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Both Conditioned Taste Preference and Aversion Induced by Corticotropin-Releasing Factor

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HEINRICHS, S. C., K. T. BRITTON AND G. F. KOOB. *Both conditioned taste preference and aversion induced by corticotropin-releasing factor.* PHARMACOL BIOCHEM BEHAV **40**(4) 717–721, 1991.—Postprandial administration in the rat of a wide variety of drugs, peptides and toxins suppresses future consumption of a meal of previously unfamiliar but otherwise attractive saccharin-flavored solution. Since the intensity of this conditioned flavor aversion in the rat is sensitive to plasma stress hormone levels, the present study examined the effects on flavor conditioning of corticotropin-releasing factor, a peptide known to be involved in behavioral and hormonal responses to stress. In two-bottle water vs. saccharin choice tests, CRF (0.5 μg ICV) increased significantly the consumption of saccharin solution following a single saccharin/CRF pairing, while a tenfold larger dose of CRF (5 μg ICV) abolished saccharin intake following two saccharin/CRF pairings. Hence, exogenous CRF is capable of inducing both flavor preference and aversion in a dose- and situation-dependent manner. Further, direct neurotropic actions of CRF probably subserve its aversive effect since dexamethasone pretreatment weakened but did not prevent CRF-induced conditioned taste avoidance. These results suggest that at low doses CRF can produce arousal actions that result in taste preference and at higher doses produces aversive effects that are reflected in taste avoidance.

Corticotropin-releasing factor Conditioned taste aversion Flavor preference Dexamethasone
Lithium chloride Saccharin Rat

PREVIOUS work has shown that corticotropin-releasing factor (CRF) exerts aversive stimulus properties in the conditioned taste paradigm by suppressing in a single-bottle test the consumption of a palatable saccharin solution associated previously with CRF administration (7). This inhibition parallels acute CRF effects on ingestive behavior in which CRF pretreatment reduces intake in animals motivated by deprivation to seek food (7,14) or water (17). Food or water intake suppression associated with CRF administration may reflect a general malaise (7) or a disruption of behavioral output (12) in which increased emission of stress-related behaviors such as autogrooming (17) reduces the motivation or opportunity to feed. Such changes in appetite are expected given the central role of CRF in coordinating behavioral, endocrine and physiological responses to stress (12,20).

While CRF shares with many psychotropic drugs and numerous toxic treatments the ability to condition a taste aversion [see reviews (8, 10, 22)], at least two compounds, mu-opioid receptor agonists and nicotine, are aversive at some doses but condition a positive flavor preference at others (11, 16, 18). Such paradoxical results are attributable to an interaction of the euphorigenic, positively reinforcing actions of these drugs with the rat's tendency to regard as aversive any novel, drug-induced state or sensations of illness in particular (10). The data of Krahn et al. (14) suggest an analogous distinction in which doses of CRF with comparable anorexic effects may differ in their ability to produce significant taste conditioning. These workers report that a 5 μg intracerebroventricular (ICV) dose of CRF produced a significant conditioned taste aversion to saccharin in a single-bottle test (7), while a replication with 0.5 μg CRF administered into the paraventricular hypothalamic nucleus conditioned a nonsignificant increase in saccharin intake (14). While these contrasting results employ different doses and routes of CRF administration, low doses of CRF described to activate naturally occurring exploratory behavior in familiar locomotor-cage environments could potentially condition a different response to taste than higher doses of CRF known to disrupt such exploratory behavior (12). Accordingly, one purpose of the present studies was to examine the effect of a 100-fold CRF dose range on single and multiple CRF/saccharin pairings in the conditioned taste paradigm using a two-bottle test. The two-bottle test provides a sensitive index of taste preference by controlling for nonspecific changes in drinking through the availability of both saccharin solution and plain water in a choice situation.

