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Attenuation of Conditioned Taste Aversions by External Stressors

SAM REVUSKY AND STEVE REILLY

Department of Psychology, Memorial University of Newfoundland
St. John's, Newfoundland A1B 3X9, Canada

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REVUSKY, S. AND S. REILLY. *Attenuation of conditioned taste aversions by external stressors.* PHARMACOL BIOCHEM BEHAV **33**(1) 219–226, 1989.—Conditioned taste aversions (CTAs) were produced by low doses of toxins injected 30 or 60 min after rats finished drinking saccharin solution. Attempts were made to attenuate these CTAs by subjecting the rats to stress or to injections of glucocorticoids (primarily dexamethasone) during the interval between saccharin consumption and injection of the toxin. The stressors used were statistically indistinguishable in their effects: swimming, constant footshock (for 2 min), or intermittent footshock (for 10 min). The extent to which different agents attenuated CTAs depended on which toxin was used to produce the CTA as follows. The stressors produced marked CTA attenuation when lithium was the toxin, but none when cisplatin was the toxin. The glucocorticoids exhibited an opposite pattern of marginal CTA attenuation with lithium and marked CTA attenuation with cisplatin. CTAs produced by morphine were more like those produced by cisplatin than like those produced by lithium. Our belief that the CTA attenuation demonstrated here indicates alleviation of the distress produced by the toxin was supported by the results of the final two experiments as follows: 1) The stress does not raise saccharin preference independently of interference with the aversiveness of the toxin since, in similar experiments in which toxins were not administered, footshock administered in conjunction with exposure to saccharin solution reduced later saccharin preference. 2) Probably CTA attenuation does not occur because stress interferes with the taste-toxin association since footshock administered before the saccharin drinking session (instead of after it) also produced CTA attenuation.

Conditioned taste aversion Stress Glucocorticoids Cisplatin Lithium chloride Morphine

CAIRNIE and Leach (4) and Revusky and Martin (20) have shown that glucocorticoids (Glucs), when injected into rats following consumption of saccharin solution and before exposure to a toxin, attenuate the conditioned taste aversion (CTA) normally produced by the toxin. Following Garcia *et al.* (8) and Munck *et al.* (14), Revusky and Martin interpreted this result as evidence that Glucs attenuate the normal defensive reaction against toxins and, because they do so, reduce the aversive effects of the toxin. They suggested that if this palliative theory (as they called it) correctly explains instances of CTA attenuation in animals, it is likely that techniques that attenuate CTAs in rats would reduce the distress of human patients forced to endure toxic levels of drugs or radiation in, for instance, cancer therapy. Their detailed exposition (20) justifies 1) reference to the agents used to induce CTAs as toxins because of their role in the CTA paradigm although the doses employed are usually below a toxic level; and 2) the expectation that if a drug or stressor weakens CTAs, it does so by reducing the distress produced by the toxin (provided certain potential artifacts are excluded).

The present research was designed to determine if stress, which causes endogenous release of Glucs, also attenuates CTA. We used three types of stressors: 1) constant footshock (CFS), similar to that found to produce analgesia by nonopioid mechanisms (21); 2) intermittent footshock (IFS), similar to that found to produce analgesia by elicitation of endogenous opiates (21); 3) swimming for 5 min in water at room temperature.

In Experiments 1 and 2 of this series, we found that these stressors attenuate CTAs produced by lithium at least as effectively as Glucs (dexamethasone or methylprednisolone); there was no difference among stressors or between the two Glucs. However, when we tried to demonstrate the generality of this effect by substituting cisplatin (Experiment 3) or morphine (Experiment 6) for lithium as the toxin, the Gluc (dexamethasone) produced very marked CTA attenuation and the stressors seemed to produce no CTA attenuation whatsoever. Most of the remaining experiments reported here followed up this difference.

EXPERIMENTS 1–7

METHOD

Subjects

The naive male Sprague-Dawley rats weighed 170–215 grams just prior to each experiment and were maintained in individual stainless steel home cages, where all eating and drinking, including that involved in testing, occurred. Artificial light was present for 24 hours per day.

Injections

Cisplatin (CIS) was dissolved in isotonic saline at 0.05 mg/ml and injected IP. Lithium chloride (LiCl) was dissolved in distilled

water at 6.36 mg/ml and injected IP. Morphine sulfate was dissolved in isotonic saline at 4 mg/ml and injected IP. Glucs were injected IM. If the Gluc dose is indicated per rat, the drug was diluted in normal saline to form an injection of 0.2 ml; if the dose is in mg/kg, it was diluted in saline for injection at 1.0 ml/kg.

Stressors

An E1064 Grason-Stadler shock source was used to produce either IFS (defined as 2.0 mA in a cycle of 1.0 sec on and 4.0 sec off for 10 min), or CFS (defined as 2.0 mA continuously present for 2 min). These shocks were administered after the rat was placed in an operant chamber, 23.4 × 20.3 × 19.2 cm with 0.4 cm steel grids placed 1.0 cm apart. The swim (SWIM) stressor was 5 min in a plastic garbage container (49.5 cm dia. and 53.3 cm h) three-quarters full with room temperature water. It usually required 3 to 10 sec to transport a rat from its home cage to the nearby stress apparatus.

