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Chin Rub CRs are Elicited by Flavors Associated With Apomorphine, Scopolamine, Methscopolamine, Physostigmine and Neostigmine[1]

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SMITH, R. J. AND L. A. PARKER. *Chin rub CRs are elicited by flavors associated with apomorphine, scopolamine, methscopolamine, physostigmine and neostigmine.* PHARMACOL BIOCHEM BEHAV 23(4) 583–589, 1985.—Three experiments were conducted in order to determine the pattern of behavioral conditioned responses (CRs) elicited by flavors paired with each of various drugs which effectively establish avoidance of a flavored solution. Each of the drugs employed supported both chin rub CRs and avoidance of a flavored solution. Experiment 1 employed apomorphine, a classic emetic agent which pharmacologically acts as a dopaminergic agonist. Experiment 2 and 3 employed cholinergic agonists and antagonists which were either peripherally or both peripherally and centrally acting agents. The results suggest that chin rub CRs may be produced by means of the activation of a system which is peripheral to the CNS. Furthermore, flavor avoidance produced by drugs which support chin rub CRs may be mediated by a shift in the hedonic rating of the flavored solution; whereas, flavor avoidance produced by drugs which do not support chin rub CRs is probably mediated by a mechanism other than a hedonic shift.

Conditioned taste aversion Conditioned flavor aversion Behavioral CRs Chin rub CRs Conditioned responses Apomorphine Methscopolamine Scopolamine Physostigmine Neostigmine Eserine

SEVERAL drugs have been used to produce conditioned flavor avoidance in man and animals (e.g., [22]). A question that has sparked much research in the area of conditioned flavor avoidance learning asks whether the mechanisms producing the avoidance response are similar or dissimilar across the various drugs employed (see [4,7]). Because it was once thought that flavor avoidance was produced by agents which specifically induce sickness, drugs such as lithium were often employed in such studies because they induce the Unconditioned Response (UR) of nausea [2]. Researchers began to discover, however, that many drugs that do not produce symptoms indicative of a sickness UR were also capable of producing conditioned flavor avoidance. For instance, Garcia, Kimeldorf and Koelling [8] had reported that radiation, at doses that produce no symptoms of illness (inactivity, anorexia, diarrhea), was capable of producing a flavor avoidance response in rats. Berger [1] found that moderate doses of amphetamine, a drug which also serves as a positive reinforcer in an operant paradigm (e.g., [21]), were capable of producing a conditioned flavor avoidance response even though no symptoms of illness were apparent at these doses. The strongest evidence which demonstrates the ability of amphetamine to serve as both an aversive and an appetitive stimulus was presented by Reicher and Holman [21]. When rats were injected with amphetamine before consuming a novel flavored solution in a distinctive location, they later avoided the flavored solution but approached the distinctive location. Because the same injection of amphetamine can be used to produce a flavor avoidance response and yet serve as a positive reinforcer, it is unlikely that amphetamine produces a sickness UR.

The evidence presented above suggests that not all conditioned flavor avoidance responses are the result of symptoms which suggest sickness being paired with a flavor. Drugs from various pharmacological classes may produce flavor avoidance by different mechanisms; however, the standard flavor avoidance test used in such research is incapable of differentiating among the various drug-induced mechanisms that may be operating to produce an avoidance response. As long as a drug is effective in producing an avoidance response, rats will suppress their intake of the

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TABLE 1
DEFINITION OF BEHAVIORAL CATEGORIES

Category Name	Description	Measurement
Line Crossing	Crossing over thirds of cage	Frequency
Rearing	Forepaws off the floor simultaneously, not grooming, may touch side walls	Frequency and Duration
Stretching	Elongated stretching of the body along the floor of the cage	Frequency and Duration
Facewashing	Rubbing forepaws over any part of the head	Frequency and Duration
Body washing and biting	Licking or biting any part of the body	Frequency and Duration
Limb Flicks	Rapid Shaking of forepaws.	Frequency
Doggy Scratch	Scratching the body with hind leg	Frequency
"Wet dog" shake	Sudden, brief body or head twitches resembling a dog shaking water off its back.	Frequency
Chin Rubbing	Lowering the head which brings the mouth in direct contact with a substrate (i.e., floor, wall) and projecting the body forward by flexion of the dorsal neck, pectoral and forelimb musculature (definition from Grill and Norgren [12]).	Frequency
Freeze	No head or body movement with at least three paws touching the floor, not rearing.	Duration