A salient role has been hypothesized for both circulating pituitary-adrenal hormones and central neurochemical substrates in the acquisition and retention of taste learning (9, 10, 22, 23). Since centrally administered CRF promotes ACTH and β-endorphin release from the anterior pituitary (19) but still produces activating, anxiogenic and sympathetic arousal effects when the pituitary-adrenal axis is impaired surgically or chemically (1, 3, 12), an experiment was designed to test the ability of CRF to produce taste conditioning in animals which had the release of

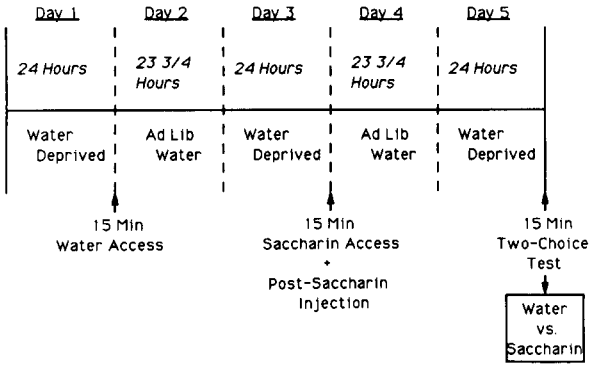

FIG. 1. Schematic representation of the protocol used in Experiment 1 for single pairing of either lithium chloride or corticotropin-releasing factor administration with drinking of a saccharin-flavored solution.

ACTH blunted by dexamethasone pretreatment.

METHOD

Subjects

One hundred and eight male, Wistar rats weighing 250–350 g served as subjects. Animals were group housed in a colony lighted from 0500 to 1700 h. Laboratory chow was available ad lib except when subjects were transferred to individual cages in a separate procedure room as required by the experimental protocols (Figs. 1 and 2).

Surgery

For intracerebroventricular (ICV) injections, rats were equipped with a cannula aimed above the lateral ventricle. This surgery requires anesthetized (Nembutal, 1 ml/kg) subjects to be secured in a Kopf stereotaxic instrument where a 23-gauge, 7-mm long stainless steel guide cannula is lowered to within 1 mm of the ventricle and anchored to the skull with three stainless steel screws and dental cement. With the tooth bar 5.0 mm above interaural zero, implantation coordinates were 0.6 mm posterior to bregma, ±2.0 mm lateral and 3.2 mm below the skull surface at point of entry. After a seven-day postsurgical recovery period, cannula patency was confirmed by gravity flow through a

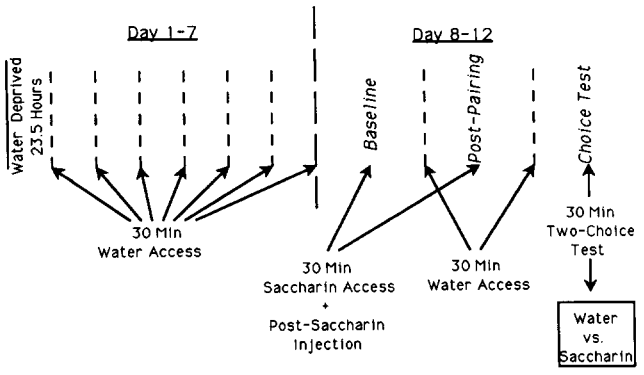

FIG. 2. Schematic representation of the protocol used in Experiments 2 and 3 for two pairings of corticotropin-releasing factor administration with drinking of a saccharin-flavored solution.

30-gauge injector inserted within the guide to 1 mm beyond its tip (13).

Drugs

A 0.4 M solution of lithium chloride (LiCl, Sigma) dissolved in 0.9% physiological saline was administered intraperitoneally (IP) at 7.5 ml/kg. This dose is known to induce taste aversion via gastrointestinal toxicosis (9). CRF was synthesized at the Clayton Foundation Laboratory for Peptide Biology of the Salk Institute by Dr. Jean Rivier. CRF was dissolved in distilled water and administered ICV in doses of 0.05, 0.5 and 5 μg/5 μl/rat using Hamilton microsyringes. Dexamethasone (Sigma) dissolved in 0.9% saline was administered IP at 100 μg/kg body weight.

Experiment 1

Colony room water bottles were removed at 1100 h to begin the five-day, single-pairing taste conditioning procedure (Fig. 1). Twenty-four hour water-deprived animals were first given a 15-minute free access to Richter tubes containing distilled water. Colony water bottles were replaced when subjects returned to their home cages. On the third day, colony water was again removed at 1100 h for 24 hours at which time subjects had 15 minutes of access to tubes containing 0.2% saccharin solution. Immediately afterwards, rats were injected with 0 or 7.5 mg/kg LiCl IP or with 0, 0.05, 0.5 or 5 μg CRF ICV and returned to their home cages equipped with water bottles. On Day 5, water was removed at 1100 h and after 24 hours there ensued a 15-minute choice test between tubes filled with either distilled water or a 0.2% saccharin solution. A pair of such tubes counterbalanced for location was offered to each animal and the volume of consumption was measured in milliliters by visual inspection of a graduated scale along the length of each tube.