Experiment 1 will be described in more detail than the other experiments. When describing each of the later experiments, the procedures will be the same as for the immediately preceding experiment in unspecified respects.

Experiment 1

The rats had unrestricted access to dry chow and 30 min of tap water per day. After drinking stabilized, 0.4% (by weight) sodium saccharin solution was substituted for the water on every second day and LiCl (15.9 mg/kg) was injected 60 min after the saccharin solution was removed. Groups of these rats differed with regard to the putative CTA attenuation agent. Group Only-Li (n = 12) was not subjected to any treatment during the interval between saccharin removal and the LiCl. The other groups (n = 8 per group) were subjected to the indicated treatment beginning 30 min after removal of the saccharin: CFS-Li, IFS-Li, SWIM-Li, DEX-Li, and MPRED-Li. DEX refers to 0.1 mg per rat of dexamethasone sodium phosphate (Decadron) and MPRED to 0.4 mg per rat of methylprednisolone. Finally, the rats in Group No-Tox (n = 8) were not injected with LiCl after drinking saccharin; 30 min after the saccharin bottle was removed, 2 rats in this group were subjected to CFS, 2 were subjected to IFS, and 4 were subjected to SWIM. Because the CTAs produced were weak, on Trial 7, the LiCl dose was increased from 15.9 mg/ml to 31.8 mg/kg and on Trial 8 to 63.6 mg/kg at the same 6.36 mg/ml concentration. The experiment ended with Trial 9.

Experiment 2

Except for the lack of a SWIM-Li group, the groups had the same names as in Experiment 1 with 10 rats in Groups CFS-Li, IFS-Li, DEX-Li, and MPRED-Li, 16 rats in Group Only-Li, and 4 rats in Group No-Tox. The rats in the last group received no treatments at all after their saccharin drinking sessions. There were 8 saccharin trials. The LiCl dose was 31.8 mg/kg during Trials 1–6 and 63.6 mg/kg thereafter.

Experiment 3

Instead of LiCl, the toxin was CIS (0.5 mg/kg) administered in saline IP at 0.05 mg/ml. Groups CFS-CIS, IFS-CIS, SWIM-CIS, and Gluc-CIS had 5 rats each, Group Only-CIS had 6 rats and Group No-Tox had 4 rats. MPRED was not used after Experiment 2. The rats were maintained on 15 min per day of water, which was flavored with saccharin on every third day for 7 trials. The CIS was injected 30 min after the saccharin solution was removed and the stressors or the DEX were administered 15 min prior to the CIS. The rats in Group Only-CIS and No-Tox were given control injections IP of 1.0 ml/kg normal saline 15 min after the saccharin bottle was removed.

Experiment 4

Both CIS (0.5 mg/kg) and LiCl (31.8 mg/kg) were used as toxins. There were two groups designated Only-Tox depending on whether CIS (n = 10) or LiCl (n = 12) was the toxin and one Gluc-Tox group for each toxin (ns = 8). The various stress groups, CFS-CIS, IFS-CIS, SWIM-CIS, CFS-Li, IFS-Li, and SWIM-Li, also had 8 rats each. Group No-Tox, with 4 rats, was subjected to no treatment whatsoever after drinking saccharin solution. One rat died in Group SWIM-CIS and one rat died in Group Gluc-Tox, where the toxin was LiCl. The Gluc used was 0.2 mg/kg of DEX diluted in isotonic saline. There were 8 saccharin trials. Following Trial 3, rats subjected to LiCl were subjected to an extinction procedure: the saccharin solution was consumed without any later treatment (neither LiCl, stressor, nor Gluc). This was done because the CTAs were stronger than expected, producing a floor effect that we tried to attenuate by extinction.

Experiment 5

The toxins were CIS (1.0 mg/kg) and LiCl (15.9 mg/kg). The groups were designated as in Experiment 4. Group Only-Tox contained 12 rats when CIS was the toxin and 11 rats when LiCl was the toxin. Group No-Tox contained 4 rats. The other groups contained 8 rats, except for Groups CFS-CIS and IFS-Li with 7 rats each. For the rats subjected to CIS, the saccharin solution was consumed without any aftereffect (neither CIS, stressor, nor Gluc) after Trial 4 because the CTAs were stronger than expected.

Experiment 6

The toxins were LiCl (15.9 mg/kg) and morphine sulfate (4.0 mg/kg). The methods of CTA attenuation were the same as in Experiment 5. Group No-Tox was injected IP with 4% body weight of normal saline at the time other rats were injected with a toxin. Group Only-Li and Only-Morphine contained 9 rats each. Groups CFS-Li, CFS-Morphine, IFS-Li, and IFS-Morphine, and No-Tox contained 5 rats each. The SWIM group for each toxin contained 6 rats and the Gluc group contained 7 rats. There were 9 saccharin drinking trials.

