_2O in the morning and 1 h in the afternoon at the front of the cage for the water-deprived rats). Sodium saccharin (Sigma, St. Louis, MO) was dissolved in dH_2O and presented at room temperature. Cocaine hydrochloride was provided by the National Institute on Drug Abuse and was dissolved in saline immediately before each experimental session.

2.2. Results and discussion

Two water-deprived rats died during the experiment, one from the saline group due to a bladder infection and one from the 10-mg/kg group due to a misplaced injection. The data from these subjects were omitted. The remaining data were analyzed using a $2 \times 3 \times 8$ mixed factorial analysis of variance (ANOVA) varying deprivation state (water-deprived or nondeprived), dose (saline, cocaine 10, or cocaine 20), and trials (1–8). When appropriate, post hoc tests were conducted using Newman–Keuls tests with α set at .05.

2.2.1. CS intake (ml/5 min)

The results showed that, although cocaine often is ineffective when administered intraperitoneally (Foltin and Schuster, 1982; Mayer and Parker, 1993), both doses used in this experiment significantly suppressed CS intake relative to the saline-injected controls following saccharin–cocaine pairings. Suppression occurred when using a water deprivation regimen that allowed for daily rehydration and, perhaps more importantly, when the animals were tested in a nondeprived state as well (see Fig. 1).

Support for this conclusion is provided by post hoc tests of a significant State × Dose × Trials interaction, $F(14,259)=4.50$, $P<.001$. The results showed that water-deprived rats (Fig. 1, left panel) treated intraperitoneally with the 10-mg/kg dose of cocaine consumed less of the saccharin CS on Trials 4–7 than did the saline-injected controls, P's $<.05$. This same dose, however, failed to significantly reduce saccharin intake on Trial 8 compared to the control subjects, $P>.05$. The 20-mg/kg dose of cocaine, on the other hand, significantly reduced CS intake on Trials 3–8 relative to the saline-injected controls, the rats treated with the 10-mg/kg dose of cocaine, and relative to their own Trial 1 intake, Ps $<.05$. This finding is consistent with that of Goudie et al. (1978) and demonstrates that even a 10-mg/kg dose of cocaine can be effective when administered intraperitoneally if the rats are maintained on a less restrictive water deprivation regimen.

Post hoc analyses of the data collected in the nondeprived rats (Fig. 1, right panel) revealed that saccharin intake was suppressed by both the 10- and the 20-mg/kg dose of cocaine on Trials 4–8 relative to intake by the saline-injected controls, $P<.05$. There were no significant differences between the two doses of the drug and intake of the saccharin CS was lower on Trials 5–8 than it was on Trial 1 for the drug-treated animals, but this effect attained statistical significance only when the data from the two doses were collapsed and analyzed separately in a 2×8 factorial ANOVA varying drug (saline vs. cocaine) and trials (1–8), $F(7,152)=16.7$, $P<.0001$. The failure to obtain a dose effect in the nondeprived subjects is likely due to a floor effect, given that both doses induced nearly complete

