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Time-dependent exacerbation of amphetamine-induced taste aversions following exposure to footshock

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Abstract Previous studies have shown that stressors attenuate LiCl-induced conditioned taste aversions (CTA) but not morphine-induced CTA. The current studies examined the effects of footshock on the acquisition and extinction of amphetamine-induced CTA. Experiment 1 demonstrated that exposure to 30 footshocks between saccharin consumption and amphetamine injections did not alter either the acquisition or the extinction of amphetamine-CTA. Experiment 2 demonstrated that exposure to the same shock parameters 2 and 4 days before saccharin-amphetamine pairing increased the magnitude of amphetamine-CTA after one saccharin-amphetamine pairing and delayed the recovery from the CTA. Experiment 2 also demonstrated that footshock increased the initial neophobic response to novel saccharin but did not alter subsequent saccharin consumption among saline-injected animals. These results indicate that stress-induced facilitation of amphetamine CTA are time-dependent and contrast with reports that stressors attenuate LiCl CTA. They also add support to the contention that CTAs induced by self-administered drugs like amphetamine are qualitatively different from CTAs induced by toxic substances like LiCL.

Key words Footshock · Stress · Conditioned taste aversion · Amphetamine · Saccharin

Introduction

A number of studies have evaluated the influence of exposure to stressors on the development and extinction of conditioned taste aversions (CTA) (Lasiter and Braun 1981; Dess et al. 1988; Holder et al. 1989; Revusky and Reilly 1989; Bourne et al. 1992). These studies have reported that exposure to stressors can decrease (Revusky and Reilly 1989; Bourne et al. 1992), increase (Lasiter and Braum 1981) or do not affect CTA (Holder et al. 1989). While there are few studies available, there are two potential explanations for these inconsistent results. First, these studies employed a variety of different stressors (e.g., swim, shock, heat, hypertonic saline) and the stressor parameters vary considerably between studies (e.g., repeated versus acute, two shocks versus 120 shocks). Despite these differences, LiCl-induced CTA is attenuated by both swim stress and footshock (Dess et al. 1988; Revusky and Reilly 1989; Bourne et al. 1992). Indeed, Revusky and Reilly (1989) have reported that swim and footshock produce indistinguishable attenuation of LiCl CTA. Moreover, stressor chronicity does not appear to be a critical factor as LiCl CTA is attenuated by both two and eight exposures to 5-min swim (Revusky and Reilly 1989; Bourne et al. 1992). Similarly, both a single session of 90 inescapable shocks and eight sessions of 120 inescapable shocks attenuate LiCl CTA (Dess et al. 1988; Revusky and Reilly 1989). In contrast to these results, however, two exposures to either hypertonic saline injections or two footshocks does not alter LiCl CTA (Holder et al. 1989). These results suggest that stressor parameters are, in fact, important in the attenuation of LiCl CTA.

A second possible explanation for the inconsistent effects of stressors on CTA is that stressors may differentially alter CTA depending on the specific conditioning agent employed. For instance, Revusky and Reilly (1989) reported that while both swim and footshock attenuate LiCl CTA, neither of these stressors alters morphine CTA. Similarly, Lasiter and Braum (1981) employed stressor parameters almost identical to those of Holder et al. (1992). While Lasiter and Braun (1981) found that shock facilitated both rotation- and apomorphine-induced CTA, Holder et al. (1992) found that shock did not affect LiCl CTA. These results leave open the possibility that the direction of the effect of stressors

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on CTA (i.e., attenuation versus facilitation) may be related to the specific treatment employed as the unconditioned stimulus (CS). This possibility is consistent with the suggestion that CTA produced by illness-inducing substances (e.g., LiCl) are qualitatively different from CTA induced by self-administered drugs (e.g., morphine, apomorphine, amphetamine) (see reviews in Goudie et al. 1982; Hunt and Amit 1986; Grant 1987).