Experiment 7

The toxins were CIS (0.6 mg/kg) and morphine sulfate (3.0 mg/kg). The treatments corresponded to those in Experiment 6 with 9 rats per group except for the Gluc-Toxin groups with 7 rats each and Group No-Toxin with 4 rats. This last group received 1.2% body weight of normal saline IP in lieu of a toxin.

Inferential Statistics

Results are shown as preferences for saccharin, S/(S+W), where S is the weight of saccharin solution consumed and W is the weight of water consumed on the preceding day. The lower this preference is, the stronger is the CTA. Although all preference data are shown, a standard method was used for statistical inference on the basis of what we know about CTA attenuation (20). It is a two-tailed, 0.05 level analysis of covariance on the preference scores obtained on the final trial with scores from the first exposure to saccharin as the covariate to control for individual differences. The groups not subjected to a toxin were usually very small and were not used for inferential statistics; their purpose was

TABLE 1

SUMMARY OF LEVELS OF SIGNIFICANCE OBTAINED THROUGH ANALYSES OF COVARIANCE ON THE FINAL SACCHARIN DRINKING TRIAL FOR EACH EXPERIMENT SEPARATELY FOR WHETHER CISPLATIN OR LiCl WAS THE TOXIN

	Agent Used to Attenuate CTAs					
	Cisplatin			LiCl		
Experiment No.	Att by Gluc?	Att by Str?	Gluc or Str	Att by Gluc?	Att by Str?	Gluc or Str
1				0.005	0.001	ns
2				0.05	0.001	0.05 S
3	0.01	ns	0.01 G			
4	0.005	ns	0.001G	0.10	0.001	ns
5	0.025	ns	0.005G	ns	0.001	0.005S
6				0.005	0.005	ns
7	0.001	0.10	0.001G			
Combined Result	0.001	ns	0.001G	0.005	0.001	0.01 S

The first column for each condition, labelled "Att by Gluc," indicates the two-tail significance level if the glucocorticoid(s) produced significant CTA attenuation; "ns" means that there was no significant effect. The second column, labelled "Att by Stress," supplies similar information about the effects of the pooled stressors. The third column, labelled "Gluc or Str," indicates whether there was a significant difference between the CTA attenuation produced by glucocorticoids and that produced by stress; the initials "G" and "S" are used to indicate whether glucocorticoids or stress produced the stronger CTA attenuation. The bottom row shows the significance of the combined results in each column.

to supply a visual reference point in graphs. It is well established that all these toxins produce CTAs and that the attenuation of these CTAs by the Glucs is incomplete (20). Inferential statistics for trials prior to the final saccharin trial are not reported because they are not germane to the present concern with whether or not CTA attenuation was obtained. There are serious statistical drawbacks resulting from too wide a net of statistical tests (13).

For attenuation of a CTA by Glucs to be demonstrated, the dose of the toxin used to establish the CTA must be near the threshold for induction of a CTA (20) and we found the same to be true of CTA attenuation by stress. Because such weak CTAs are very variable and because there was no a priori basis for the obtained results (which were difficult for us to believe), we felt we needed substantial replication. Hence, an unusually large number of experiments were conducted. Where results of different experiments were relevant to the same issue, we combined probabilities by the following method. The individual analyses of covariance were interpreted as *t*s with signs corresponding to the direction of the result. The mean of these *t*s was multiplied by the square root of the number of *t*s, and evaluated as *t* with degrees of freedom equal to the total for the individual *t*s. At present, this method is less popular than meta-analysis. But we are more certain of its validity because it relies on the basic theorem for the probability distribution of the mean of normal deviates.

RESULTS AND DISCUSSION

In this paper, we treat the Glucs as a single entity on the basis of common pharmacological practice (9), as well as many findings that CTA attenuation by Glucs is remarkably independent of the Gluc dose or of the specific type of Gluc (20). This was confirmed in Experiments 1 and 2, where the results for the two Glucs used were statistically indistinguishable by our standard test, the analysis of covariance. The three stressors were also pooled and treated as a single entity because there was no significant difference in the effects of the different stressors used on any of the 10 occasions in these experiments when two or more stressors were used. However, there was an interaction between the effectiveness of each type of CTA attenuation and the type of toxin. Table 1 shows the significance level of each individual statistical test relevant to an indicated question when either cisplatin or lithium was the toxin; if there is no entry for a particular experiment, the experiment did not include a relevant statistical comparison. The combined significance level for all experiments in a column is shown in its bottom row. When CIS was the toxin, the glucocorticoids produced CTA attenuation and the stressors did not. When