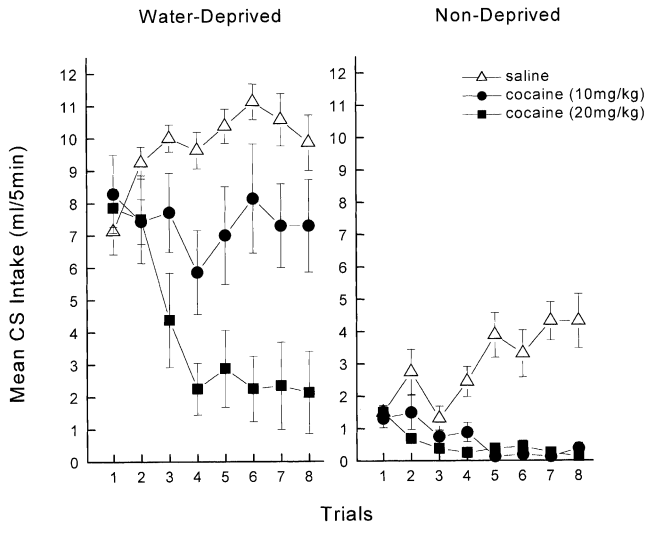

Fig. 1. Mean (±S.E.M.) intake (ml/5 min) of 0.15% saccharin in water-deprived (left panel) and nondeprived (right panel) rats following seven saccharin–saline or saccharin–cocaine (10 or 20 mg/kg) pairings, followed by one saccharin-only test. The cocaine hydrochloride was injected intraperitoneally and the taste–drug pairings occurred at 48-h intervals.

suppression of CS intake. Even so, the results clearly demonstrate that the intraperitoneal administration of either a 10- or a 20-mg/kg dose of cocaine can induce a robust, highly reliable suppression of CS intake, with little or no between-subject variability if the experimental subjects are maintained on food and water ad libitum.

2.2.2. Morning dH_2O intake (ml/5 min)

In this experiment, both the water-deprived and the nondeprived subjects were given 5 min access to dH_2O at the front of the cage on the days between injections. The results of a $2 \times 3 \times 8$ mixed factorial ANOVA varying deprivation state (water-deprived or nondeprived), dose (saline, cocaine 10 mg/kg, or cocaine 20 mg/kg), and days (1–8) showed that, while water-deprived rats consumed more morning water than nondeprived rats overall [state, $F(1,34) = 1020$, $P < .0001$], treatment with cocaine tended to reduce morning dH_2O intake for rats in both deprivation conditions. Thus, although neither the main effect of dose [$F(2,34) = 2.16$, $P = .13$], nor the State × Dose × Day interaction, $F < 1$, were significant, the Dose × Day interaction was statistically significant, $F(14,238) = 1.96$, $P < .02$. Post hoc tests of this interaction, however, showed that 5 min dH_2O intake was suppressed only on the morning after the seventh cocaine injection, Ps < .05. Finally, we should note that there was a nonsignificant tendency for this effect (i.e., reduced 5 min dH_2O intake between trials) to be greater in the nondeprived rats, possibly reflecting an aversion to other features of the conditioning procedure including, for example, spout or temporal cues.

2.2.3. Afternoon dH_2O intake (ml/h)

Afternoon dH_2O intake for the rats in the water-deprived condition was evaluated using a 3×15 ANOVA varying dose (saline, 10, or 20 mg/kg cocaine) and day (1–13). Post hoc tests of a significant main effect of day, $F(14,266) = 5.25$, $P < .0001$, showed that afternoon dH_2O intake was elevated on Injection Days 4, 6, and 8 and then reduced on the days following the fourth, sixth, and the seventh injection, Ps < .05 (data not shown). The Dose × Day interaction, however, was not significant, $F(28,266) = 1.0$, $P = .46$, confirming that the changes in afternoon dH_2O intake were related to the injection regimen itself (including CS access and/or the injection), rather than to the nature of the injected substance, per se. This finding differs from that obtained with morphine and heroin, where afternoon water intake clearly is elevated following the morning injection of either of these substances (Grigson et al., 1999, 2000b).

3. Experiment 2

The data from Experiment 1 show that the intraperitoneal administration of cocaine, even at a dose of 10 mg/kg, can exert clear and sustained suppressive effects. Significant dose effects were evident in the water-deprived subjects, with the 20-mg/kg dose of cocaine exerting a greater reduction in CS intake than the 10-mg/kg dose. As stated, the 10-mg/kg dose suppressed intake only across Trials 4–7 in the water-deprived rats relative to their saline-injected controls. This finding contrasts with that obtained in the nondeprived subjects. That is, when assessed in rats maintained on free food and water, orderly dose effects were not evident because both doses of cocaine induced complete suppression of CS intake when compared to the saline-treated controls. This finding is consistent with other reports showing that drug-induced suppression of CS intake is greatest when examined in nondeprived rats (Grigson et al., 2000b; Wheeler et al., 1999) and calls for an analysis of the suppressive effects of a lower dose of cocaine. As a consequence, the final experiment evaluated the suppressive effects of a 5-mg/kg dose of cocaine in a group of water-deprived or nondeprived rats. On the basis of the literature, this dose is not expected to be effective when administered intraperitoneally in the water-deprived subjects (Goudie et al., 1978). It may, however, prove effective when examined in nondeprived rats for whom the need for food and fluid will not offset the potential suppressive effects of the drug.