If the effects of stressors on taste aversions are related to the nature of conditioning agent, then stressors should exert different effects on taste aversions induced by toxic substances (e.g., LiCl) and non-toxic substances (e.g., morphine or amphetamine). Amphetamine-induced taste aversion is an ideal choice to evaluate this. Amphetamine reliably produces a CTA after a single CS-UCS pairing. Amphetamine-induced taste aversions are disrupted by manipulations of dopaminergic activity unlike LiCL-induced taste aversions (Goudie et al. 1975; Roberts and Fibiger 1975; D'Mello et al. 1977; Grupp 1977; Sklar and Amit 1977). There is also considerable evidence showing that stressors enhance the behavioral responses to amphetamine (Herman et al. 1984; Robinson et al. 1985; Antelman 1988; Antelman et al. 1992). Lastly, amphetamine is known to alter brain dopaminergic activity (Kuczenski 1981) and prior exposure to stressors enhance the dopaminergic response to amphetamine (Antelman and Chiodo 1983; Robinson et al. 1985; Robinson and Becker 1986; Antelman 1988; Kalivas and Stewart 1991). Since stressors enhances the biochemical and behavioral response to amphetamine, we expected that, contrary to the results with LiCl, footshock would enhance the acquisition and delay the recovery of amphetamine-induced CTA.

Experiment 1

Experiment 1 was designed to evaluate the effects of exposure to footshock between saccharin consumption (CS) and amphetamine injections (UCS). Two taste aversion training trials were conducted to ensure that the amphetamine-CTA was large enough to detect any stressor-induced attenuation in CTA. This also ensures that animals are exposed to footshock on two occasions and permits comparison to Bourne et al. (1992) where they exposed rats to swim stress following CS exposure on two occasions. The shock parameters employed were selected because 30 min of intermittent footshock has been shown to increase dopaminergic activity (Herman et al. 1982; Abercrombie et al. 1989) and because amphetamine-induced CTA has been demonstrated with a 30-min CS-UCS interval (D'Mello et al. 1977). Thus, our shock procedure employed fewer shocks than used in studies reporting shock-induced attenuation of LiCl CTA (Dess et al. 1988; Revusky and Reilly 1989) but more shocks than studies reporting shock-induced facilitation of rotation- or apomorphine-induced CTA (Lasiter and Braun 1981).

Materials and methods

Subjects

Subjects were 40 male Long-Evans rats that were individually housed in standard hanging wire cages and acclimatized to the colony room for 7 days. Animals were maintained at 23°C on a 12-h on/12-h off light-dark cycle and permitted free access to food and water, except where specified. Subjects weighed between 260 and 390 g on day 1 of amphetamine injections. All consumption tests were conducted during the second quarter of the light cycle. Subjects were treated in accordance with the guidelines of the Canadian Council for Animal Care.

Apparatus

All fluid consumption tests were conducted in home cages by inserting 100 ml plastic centrifuge tubes with ball bearing spouts into the front wall of the cage. Unsignalled footshock was applied in a separate room in shock chambers measuring 31 cm by 20 cm by 19 cm with stainless steel sides, a grid floor constructed of stainless steel rods spaced 1.7 cm apart, and a translucent Plexiglas top. Shock treatment consisted of 30 min of footshock (30 shocks, 1.0 mA, 1.5 s duration, 60 s ITI) delivered through the floor rods connected to a shock generator (Grason-Stadler Model 700). No-shock treatment was administered by placing animals in identical chambers in a different room but shock was not applied. Drugs were injected IP and consisted of either 0.9% saline or 2.0 mg/kg *d*-amphetamine sulfate dissolved in 0.9% saline. Saccharin solutions were mixed daily in tap water in a concentration of 0.1%.