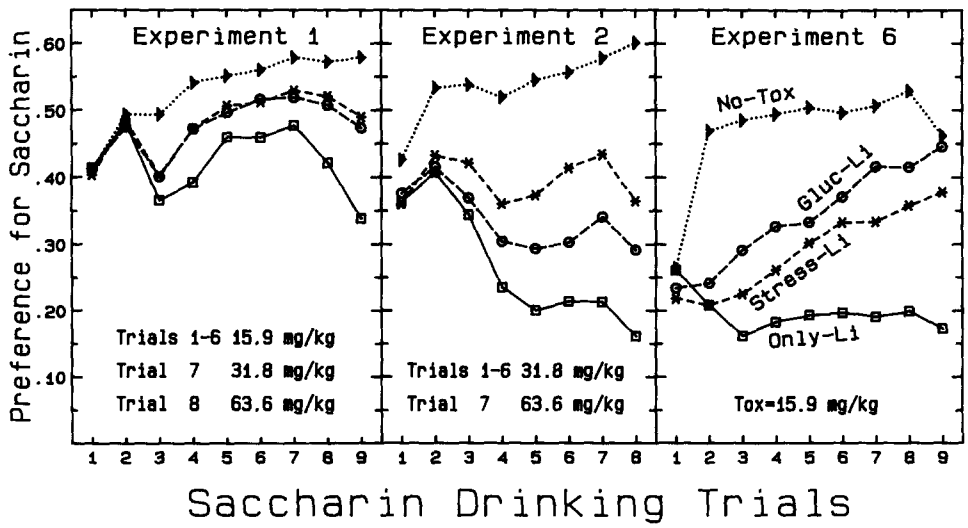

FIG. 1. Saccharin preferences over trials when LiCl was the toxin in Experiments 1, 2, and 6. The curve designations shown in the extreme right apply to the remaining sections also. The references to "mg/kg" for different trials of Experiments 1 and 2 refer to doses of LiCl.

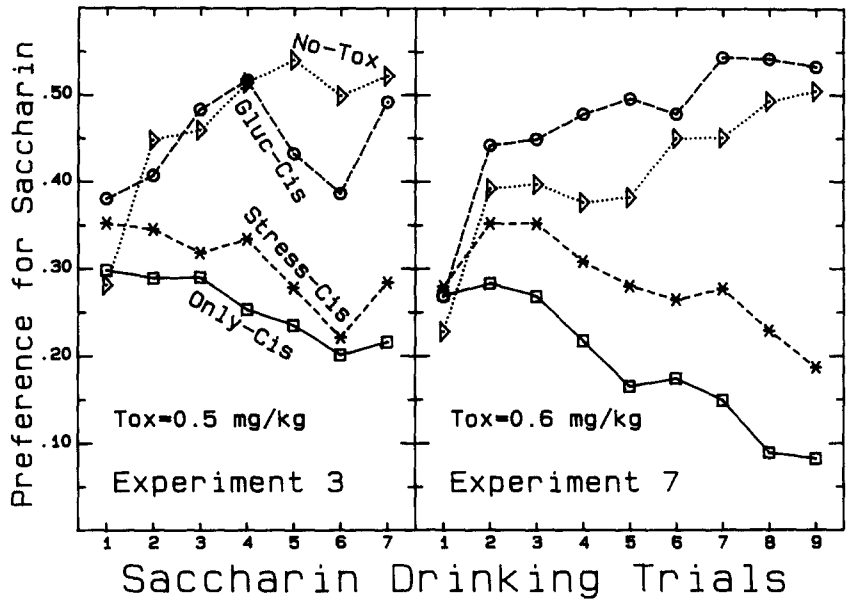

FIG. 2. Saccharin preferences over trials when CIS was the toxin in Experiments 3 and 7. The curve designations shown in the left section also apply to the right section.

LiCl was the toxin, both glucocorticoids and stressors produced CTA attenuation, but the stressors were more effective on an overall statistical basis as indicated in the third column ("Gluc or Str") for LiCl in the bottom row. When CIS was the toxin, the corresponding "Gluc or Str" result was significant in the opposite direction.

Figures 1–3 contain the data statistically summarized in Table 1. They do not change the conclusions already reached about the relative effectiveness of different methods of CTA attenuation for CIS and for LiCl. On the basis of detailed examination of the data, we conclude that any nonchance differences over Experiments 1–7 in the relative capacities of stress or the Glucs to attenuate CTAs produced by any specific toxin are indirect results of changing the strengths of the CTAs and hence their capacity to allow detection of attenuation. We kept changing procedures throughout these experiments in a continuing attempt to obtain CTAs weak enough to be attenuated (4,20), but not so weak that there is no appreciable CTA to be attenuated. The LiCl doses used were usually 15.9 or 31.8 mg/kg even though the dose most commonly used in CTA experiments has been 127.2 mg/kg (19). Similarly the CIS doses used here were a fraction of those used in human cancer chemotherapy (20). Another determinant of CTA strength was the delay of toxicosis. In Experiments 1 and 2, the saccharin drinking periods were 30 min in duration and the delay between the removal of the saccharin and the injection of the toxin was 60 min. In Experiments 3–7, the saccharin drinking period was 15 min and the delay between the removal of the saccharin and injection of the toxin was 30 min, so that, other things being equal, the CTAs were stronger. In Experiment 1, when the delay of toxicosis was 60 min, a 15.9 mg/kg dose of LiCl produced a CTA so weak that the magnitude of CTA attenuation was small (Fig. 1). When the delay of toxicosis was reduced to 30 min, the same 15.9 mg/kg LiCl in Experiment 5 (Fig. 3) and Experiment 6 (Fig. 1) produced CTAs that were strong enough to allow observation of CTA attenuation. The 31.8 mg/kg dose of LiCl allowed clearcut effects in Experiment 2 (Fig. 1), with the longer delay of toxicosis. When this delay was shortened in Experiment 4 to strengthen the CTA, the same 31.8 mg/kg dose produced a floor effect so that CTA attenuation was apparent only in extinction (Fig. 3). In the case of CIS, the same delay of toxicosis was used throughout, but it is apparent in Fig. 3 that when the dose was increased from 0.5