Experiment 2

Colony water bottles were removed at 1100 h for the duration of the 12-day multiple-pairing taste conditioning procedure described previously (13) and illustrated in Fig. 2. On Days 1–7 at 1100 h, subjects had 30 minutes of access to distilled water in Richter tubes. Animals drank a 0.2% saccharin solution on Day 8 and Day 10 and were administered ICV doses of 0, 0.05, 0.5, 5 μg CRF immediately following the 30-minute access period. Distilled water was available at 1100 h for 30 minutes on Day 9 and Day 11. On Day 12, each subject chose over a 30-minute period between a pair of Richter tubes filled with distilled water or 0.2% saccharin solution. Drinking volume was measured from tubes counterbalanced for location.

Experiment 3

The design of Experiment 2 is replicated using 0 and 5 μg doses of CRF. Six hours prior to CRF treatment on both Days 8 and 10, half of the subjects were pretreated with 100 μg/kg dexamethasone administered intraperitoneally while the remainder received vehicle injections.

Statistical Analysis

For Experiment 1, saccharin consumption of LiCl vs. IP vehicle and of 0.5 μg CRF vs. ICV vehicle-treated groups was compared using independent group, two-tailed, Student's *t*-tests. For Experiments 2 and 3, two- and three-factor ANOVAs compared differences in saccharin consumption over experimental

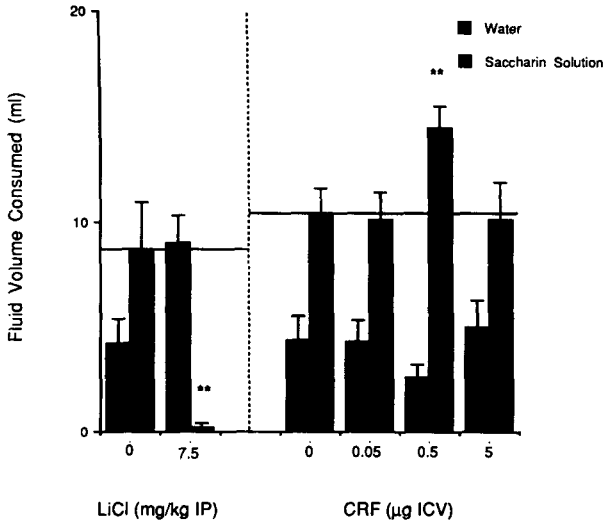

FIG. 3. Mean (±SEM) choice test intake over 15 minutes of water and 0.2% saccharin-flavored water by subjects injected 48 hours previously with 0 (N=6) or 7.5 (N=6) mg/kg lithium chloride (LiCl) or 0 (N=14), 0.05 (N=13), 0.5 (N=14) or 5 (N=14) μg corticotropin-releasing factor (CRF) following a meal of saccharin solution. Asterisks indicate significant differences ($p<0.01$) in saccharin solution intake relative to appropriate vehicle-treated controls.