Procedures

Following acclimatization to the colony room, animals were placed on a restricted water schedule for 6 days with water available at the same time each day (± 30 min) for 20 min daily. Fluid consumption was measured to the nearest ml. Food was always available. Twenty-four hours after day 6 of restricted water access (i.e., pairing day 1: PD1), rats were matched on the basis of baseline water intake and assigned to one of two drug treatment groups (saline or amphetamine). Each drug treatment group was further subdivided such that half the animals in each drug group were assigned to the shock treatment group while the remaining animals were assigned to the no-shock control group. All animals were presented with saccharin for 20 min. Immediately thereafter, animals were transported to the appropriate shock treatment room and exposed to either 30 min of intermittent unsignalled footshock or no-shock treatment. Immediately following the shock treatment, animals were returned to the colony room, injected with either saline or amphetamine and returned to their home cages. On the next day (day 8), all animals were given 20-min access to water. On day 9 (PD2), the treatment given on PD1 was repeated. Water was again presented on day 10. Extinction trials began on day 11 (EXT1) and were repeated on alternate days (EXT2, EXT3, EXT4). Extinction testing consisted of a 20-min presentation of saccharin to all animals. Water was presented for 20 min on days between extinction trials. Thus water consumption and saccharin consumption tests were always conducted 24 h apart.

Data analysis

Only animals consuming at least 10 ml saccharin on the first exposure to saccharin were included in data analysis. This criterion eliminated three animals from the no shock group and four animals from the shock group. Baseline water intake values were computed by taking a weighted average of the last four water days prior to saccharin exposure. Baseline water intake was analyzed with a 2×2 ANOVA to ensure that treatment groups consumed comparable amounts of water prior to drug and shock treatments.

Saccharin consumption data were analyzed with a 2×2×5 mixed-factors repeated measures ANCOVA with Days as the repeated measures factor. The covariate used was the difference between baseline water intake and initial saccharin consumption. This covariate was selected to ensure that the effects of footshock on amphetamine-CTA took into account both baseline water consumption values as well as initial taste neophobia. Following the omnibus *F*-test, simple effects analysis was used to probe main effects and interactions.

Results

ANOVA revealed that there were no group differences in baseline water intake ($Fs<3.0$, $Ps>0.07$), although there was a trend for animals assigned to the footshock treatment to consume slightly more water ($F_{1,29}=3.325$, $P=0.079$). A separate ANOVA on saccharin consumption on PD1 revealed no group differences ($Fs<1.0$). A separate ANOVA on water intake on days between saccharin consumption tests indicated that neither shock nor amphetamine influenced water intake following CS-UCS pairings (see Table 1). Thus, water intake was comparable between treatment groups both prior to and following treatments.

Repeated measures ANCOVA on saccharin consumption from pairing day 2 (PD2) to extinction trial 4 (EXT4) revealed that saccharin-amphetamine pairing reduced saccharin consumption ($F_{1,28} = 45.03$, $P<0.001$). Inspection of Fig. 1 shows that the suppression in saccharin consumption induced by saccharin-amphetamine pairing varied over test days. This was confirmed by a significant Drug by Days interaction ($F_{4,116} = 5.67$, $P<0.001$).

Simple effects analysis of the Drug by Days interaction revealed that amphetamine-injected animals consumed significantly less saccharin than saline-injected animals from PD2 to EXT3 ($F_{1,28}s>5.0$, $Ps<0.03$) but recovered to saline control values on the last extinction trial (EXT4) ($F_{1,28}=1.69$, $P=0.204$). Footshock did not alter saccharin consumption nor did it interact significantly with any other factor ($Fs<2.0$, $Ps>0.20$).