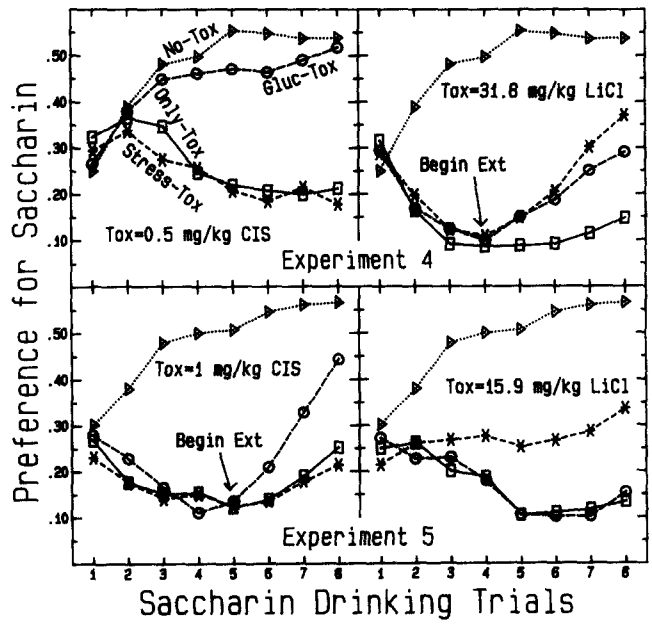

FIG. 3. Saccharin preferences over trials shown separately for whether CIS (left quadrants) or LiCl was the toxin (right quadrants) and for Experiment 4 (top quadrants) and Experiment 5 (bottom quadrants). The curve designations, which indicate the aftereffects of consumption of saccharin solution as described in the text, are shown in the upper left quadrant. These apply to all four quadrants. The No-Tox curve is the same in each experiment regardless of which toxin was used. Where the arrow indicates "Begin Ext" (upper right and lower left quadrants), the rats drank saccharin solution without any later injections or stress procedures.

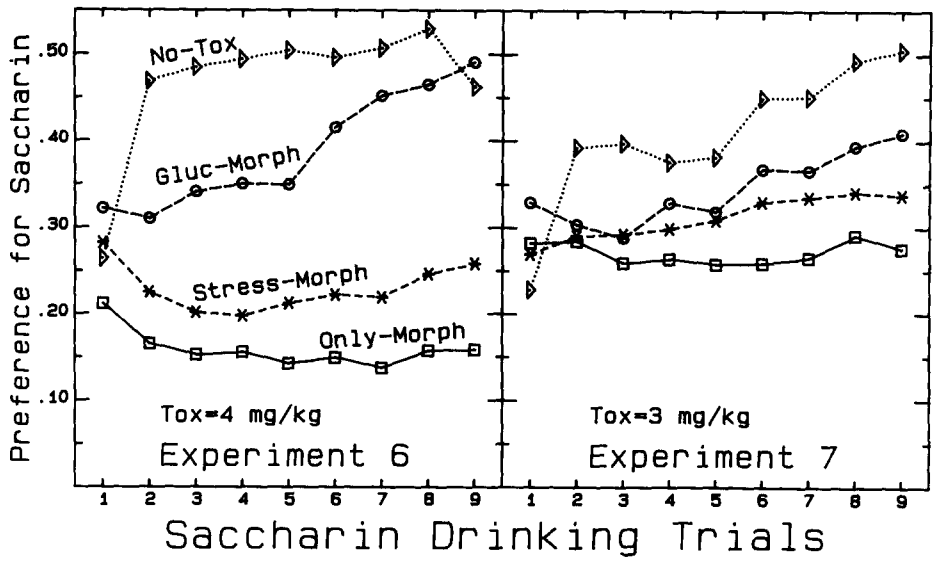

FIG. 4. Saccharin preferences over trials for when morphine was the toxin in Experiments 6 and 7. The curve designations shown on the left also apply to the right of the figure. The references to "mg/kg" are in terms of morphine sulfate.

mg/kg in Experiment 4 to 1.0 mg/kg in Experiment 5, the CTA attenuation produced by the Gluc was hidden by a floor effect until after a number of extinction trials.