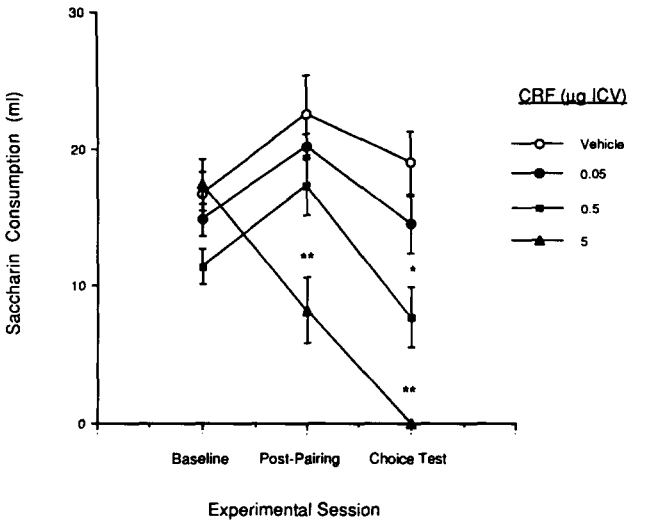

FIG. 4. Mean (±SEM) intake over 30 minutes of 0.2% saccharin-flavored water immediately prior to the first injection (Baseline), 48 hours after the first injection (Post-pairing) and 48 hours after the second injection (Choice Test) of 0 (N=6), 0.05 (N=6), 0.5 (N=7) or 5 (N=5) μg corticotropin-releasing factor (CRF). Saccharin solution alone was available in the Baseline and Post-pairing sessions, while subjects selected between saccharin solution and water (data not shown) during the choice test. Asterisks indicate significant reductions ($p<0.025$) in saccharin solution intake relative to the previous experimental session.

sessions (repeated factor) and among CRF and dexamethasone treatment groups (between subjects factors). Individual means were compared with the Newman-Keuls test a posteriori.

RESULTS

In Experiment 1 (Fig. 3), LiCl-pairing suppressed significantly saccharin consumption relative to the vehicle-paired group, $t(10)=4.04$, $p<0.003$. This molarity of lithium chloride has a proven aversive effect and was employed as a positive control in Experiment 1 to demonstrate sensitivity of the experimental design to flavor conditioning effects. In contrast, the 0.5 μg dose of CRF conditioned a significant preference for saccharin relative to vehicle-treated subjects, $t(26)=2.87$, $p<0.009$. This conditioned increase in saccharin intake was observed repeatedly in four separate replications of the single-pairing design each employing 3–4 subjects per treatment group.

In Experiment 2 (Fig. 4), saccharin consumption was affected significantly by CRF dose, by Experimental Session and by an interaction of the two factors, $F(3,20)=12.4$, $p<0.0001$; $F(2,40)=16.9$, $p<0.0001$; $F(6,40)=8.2$, $p<0.0001$. Comparing individual means, the 0.5 μg dose of CRF suppressed significantly intake from Post-pairing to Choice Test, $F(2,12)=6.09$, $p<0.05$, while the 5 μg dose of CRF decreased significantly consumption in the Post-pairing period and again in the Choice Test, $F(2,8)=33.58$, $p<0.01$. The nonsignificant reduction in saccharin intake from Post-pairing to Choice Test sessions for vehicle-treated subjects reflects the simultaneous availability during the Choice Test of plain water as well as saccharin solution in separate drinking tubes. Given the variability of treatment groups in Baseline saccharin consumption, an appropriate indicator of conditioned taste aversion is more of a decline in saccharin intake from one session to the next than that of the vehicle-treated group.

In Experiment 3 (Fig. 5), saccharin intake was altered by CRF, $F(1,16)=139.81$, $p<0.001$, by Experimental Session, $F(2,32)=19.31$, $p<0.001$, and by an interaction of the two factors, $F(2,32)=32.58$, $p<0.001$. As in the previous experiment, CRF (5 μg) reduced saccharin consumption from Baseline to Post-pairing sessions and again in the Choice Test, $F(2,10)=58.43$, $p<0.01$. In contrast, dexamethasone (100 μg/kg) pretreatment prevented a significant decline in saccharin drinking following one pairing with CRF (5 μg) although a significant aversion did appear in the Choice Test following two pairings, $F(2,8)=15.67$, $p<0.01$.

DISCUSSION

These data confirm an earlier report (7) of aversive effect in the conditioned taste paradigm with a single high dose (5 μg) of centrally administered corticotropin-releasing factor and demonstrate for the first time a contrasting positive preference using a lower dose (0.5 μg). The 0.5 μg dose of CRF falls within a low range (0.01 to 1 μg) which affects behavior in locomotor cage environments in a manner consistent with the proposed activating properties of the peptide (12). In contrast, the 5 μg dose of CRF approaches a high dose range (≥10 μg) which elicits in rats uncommon, abnormal behaviors such as elevated walking, aimless or repetitive locomotion and rapid pawing of cage walls (12). These contrasting, dose-dependent behavioral profiles may be manifested in the opposing positive and negative preference effects of CRF in the conditioned taste paradigm.