3.1. Method

3.1.1. Subjects

The subjects were 32 male Sprague–Dawley rats (Charles River, Wilmington, MA) weighing between 222 and 248 g at the start of the experiment. They were housed and maintained as described in Experiment 1.

3.1.2. Apparatus

All testing was conducted on the home cages as described above.

3.1.3. Procedure

3.1.3.1. Water training. All rats were initially trained to drink dH_2O at the front of the cage for 5 min each morning (8:00 a.m.) and for 1 h each afternoon (3:00 p.m.). Once all of the rats were approaching the bottles and drinking (after 5 days), 16 of the subjects (designated to the nondeprived group) were returned to water ad libitum, matched on 5 min dH_2O intake on Days 4 and 5, and assigned to either the saline group ($n = 8$) or the 5-mg/kg cocaine group ($n = 8$). Thereafter, water was continuously provided only at the back of the cage for the nondeprived subjects (i.e., no supplemental water was provided at the front of the cage between conditioning trials for these animals). This small procedural change was implemented to more closely associate the front of the cage with the delivery of the saccharin CS in an effort to increase baseline CS intake in the nondeprived subjects above that which was obtained in Experiment 1. The rats assigned to the water deprivation group, on the other hand, continued to have restricted access to dH_2O for a total of 7 days of baseline. They were then

matched on the basis of 5 min intake on Days 6 and 7, and assigned to either the saline group ($n=8$) or the 5-mg/kg cocaine group ($n=8$).

3.1.3.2. Conditioning. Conditioning was conducted as described in Experiment 1, except that the water-deprived and nondeprived subjects were injected intraperitoneally with either saline or a 5-mg/kg dose of cocaine and, as described above, only the water-deprived rats were given dH_2O (5 min a.m./1 h p.m.) at the front of the cage on the days between injections. Sodium saccharin and cocaine hydrochloride were obtained and prepared as described in Experiment 1.

3.2. Results and discussion

The data were analyzed using a mixed factorial $2 \times 2 \times 8$ ANOVA varying deprivation state (water-deprived or nondeprived), dose (saline or 5 mg/kg cocaine), and trials (1–8). When appropriate, post hoc tests were conducted using Newman–Keuls tests with α set at .05.

3.2.1. CS intake (ml/5 min)

The change in the regimen for the nondeprived animals (i.e., eliminating supplemental water access at the front of the cage between trials) did serve to increase CS intake at the front of the cage overall. Even with this increase in baseline responding, however, the results of the analysis verified that the intraperitoneal administration of the 5-mg/kg dose of cocaine still suppressed intake of the saccharin CS in the nondeprived rats relative to intake by the saline-treated controls. This same pattern was not evident for the water-deprived rats (see Fig. 2).

Support for this conclusion is provided by post hoc tests of a significant Dose × State × Trials interaction, $F(7,196)=3.13$, $P<.005$, which show that, while there was no significant difference in CS intake between the water-deprived rats injected with saline and those injected with the 5-mg/kg dose of cocaine (Fig. 2, left panel), the same dose of the drug significantly suppressed CS intake relative to the saline-injected controls in the nondeprived rats. Post hoc analysis indicated that these suppressive effects were statistically significant on Trials 7 and 8, P's $<.05$.

3.2.2. Morning dH_2O intake (ml/5 min)

The results of a 2×8 ANOVA varying Drug × Day showed that the injection regimen did not alter morning dH_2O intake in the water-deprived rats. In accordance, neither the main effect of drug, $F(1,14)=1.28$, $P>.05$, nor the Drug × Trials interaction, $F<1$, was significant.