Morphine

The relative effectiveness of the different CTA-attenuating agents on CTAs induced by morphine was similar to what it was for CIS. On the final trial of Experiment 6 (left side of Fig. 4), the Gluc attenuated the CTA ($p<0.005$) produced by morphine, but the pooled stress did not. Similarly, the preferences resulting from Gluc plus morphine were significantly higher than those resulting from the pooled stress plus morphine ($p<0.01$). In Experiment 7, the dose of morphine was reduced by 25% to weaken the CTA in the expectation that it would be more readily attenuated, but the contrary result was CTAs too weak to permit significant CTA attenuation to be observed (right side of Fig. 4). Still, the insignificant trends in Experiment 7 were similar to those of Experiment 6 and an overall analysis of both morphine experiments yielded the same significant effects found for Experiment 6 by itself ($ps<0.05$).

EXPERIMENT 8

Revusky and Martin (20) supplied evidence against various alternatives to the theory that Glucs attenuate CTAs because they reduce the noxiousness of the aftermath of exposure to the toxin; as indicated earlier, this interpretation is called the palliative theory. In the case of CTA attenuations by stressors, one alternative to the palliative interpretation depends on the fact that sometimes electrical shock administered while or just immediately after a rat drinks a flavored solution increases the subsequent preference for the flavor (5, 7, 12). If this were true with the procedures used here, the CTA attenuation produced by the stressors might have occurred because the stressors raised saccharin preference and thus counteracted the reduction in saccharin preference usually produced by the toxin. If so, the resulting CTA attenuation would not indicate that the stressors palliate the aftereffect of the toxin; the CTA might be attenuated because of exposure to a reward prior to the toxin injection and there would be no reason to postulate attenuation of the noxiousness of the toxin.

This alternative to the explanation of CTA attenuation in terms of a reduction in the noxiousness of the toxin presupposes that CFS of the type that attenuates CTAs produced by LiCl would increase saccharin preference if administered in the absence of a toxin. Experiment 8 tested this possibility. Group Pre was administered 2 min of CFS beginning 15 min prior to presentation of the saccharin solution and Group Post received the CFS beginning 15 min after removal of the saccharin solution. Group No-CFS, the control group, drank saccharin solution for 15 min every second day. The concentration of saccharin in the solution was increased to 2.0% from the 0.4% used in Experiments 1–7. The purpose was to lower intake of saccharin solution and thus facilitate detection of any increase in saccharin preference produced by the shock.

METHOD

The three groups (ns = 12) each received 15 min per day of water which, on alternate days, was flavored with 2.0% (w/v) of sodium saccharin. Group Pre was subjected to 2 min of CFS beginning 15 min prior to presentation of the saccharin solution. For Group Post, 2 min of CFS began 15 min after removal of the saccharin bottle. Group No-CFS received no shock. There were no injections whatsoever. On the seventh (and last) saccharin drinking trial, the CFS was omitted so that drinking could be monitored under identical conditions for each group. In unspecified details, the methods were those of Experiment 7.

RESULTS AND DISCUSSION

On the final saccharin drinking trial, when the CFS was omitted, both Group Pre and Group Post had reliably lower saccharin preferences than Group No-CFS ($ps<0.01$) and were not significantly different from each other (Fig. 5). The same pattern of results was significant from Trial 5 and thereafter. Thus, CFS administered either before or after consumption of saccharin solution reduced saccharin preference relative to a control not

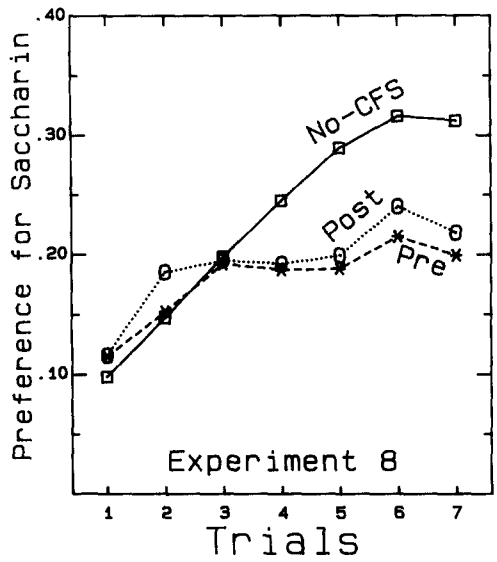

FIG. 5. Preferences for 2.0% saccharin solution as a function of whether CFS was administered 15 min prior to drinking ("Pre"), 15 min after drinking ("Post"), or was not administered at all ("No-CFS").

exposed to CFS. Therefore, it is untenable that stressors raise saccharin preference and thereby counteract the reduction in saccharin preference usually produced by the toxin.

EXPERIMENT 9

Another alternative to the palliative theory is that stressors cause CTA attenuation by producing an associative deficit that interferes with learning the association between the saccharin taste and the toxic effects of LiCl. For instance, the stressor might interfere with the ability of the rat to remember the saccharin taste at the time that the effects of the toxin begin to produce the CTA (22). Or the stressor might become associated either with the taste or with the toxic effects and thus interfere with the taste-toxin association (16). Three intuitive considerations contradict such theories as follows.