Reports of conditioned taste preference are rare for drug (11, 16, 18) and nondrug (4) reinforcers. When such effects are encountered, they are attributed commonly to the fortuitous ability of a particular treatment to stimulate central nervous system reward substrates while at the same time avoiding or masking the association of flavor cues with separate, undesirable effects of the same treatment such as gastrointestinal discomfort, sickness or a state of drug-induced novelty (10,16). For instance, low

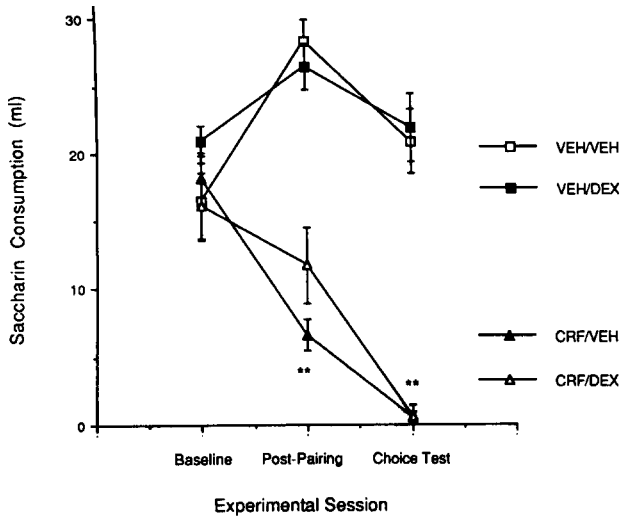

FIG. 5. Mean (±SEM) intake over 30 minutes of 0.2% saccharin-flavored water six hours following injection of dexamethasone (0 or 100 μg/kg IP) and immediately prior to administration of CRF (0 or 5 μg ICV) on the first (Baseline) and second (Post-pairing) conditioning days [veh/veh N=4, veh/crf N=6, dex/veh N=5, dex/crf N=5]. The Choice Test measured preference for saccharin vs. water (data not shown). Asterisks indicate significant reductions in saccharin solution intake relative to the previous experimental session. $^{**}p<0.01$.

doses of nicotine, sufentanil and morphine condition a taste preference, whereas incrementing the dose reverses the direction of conditioning and produces a corresponding increase in the intensity of aversion (11,18), perhaps as a result of untoward effects characteristic of high dose administration (16). Such data argue for the coexistence of "rewarding" and "aversive" consequences of drug treatment which arise in a dose- and situation-dependent fashion (21).

While there is no evidence that CRF is rewarding in the same sense as psychostimulants or opiates, the positively reinforcing effects of these drugs on taste conditioning could be mimicked by a CRF-induced increase in behavioral output as reflected by a conditioned hyperactivity. For instance, placement of an animal in a distinctive testing environment associated previously with CRF administration could produce a conditioned behavioral activation like that seen with drugs which stimulate locomotion (6) and result in increased consumption of an attractively flavored saccharin solution available therein. Such an outcome would be consistent with the general behavioral arousal produced by low doses of CRF in testing environments sensitive to exploratory activity (12).

The dependence of such conditioned effects on the number of CRF exposures is supported by the Choice Test results of Experiments 1 and 2 in which the preference conditioned by one pairing with the 0.5 μg CRF dose contrasts with the weak aversion following two CRF/saccharin pairings. However, the lack of effect following one pairing with the 5 μg dose fails to forecast the potent aversion following two pairings (see Figs. 3 and 4). A wide CRF dose range has been tested in the place preference paradigm, another procedure used commonly to assay the reinforcing properties of various treatments by monitoring the amount of time spent in a distinct portion of a multicompartment chamber paired previously with drug administration (M. Cador et al., in preparation). These data reveal a conditioned place avoidance as reflected by a reduction in time spent in CRF-paired compartments which becomes more pronounced both with repeated pairing and with increasing doses of CRF. As both place conditioning and flavor conditioning in Experiments 2 and 3 employ repeated pairing of conditioned stimuli with CRF administration, continued experience of centrally administered CRF seems to produce a consistent and robust aversive effect which is dose dependent.