3.2.3. Afternoon dH_2O intake (ml/h)

Likewise, the injection of the 5-mg/kg dose of cocaine also failed to alter afternoon dH_2O intake in the water-deprived subjects as evidenced by a nonsignificant main effect of drug and Drug × Day interaction, F's <1. As in the preceding experiment, however, the main effect of day was significant, $F(14,196)=2.21$, $P<.008$, and post hoc tests showed that afternoon dH_2O intake was significantly elevated, but only on the day of the sixth injection, $P<.05$.

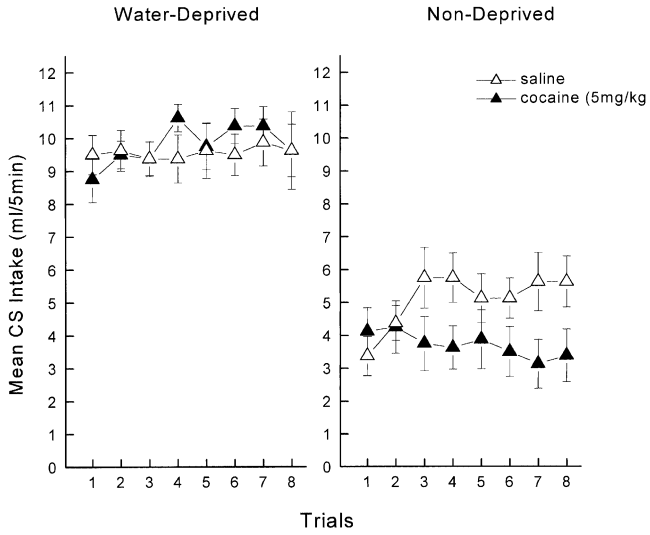

Fig. 2. Mean (±S.E.M.) intake (ml/5 min) of 0.15% saccharin in water-deprived (left panel) and nondeprived (right panel) rats following seven saccharin–saline or saccharin–cocaine (5 mg/kg) pairings, followed by one saccharin-only test. The cocaine hydrochloride was injected intraperitoneally and the taste–drug pairings occurred at 48-h intervals.

4. General discussion

Unlike other drugs of abuse, cocaine historically has been thought to be more effective in suppressing CS intake when administered subcutaneously than when administered intraperitoneally (Ferrari et al., 1991; Foltin and Schuster, 1982; Mayer and Parker, 1993). As discussed, however, the subcutaneous administration of cocaine can induce necrosis if not diluted and injected in a larger volume (Durazzo et al., 1994). This finding led us to reexamine the suppressive effects of intraperitoneal cocaine using deprivation conditions that are known to augment the magnitude of the effect with other drugs of abuse and with cocaine when administered subcutaneously (Grigson et al., 2000b; Wheeler et al., 1999). The results showed that the suppressive effects of intraperitoneal cocaine are dependent upon both the dose of the drug and the deprivation state of the animal. That is, when evaluated in water-deprived rats, intake of the saccharin CS was suppressed following pairings with a 10- and 20-, but not a 5-mg/kg dose of cocaine. Moreover, while the suppressive effects of the 10-mg/kg dose of cocaine were clear, they were smaller than those induced by the 20-mg/kg dose. These findings differed from those obtained when evaluated in the absence of need in Experiment 2. Rats maintained on free food and water significantly avoided the saccharin CS when paired with the 5-, 10-, or the 20-mg/kg dose of cocaine. In fact, both the 10- and the 20-mg/kg dose

induced complete and sustained suppression of CS intake following four saccharin–cocaine pairings. Thus, while it is likely that the subcutaneous administration of cocaine is more efficacious than the intraperitoneal route overall (Ferrari et al., 1991; Mayer and Parker, 1993), the data from the present report show that intraperitoneal cocaine can serve as an effective unconditioned stimulus in this paradigm, particularly if the rats are tested in an unrestricted state.