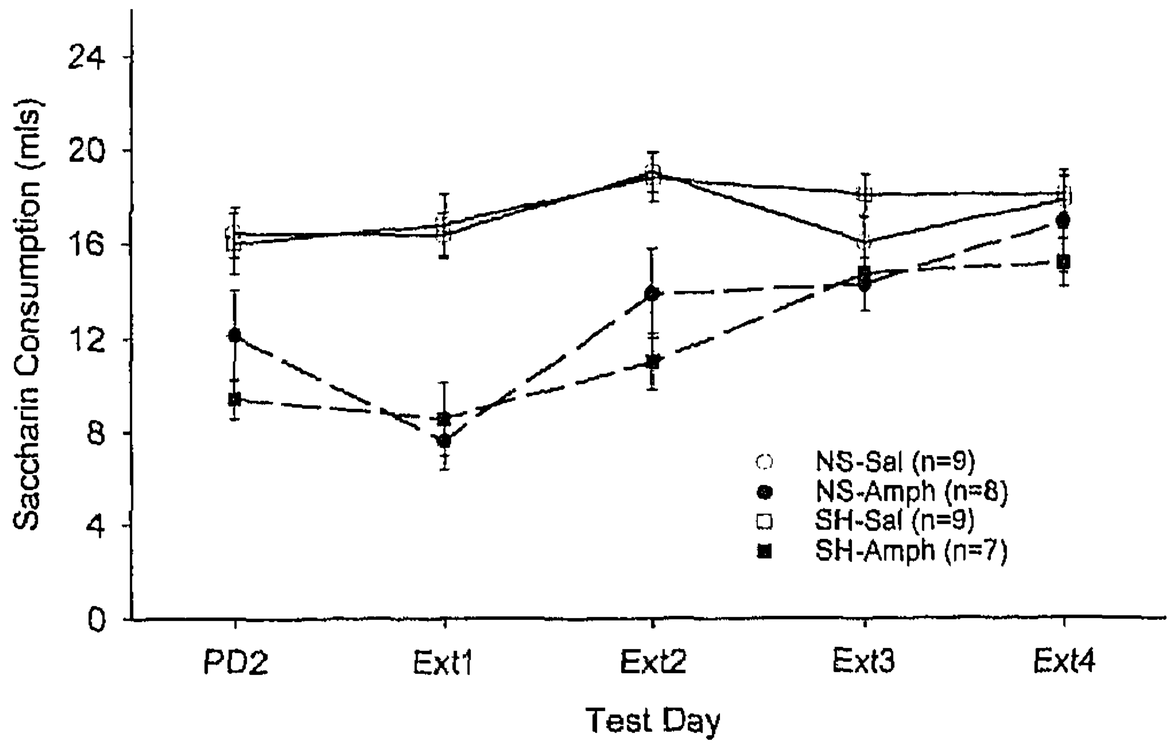

Fig. 1 Mean (±SEM) saccharin consumption in non-shocked (*NS*) and shocked (*SH*) rats following either saline (*Sal*) or amphetamine (*Amph*) injections. Data are shown for saccharin consumption for the second pairing day (*PD2*) and four extinction trials (*EXT1* to *EXT4*). Shocked animals were exposed to footshock between saccharin consumption and amphetamine injections

Discussion

One saccharin-amphetamine pairing is sufficient to induce an avoidance of saccharin. Following a second saccharin-amphetamine pairing, saccharin avoidance persists for three extinction trials. Exposure to footshock between saccharin consumption and amphetamine injections does not alter amphetamine CTA. Similarly, water intake on days between saccharin tests was unaffected. We had expected that footshock would exacerbate amphetamine-induced CTA. However, stressor-induced alterations in avoidance behavior are not always evident immediately following exposure to stressors. For example, inescapable footshock produces deficits in shuttle escape performance 24–72 h after exposure to shock but escape deficits are typically not evident immediately following shock (Anisman 1975; Glazer and Weiss 1976; Anisman et al. 1978; Prince and Anisman 1984). It is therefore possible that footshock can alter amphetamine-CTA but only when footshock precedes saccharin-amphetamine pairing by 24–72 h. Experiment 2 was conducted to evaluate the impact of exposure to footshock a number of days prior to saccharin-amphetamine pair-

Table 1 Mean (±SEM) water consumption values (ml) on days prior to (*Baseline*) and between saccharin consumption tests for the four treatment groups. Animals were exposed to shock treatment immediately following saccharin consumption on PD1 (day 7) and PD2 (day 9). Days 8–16 in the table indicate water consumption on days between saccharin tests. Coefficients for the weighted mean for Baseline water consumption were 0.1, 0.2, 0.3, and 0.4 for days 3, 4, 5, and 6, respectively

Day	No shock		Shock	
	Saline	Amphetamine	Saline	Amphetamine
Baseline	14.08 (±0.712)	14.12 (±0.508)	15.98 (±0.535)	14.13 (±0.434)
Day 8	15.67 (±0.872)	14.57 (±0.685)	15.33 (±0.782)	13.43 (±0.751)
Day 10	12.78 (±1.41)	11.88 (±1.50)	13.56 (±1.09)	14.57 (±3.89)
Day 12	18.11 (±0.889)	15.88 (±0.854)	16.89 (±0.539)	14.71 (±1.29)
Day 14	18.22 (±0.683)	16.00 (±0.779)	17.00 (±1.04)	16.29 (±0.644)
Day 16	16.11 (±1.11)	18.63 (±0.885)	17.00 (±0.601)	17.43 (±1.31)

ing on the acquisition and extinction of amphetamine CTA.