One potential index of aversive stimulus efficacy in the conditioned taste paradigm is a concordant rise in stress-related plasma hormone levels (10). Significant aversion induced by peripheral toxicosis is often linked (24) or correlated (9,10) with stimulated release of adrenocorticotropin (ACTH) and glucocorticoids from the pituitary and adrenal glands, respectively. The strength and persistence of aversion can be reduced by simulating adrenal activation with the synthetic glucocorticoid, dexamethasone, in some (8,10) but not all (15) cases. Central blockade of ACTH/corticosteroid release by implantation of hydrocortisone into the median eminence prior to the time of conditioning attenuates aversion to the classical toxic agent, lithium chloride (22). In one study characterizing a dose-response curve for nicotine-induced conditioned taste aversion (11), all doses of nicotine found to produce significant flavor aversion also elevated plasma β-endorphin, a reliable marker of physiological stress, while the highest nonaversive dose of nicotine failed to increase significantly the concentration of β-endorphin in plasma. If endocrine factors participate in the acquisition of flavor aversion, one might expect centrally administered CRF to affect taste conditioning by means of its ability to deliver hypophyseal adrenocorticotropin and β-endorphin directly into systemic circulation (19,20).

While these findings suggest that ACTH release and concomitant rise in corticosterone are important antecedents to conditioned flavor aversion, such hormonal and behavioral indices do not always change in parallel. For instance, markedly elevated levels of plasma corticosterone induced by forced intake of a concentrated sucrose solution do not result subsequently in a conditioned aversion to the flavor of sucrose (22). Similarly, repeated post-drinking injection of exogenous ACTH or corticosterone fails to condition an aversion (23). The converse result of significant taste aversion unaccompanied by elevation in plasma levels of corticosterone has also been reported (22). Since the salience of neuroendocrine activation in the acquisition of conditioned flavor aversion is apparent in some experimental results but not in others, investigators have suggested that the study of naturally occurring peptide-releasing factors, such as CRF, may provide insight into this question (23).

The present findings suggest that pituitary activation is not required for direct neuronal actions of CRF to condition a taste aversion since dexamethasone pretreatment blunted but did not prevent the reduction in preference for a CRF-paired saccharin solution. Other reports (3,17) also describe locomotor activating and anorectic actions of centrally administered CRF which are not altered in hypophysectomized animals by removal of pituitary hormones. Further, dexamethasone inhibition of ACTH release in response to ICV CRF infusion did not alter the proconflict action of CRF on operant responding (1). Following one method (1) of blocking the CRF-induced release of corticosterone, the present studies employed a 100 μg/kg IP dose of dexamethasone six hours prior to ICV administration of CRF. Dexamethasone is also a very effective blocker of the plasma ACTH response to ICV CRF under these conditions (R. Hauger, personal communication). These data suggest that CRF exerts some behavioral actions including conditioned taste avoidance via central nervous system CRF mechanisms which are functionally independent of pituitary-adrenal activation (12).

Although neurotropic actions of CRF are sufficient to account for the abolition of saccharin intake following two CRF pairings,

the attenuation of CRF-induced taste avoidance by dexamethasone in the Post-pairing session of Experiment 3 supports the ability of ACTH/corticosterone to modulate the acquisition and retention of a conditioned taste aversion. Dexamethasone pretreatment blunted a LiCl-induced aversion to a sweetened milk solution in a single-bottle test (9), while exogenous administration of ACTH had the opposite effect in delaying the extinction of a conditioned taste avoidance (23). However, exogenous ACTH does not itself condition a taste aversion (23) suggesting that ACTH may have exerted its well-known modulating effect on the acquisition and production of avoidance behaviors (9,12).

Many self-administered drugs produce conditioned flavor aversion at doses which also stimulate the release of pituitary hormones (10), a stress-like activation which may be necessary for the development of significant aversive effect (11). Conversely, opiate-conditioned flavor preferences are achieved only after three to six taste-pairings (16,18) in a repeated administration procedure which may blunt or abolish the neuroendocrine response to unconditioned drug stimulation (2). Thus the expression of learned flavor preference or aversion may depend on the extent to which a given treatment produces stress-related release of CRF and the resulting endocrine cascade at the time of conditioning. Given the present data which suggest that taste conditioning is sensitive to both the hormone-releasing and direct neurotropic actions of CRF, an understanding of central nervous system CRF mechanisms may provide some utility in consolidating the diverse findings within the conditioned taste learning literature. For instance, since direct stimulation of endogenous CRF systems in the present study modulates taste conditioning bidirectionally, heretofore paradoxical effects of otherwise positively reinforcing drugs which produce aversive consequences in the conditioned taste paradigm may be addressed by study of the unconditioned effects of these drugs in provoking a CRF-mediated stress response.

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