When taken with other reports, the data demonstrate that the suppressive effects induced by intraperitoneal heroin (Grigson et al., 2000b), intraperitoneal morphine, subcutaneous cocaine (Wheeler et al., 1999), and intraperitoneal cocaine (present report) are greater in magnitude, and often less variable, when evaluated in nondeprived rats. These facilitatory effects have gone largely unnoticed until now because water deprivation is standard practice for this type of testing and the rats usually are limited to no more than 30 min access to fluid a day, with no opportunity for daily rehydration (Cappell and Le Blanc, 1971; Cappell et al., 1973; Ferrari et al., 1991; Goudie et al., 1978; Nachman et al., 1970). Despite this general trend in research design, the suppressive effects of some drugs have been evaluated in rats maintained in a nondeprived state. In the first instance, Parker (1991, 1993, 1995) evaluated drug-induced suppression in nondeprived rats using Taste Reactivity measures (i.e., orofacial responses associated with ingestion and rejection of gustatory stimuli, Grill and Norgren, 1978) and using two-bottle intake tests. This design, however, did not call for a water-deprived group, and thereby did not provide an opportunity to gauge whether testing in the nondeprived state actually augmented the suppressive effects of the drugs. In the second instance, Bell et al. (1998) reported that the suppressive effects of a single dose of amphetamine and chlordiazepoxide were greater when evaluated in rats that were nondeprived than in those that were food-deprived. This finding is consistent with data collected in our laboratory showing that the suppressive effects of a range of doses of both morphine and cocaine also are larger in nondeprived than in food-deprived rats (Twining and Grigson, 1998; Wheeler et al., 1999). Thus, the data suggest that drug-induced suppression of CS intake can be attenuated not only by water deprivation, but by food deprivation as well.

So, why is drug-induced suppression of CS intake augmented when evaluated in a need-free state or, more to the point, why is it reduced when assessed in a food- or a water-deprived rat? The easy answer, and perhaps the correct one, is simply that the need for food or fluid overrides the suppressive effects of the drug. In support, it is known that water deprivation also facilitates extinction of the suppressive effects of drugs of abuse (Wellman and Boissard, 1981) and extinction of a CTA induced by the illness-inducing agent, LiCl, as well (Grote and Brown, 1973; Mikulka and Stephen, 1980). Relative to LiCl-induced CTAs, however, evidence suggests that the suppressive effects of drugs of abuse may be particularly sensitive to food and water deprivation. Specifically, while Bell et al. (1998) reported that the suppressive effects of amphetamine and chlordiazepoxide were reduced by the need for food, those induced by a standard dose of LiCl (0.15 M) were not. Similarly, although we found that the suppressive effects of a range of doses of intraperitoneal morphine and subcutaneous cocaine also were attenuated by food and water deprivation, the CTA was reduced only when evaluated using the lowest of seven doses of LiCl (i.e., 0.002 M) tested (Wheeler et al., 1999). Thus, it appears that the suppressive effects of drugs of abuse are highly sensitive to the need-state of the animal. Interestingly, this finding is consistent with that obtained when using a rewarding sucrose solution as the US (Flaherty et al., 1991; Twining and Grigson, 1998). As such, the data provide further support for the conclusion that the suppressive effects of drugs of abuse, whether administered intravenously, subcutaneously, or intraperitoneally, are mediated by the rewarding rather than the aversive properties of the drug (Grigson, 1997, 2000) and, moreover, that the suppressive effects are most robust when examined in the absence of the need for either food or water (Bell et al., 1998; Grigson et al., 1999; Wheeler et al., 1999).

Acknowledgments

This research was supported by the U.S. Public Health Service Grants DA 09815 and DA 12473. The authors would like to thank Robert Wheeler, Robert Twining, and Victor Sanchez for reading a draft of the manuscript and the National Institute on Drug Abuse for generously providing the cocaine hydrochloride.

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