Experiment 2

Materials and methods

Subjects

Subjects were 34 male Long Evans rats, weighing between 280 and 390 g on day 1 of amphetamine injections. All rats were individually housed and acclimatized to the colony room for 7 days before imposing the restricted water schedule for 6 days.

Procedures

Procedures were identical to experiment 1 with the following exceptions. Following 6 days of restricted water access, animals were matched on the basis of baseline water intake and assigned to shock treatment or no-shock treatment. Although water was provided for 20 min on days 7–10, animals were exposed to the assigned shock treatment immediately after the 20-min water presentation on days 7 and 9. Saccharin-amphetamine pairing was conducted on days 11 and 13 (PD1 and PD2). On pairing days saline or amphetamine was injected 30 min after saccharin consumption to ensure comparability of the CS-UCS delay between experiments 1 and 2. Drug doses, saccharin concentration, and shock parameters were identical to experiment 1.

Data analysis

As in experiment 1, only animals consuming at least 10 ml saccharin on the first pairing day were included in the data analysis. This eliminated four animals from the no-shock group and three animals from the shock group. Baseline water intake values were computed by taking a weighted average of the last 6 water days prior to saccharin exposure. A separate repeated measures ANOVA was conducted on baseline water intake and water intake on the 2 shock days. Saccharin consumption data were analyzed as in experiment 1. The influence of prior footshock on saccharin neophobia was assessed with a between-groups ANOVA on saccharin intake on PD1.

Results

Repeated measure ANOVA on baseline water intake and water intake on shock days indicated that there were no group differences in water intake (Fs<1.1, Ps>0.36) prior to CS-UCS pairing (see Table 2). A separate ANOVA on water intake on days between saccharin consumption tests (days 10, 12, 14, 16 and 18) also indicated that neither shock nor amphetamine influenced water intake (Fs<2.0, Ps>0.15). Thus water intake was comparable between treatment groups both prior to and after exposure to shock. A separate ANOVA on saccharin consumption on the first saccharin-amphetamine pairing day (PD1) revealed that shocked animals consumed significantly less saccharin than non-shocked animals ($F_{1,23}$=4.63, P=0.042) (see Table 2).

Repeated measures ANCOVA on saccharin consumption from pairing day 2 (PD2) to extinction trial 4 (EXT4) revealed that saccharin-amphetamine pairing reduced saccharin consumption ($F_{1,22}$=35.35, P<0.001). Figure 2 shows that the reduction in saccharin intake induced by saccharin-amphetamine pairing varied over test days. This was confirmed by a significant Drug by Days interaction ($F_{4,92}$=3.37, P=0.013). Simple effects analysis of the Drug by Days interaction revealed that amphetamine-injected animals consumed significantly less saccharin than saline-injected animals for all tests (Fs$_{1,22}$>4.00, Ps≤0.050). Thus saccharin consumption is suppressed following one saccharin-amphetamine pairing, and is reduced for at least four extinction trials following a second saccharin-amphetamine pairing. The amphetamine-induced suppression in saccharin intake, however, was modified by footshock as indicated by a significant Shock by Drug by Days interaction ($F_{4,92}$=3.00, P=0.023). As shown in Fig. 2, shocked animals exhibited a larger suppression of saccharin consumption following one saccharin-amphetamine pairing (i.e., PD2). Simple-simple effects analysis of the Shock by Drug by Days interaction revealed that shocked ani-