1) CTA learning is a gut defense function while external stressors such as shock and swimming elicit skin defense (8). Since events in one system do not readily produce associative interference with events in the second system (16,17), these stressors should not interfere with saccharin-toxicosis associations.

2) Another reason not to expect shocks or swimming to interfere with the learned association between the saccharin taste and the sickness is the robustness of CTA learning under all sorts of disorganizing circumstances. For instance, anesthetics and toxins that produce substantial disorganization of learning can still produce CTAs and, when combined with other agents, they increase the strength of the CTA rather than attenuate it (20).

3) A straightforward application of interference theory would incorrectly predict similar CTA attenuation by stress regardless of whether CIS, LiCl, or morphine was used as the toxin. The present results show that this is false.

Experiment 9 was an attempt to supply empirical evidence to augment the preceding conjectural grounds for rejecting the theory that the CTA attenuation produced by stress is due to associative interference. Two groups of rats were injected with LiCl 15 min after drinking saccharin solution. Group CFS-Li, the experimental group, was subjected to CFS 15 min before the saccharin solution was presented and group Only-Li, the control group, was not subjected to CFS. The purpose was simply to determine if CFS shortly before drinking saccharin solution would attenuate the CTA in the same way as CFS between saccharin drinking and the LiCl injection. If this were so, it would be harder to attribute any CTA attenuation by the CFS to associative interference since the stress would no longer be presented between the two events that were to become associated but prior to both elements of the association (16).

A necessary methodological shortcoming of Experiment 9 is the impossibility of equating proximity of the CFS to the toxin injection with the earlier experiments in any meaningful way. In the earlier experiments with 15-min drinking periods (Experiments 3–7), the CFS was administered 15 min prior to the toxin injection. In Experiment 9, the CFS was administered 45 min prior to the toxin injection because it was administered prior to saccharin drinking. Any attempt to equate the CFS-toxin delay with earlier experiments would create other inequities that probably are more important. Another difference from the early experiments is that the delay from the onset of saccharin drinking to the toxin injection is 30 min, at least 15 min shorter than in the earlier experiments. Probably both of these differences reduced the detectability of CTA attenuation in Experiment 9.

METHOD

The two groups (ns = 12) were maintained on 15 min of water per day flavored on alternate days with 0.4% sodium saccharin. Both groups received 15.9 mg/kg of LiCl, 15 min after the saccharin bottle was removed. Group CFS-Li, in contrast to group Only-Li, also received 2 min of 2.5 mA of CFS beginning 15 min before the saccharin bottle was made available. On the 11th saccharin drinking trial, the LiCl was injected earlier than before, within a minute after the bottle was removed. On the 12th (and last) saccharin drinking trial, there was neither CFS nor an LiCl injection. In unspecified respects, the methods of Experiment 8 were used.

RESULTS AND DISCUSSION

Administration of CFS prior to consumption of saccharin solution attenuated the CTA produced by the later LiCl injection (Fig. 6). This effect yielded $p<0.01$ on the final trial, Trial 12, when the CFS was omitted, but seemed slow to develop, not being significant at the two-tailed 0.05 level until Trial 11 or at the one-tailed 0.10 level until Trial 9. Possible reasons for this slowness were mentioned in the introduction to this experiment.

Since it is unreasonable to suppose that shock administered 15 min prior to the saccharin drinking session interferes with the acquisition of the saccharin-toxin association to any marked extent, we interpret the present result as consistent with the notion that the aftereffects of CFS reduce the capacity of LiCl to produce a CTA. Revusky and Martin (20) have supplied similar counterarguments to parallel alternatives (22) to the palliative explanation of CTA attenuation by glucocorticoids.

GENERAL DISCUSSION

Experimental Conclusions

We treated the three quite different types of stressors as a single entity because they yielded statistically identical results. But this does not mean that all stressors that produce analgesia also produce CTA attenuation. While the rats quickly recover from the effects of the stressors used here (as far as can be determined from