Table 2 Mean (±SEM) water consumption (ml) prior to (*Baseline*) exposure to shock, on shock days (*Shock 1* and *Shock 2*) and after exposure to shock. Animals were exposed to shock treatment on days 7 and 9. Saccharin-amphetamine pairing was conducted on days 11 and 13. Days 14–20 in the table indicate water consumption on days between extinction tests. Note that the value for PD1 refers to saccharin consumption on the first exposure to saccharin. Coefficients for the weighted mean for Baseline water consumption were 0.1, 0.1, 0.1, 0.2, 0.25, and 0.25 for days 5, 6, Shock 1, 8, Shock 2 and 10, respectively

Day	No shock		Shock	
	Saline	Amphetamine	Saline	Amphetamine
Baseline	17.54 (±1.28)	17.14 (±0.551)	17.71 (±0.316)	16.64 (±0.518)
PD1[a]	16.92 (±0.848)		14.60 (±0.653)	
Shock 1	16.03 (±0.876)	16.50 (±1.61)	15.52 (±0.857)	15.38 (±0.653)
Day 8	18.00 (±1.97)	16.83 (±1.95)	18.86 (±1.03)	17.13 (±1.27)
Shock 2	19.17 (±1.83)	18.00 (±1.53)	20.14 (±0.884)	18.63 (±0.981)
Day 10	17.33 (±1.58)	17.83 (±1.95)	16.43 (±1.20)	15.50 (±0.732)
Day 12	18.00 (±1.21)	14.67 (±1.02)	17.86 (±0.800)	15.13 (±0.833)
Day 14	17.33 (±0.882)	17.17 (±1.95)	16.71 (±1.15)	15.38 (±0.778)
Day 16	20.67 (±1.11)	19.17 (±0.833)	17.29 (±1.04)	18.75 (±0.559)
Day 18	18.50 (±0.806)	16.50 (±0.992)	18.43 (±0.869)	18.13 (±0.854)
Day 20	17.83 (±0.749)	18.33 (±1.61)	18.14 (±1.60)	17.00 (±0.535)

[a] Refers to saccharin consumption (ml)

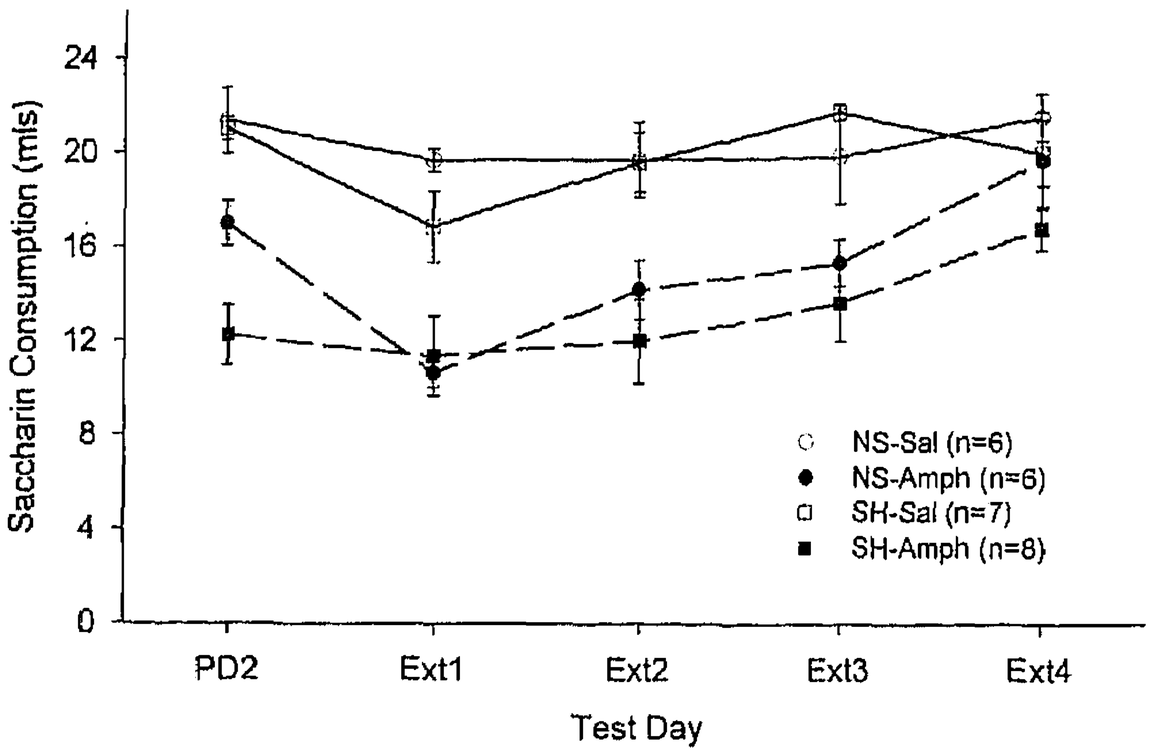

Fig. 2 Mean (±SEM) saccharin consumption in non-shocked (*NS*) and shocked (*SH*) rats following either saline (*Sal*) or amphetamine (*Amph*) injections. Data are shown for saccharin consumption for the second pairing day (*PD2*) and four extinction trials (*EXT1* to *EXT4*). Shocked animals were exposed to footshock 2 and 4 days prior to the first saccharin-amphetamine pairing

mals exhibited a significantly larger reduction in saccharin intake than non-shocked animals after one CS-UCS conditioning trial (i.e., PD2) ($F_{1,22} = 9.34$, P=0.006).

It also seems that the amphetamine-CTA is more resistant to extinction among shocked animals. Simple-simple effects analysis of drug effects for both non-shocked and shocked animals revealed that saccharin consumption was reduced in both non-shocked and shocked animals on PD2, EXT1 and EXT2 (Fs>5.0, Ps<0.025). However, on EXT3 non-shocked animals showed a tendency to suppress saccharin consumption ($F_{1,22}$=4.19, P=0.053) while shocked animals continued to suppress saccharin consumption ($F_{1,22}$=15.98, P<0.001). Non-shocked animals recovered from the amphetamine-CTA by EXT4 ($F_{1,22}$=0.96, P=0.339) while shocked animals showed a trend to continue to suppress saccharin consumption ($F_{1,22}$=3.72, P=0.067).

Discussion

As in experiment 1, one saccharin-amphetamine pairing produced a significant conditioned avoidance of saccharin. Exposure to footshock a number of days prior to drug injections reduces consumption of novel saccharin. Since footshock did not influence saccharin consumption on the second exposure to saccharin in saline-injected animals, it is unlikely that the effect of footshock on initial saccharin consumption is due to an alteration in the palatability of saccharin. Moreover, because water intake was not affected by footshock, the shock-induced reduction in consumption of novel saccharin is not due to a general suppression in fluid consumption. It is more likely that footshock enhances the neophobic response to novel saccharin and the shock effect dissipates by the second saccharin test simply because the saccharin is no longer novel.

In addition, prior exposure to footshock enhances the conditioned taste aversion after one CS-UCS pairing. While one saccharin-amphetamine pairing significantly reduces saccharin consumption in both non-shocked and shocked animals, the reduction was significantly greater in shocked animals. Moreover, the reduction in saccharin consumption in amphetamine injected animals on extinction trial 3 (EXT3) can be attributed to a significant CTA only among shocked animals. Additionally, on extinction trial 4 there was no indication of a CTA among non-shocked animals, while there was a trend for shocked animals to continue to avoid saccharin. Thus, it appears that exposure to footshock prior to CS-UCS pairing facilitates the acquisition of amphetamine-CTA and retards the extinction of amphetamine-CTA.

General discussion

Exposure to footshock can enhance the acquisition and delay the extinction of amphetamine-induced CTA but it appears that the timing of stressor exposure is a critical factor. When animals are exposed to shock immediately before amphetamine injections, footshock exerts little impact on amphetamine-CTA. In contrast, when animals are exposed to footshock a number of days prior to saccharin-amphetamine pairing, shock enhances the acquisition and increases the resistance to extinction of the amphetamine-CTA. Moreover, prior exposure to shock enhances the neophobic response to novel saccharin.