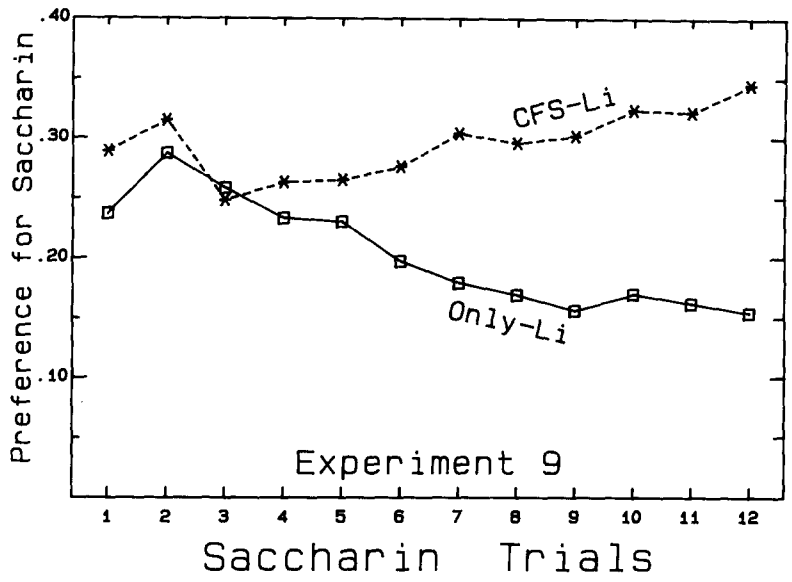

FIG. 6. Preference for saccharin solution among rats injected with LiCl 15 min after drinking. Group CFS-Li was subjected to CFS 15 min before drinking. Group Only-Li was not subjected to CFS.

informal observation of their overt behaviors), the present stressors are more severe than some of the stressors that induce analgesia. Holder *et al.* (10) were not able to obtain CTA attenuation using several short shocks although these were of a magnitude adequate to produce analgesia. In exploratory work, we have not obtained CTA attenuation with 2 min of CFS at 0.8 mA; we do not know whether this level of CFS produces analgesia.

The stressors used here produced stronger CTA attenuation than the Glucs used here when LiCl was the toxin. The Glucs produced stronger CTA attenuation than the stressors when CIS was the toxin. This implies two interrelated distinctions: 1) between CTA attenuation produced by stress and that produced by the Glucs; 2) between CTAs produced by CIS and those produced by LiCl. In this respect, morphine seems similar to CIS even though morphine is a recreational drug and cisplatin is probably the most noxious of the agents used in cancer chemotherapy. We cannot think of any important property that CIS and morphine share that should cause CTAs induced by them to be attenuated by different agents than CTAs induced by LiCl and must leave solution of this very important conundrum to others.

Incorrectness of Original Hypothesis

We correctly predicted that stress might produce CTA attenuation on the basis of a hypothesis that probably is incorrect: that stress would attenuate CTAs by causing secretion of Glucs. Because stress attenuated CTAs produced by LiCl far more effectively than the Glucs, it seems unlikely that stress produces CTA attenuation by causing endogenous release of Glucs. Another point against our original hypothesis is that stress did not noticeably attenuate CTAs produced by CIS or morphine although the Gluc did so very well. Still the possibility that Gluc release underlies CTA attenuation by stressors must not be excluded completely since natural secretion of Glucs may not be identical in its effects to injection of manufactured Glucs.

CTA Attenuation by Stress in a Larger Context

That three different types of stressor all produce statistically identical CTA attenuation when LiCl is the toxin suggests that the characteristic of stressors that attenuates LiCl-induced CTAs is not very specific or that a number of different specific mechanisms have common outcomes. The wide variety of stressors that produce analgesia (11) indicates the latter is also true for stress-induced analgesia. The adaptive role of CTA attenuation by stress is reminiscent of the adaptive role of the analgesia produced by stress as described by Bolles and Fanselow (2). According to their theory, this analgesia turns off pain so that the animal will not be distracted from its immediate task of defense against external dangers. The latter is roughly equivalent to the skin defense that Garcia *et al.* (8) have distinguished from gut defense, which is involved in maintenance of the milieu interior. The CTA is part of this homeostatic gut defense system since, although poisons can be lethal, most CTAs control ingestion of substances that produce harm that is not life threatening. Perhaps the fear involved in skin defense tends to turn off the CTA mechanism, which deals with nonemergency maintenance of the milieu interior, so that all the animal's resources can be mustered to deal with the immediate emergency.

Since the biological roles of the analgesia produced by stress and the CTA attenuation produced by stress may be similar, it is not impossible that the underlying mechanisms are similar. In contrast, the glucocorticoids are not reported to produce analgesia (9), which adds to the evidence that glucocorticoids attenuate CTAs by a different route than does stress.

Unitary or Specific CTA Mechanisms

This paper is organized around the formulation of Garcia *et al.* (8) that treats CTA learning as a part of a gut defense system. Elsewhere, one of us (20) has argued vociferously in its favor and against the contrary theory that CTAs include a number of different phenomena, all of which result in reduced flavor preference (6). For this reason, it is only fair to admit that the present demonstrations of a major difference between CTAs produced by different toxins are a point against the Garcia approach. Nevertheless, we do not believe the present results, or similar earlier findings of differences between CTAs produced by different toxins

[e.g., (1,15)], mandate rejection of Garcia's analysis. There are similar differences in instances of animal learning (18) and of vomiting (3) that have not prevented widespread adherence to a general account of these phenomena. The Garcia model is the only account that makes intuitive sense in terms of biological adaptation. We believe that any learning that, like CTAs, occurs in one or two trials must be highly adaptive or an epiphenomenon of a highly adaptive process. The models of CTA learning that oppose the Garcia model do not pay adequate attention to the adaptive role of CTAs.

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