We had hypothesized that the effects of stressors on taste aversions would vary with the specific conditioning agent and that stressors would influence amphetamine-CTA in a manner similar to morphine-induced CTA. This appears to be the case. Revusky and Reilly (1989) reported that LiCL-induced CTA is attenuated by both footshock and swim but morphine-induced CTA is not affected by either of these stressors. Moreover, Revusky and Reilly (1989) found that both 5-min swim and footshock produced indistinguishable attenuation of LiCl CTA. Bourne et al. (1992) also reported that exposure to 5-min swim between each of two saccharin-LiCl conditioning trials attenuated LiCl-induced CTA. It appears that shock and swim produce comparable attenuation of LiCl-induced CTA and that the number of stressor exposures is not a critical factor. Similar to Revusky and Reilly's (1989) finding with morphine-induced CTA, we found that footshock exerts no impact on amphetamine-induced CTA when shock is imposed between saccharin and amphetamine. Given the comparability between swim and shock and that we used two exposures to footshock similar to the procedures used by Bourne et al. (1992), it appears that exposure to stressors on CS-UCS conditioning days attenuates LiCl CTA but neither morphine nor amphetamine CTA.

It should be noted that Revusky and Reilly (1989) also reported that the toxic substance cisplatin was unaffected by stressors. They also found that dexamethasone injections attenuated both morphine and cisplatin CTA but not LiCl CTA. This contrasts with earlier reports that dexamethasone attenuates both LiCl- and radiation-in-

duced CTA (Cairnie and Leach 1982; Smotherman 1986). More importantly, their animals were maintained on a constant light cycle, a treatment employed as a stressors itself (Larsen et al. 1994). Constant light has also been shown to decrease saccharin intake and saccharin preference (Rusak and Zucker 1974). In addition, constant light blocks the development of LiCl-induced CTA (Rusak and Zucker 1974), an effect possibly mediated by alterations in intestinal acid secretion among animals housed under constant light (Larsen et al. 1994). Because dexamethasone injections can alter the corticosterone response to stressors depending upon the time in the light/dark cycle (Dunn and Carrillo 1978), it is difficult to interpret the meaning of Revusky and Reilly's (1989) data indicating that dexamethasone attenuated both morphine and cisplatin CTA. Given that constant light alters the effect of dexamethasone as well as LiCl-CTA, Revusky and Reilly's (1989) dexamethasone data cannot be attributed to a dexamethasone-simulated stressor effect.

Few studies have examined the importance of the timing of stressor exposure on CTA. Bourne et al. (1992) have reported that swim stress attenuated LiCl CTA when the stressor is applied 30 min before saccharin consumption, between saccharin consumption and LiCl injections as well as 15 min (but not 90 min) after LiCl injections. Using a much longer delay between stressor exposure and CS-UCS pairing, we found facilitation of amphetamine CTA. It is not clear why the facilitation of amphetamine-CTA is not evident when shock is applied between saccharin consumption and amphetamine injections but there are other examples of the delayed effects of stressors on avoidance responses. For example, stress-induced deficits in shuttle escape responding are typically not evident immediately following stressor exposure but are evident 24 or 48 h later (Anisman 1975; Glazer and Weiss 1976; Anisman et al. 1978; Prince and Anisman 1984; Anisman and Zacharko 1988). Studies examining cross-sensitization between stressors and stimulants like amphetamine have also shown that cross-sensitization usually requires a delay between stressor exposure and stimulant exposure (Antelman et al. 1983; Robinson and Becker 1986). It remains to be determined whether such a delay between stressor exposure and CS-UCS pairing also influences LiCl-induced CTA.

Our finding that footshock does not influence amphetamine-induced CTA when shock is administered at intervals that attenuate LiCl-induced CTA provides further support for the suggestion that taste aversions induced by illness-inducing drugs (e.g., LiCl) are mediated by biological mechanisms different from those subserving taste aversions induced by self-administered drugs like morphine or amphetamine. That prior footshock exacerbates rather than attenuates amphetamine-CTA also illustrates that stressors influence LiCl-induced CTA and amphetamine-CTA differently. Finally, these results underscore the importance of assessing the temporal relationship between stressor exposure and behavioral testing.

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