CS flavor despite the fact that drugs from different pharmacological classes are utilized. Parker [16] reported a technique (similar to that reported by Grill and Norgren, [11,12]) that was capable of differentiating among various drug states. By measuring somatic behavioral CRs elicited by lithium- and amphetamine-paired flavors, Parker found that lithium-paired flavors elicited chin rub CRs, whereas amphetamine-paired flavors did not. However, when measured by the standard flavor avoidance test both drugs produced equivalent avoidance responses. Thus, the somatic behavioral CR measure of chin rubbing differentiated between the two drug states, whereas the flavor avoidance measure did not. Additionally, Parker [17] recently reported that even after nine conditioning trials, amphetamine only minimally supported chin rub CRs.

The lithium-specific chin rub CRs reported by Parker [16,17] provide behavioral evidence that lithium and amphetamine conditioned flavor avoidance responses are produced by different mechanisms. Pelchat, Grill, Rozin and Jacobs [19] have also recently reported that lithium, but not lactose or electric shock, will support chin rub CRs, as well as other CRs which the authors suggest are indicative of a shift in the hedonic value of a flavored solution. Presumably, the rat rubs its chin along the floor or wall of the cage in order to facilitate removal of the distasteful solution from its mouth. In the experiments reported below, we were interested in determining whether or not other psychoactive drugs which have been reported to produce a flavor avoidance response would support chin rub CRs.

EXPERIMENT 1

Experiment 1 employed apomorphine, at a dosage level that has been shown to produce a flavor avoidance response (15 mg/kg), as the US drug. Apomorphine is a "classic" emetic agent that has been employed in the standard preparation for testing the antiemetic properties of other drugs [3,14]. If lithium specific chin rub CRs reflect an association

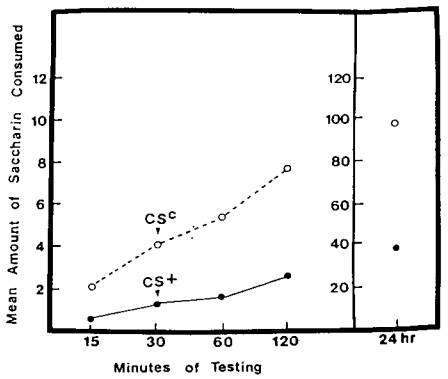

FIG. 1. Mean cumulative amount (ml) of saccharin solution consumed by the CS + group and the CSc group at each interval of testing in Experiment 1 when the US drug was apomorphine.

between the flavored solution and a sickness state, then chin rub CRs should be supported by an apomorphine US, as well as by a lithium US.

METHOD

Subjects

Twenty male Sprague Dawley rats, weighing from 281 to 340 g, were housed individually in stainless steel cages in a room on a 12 hr ON/OFF light-cycle. Except where stated otherwise, the rats were maintained on ad lib access to food and water for the duration of the experiment.

Procedure

Surgery. Each rat was surgically implanted with an intraoral cannula following the procedure described by Parker [15]. Each cannula consisted of a 10 cm length of polyethelene 90 tubing, a 20-gauge plastic adapter cap, and a 5 mm-diameter plastic washer. After a water deprivation period of 24 hr, each rat was anaesthetized with sodium pentobarbital and then implanted with an intraoral cannula. The water deprivation period was implemented in order to limit feeding to facilitate the action of the anesthetic. The rats were then permitted to recover for a period of at least three days, during which they had free access to food and water. On the last recovery day, the cannula of each rat was flushed with water to prevent blockage by food particles.

Conditioning trials. The 20 rats were randomly assigned to two groups of ten subjects each: the experimental (CS +) group and the control (CSc) group. The rats received three conditioning trials in their home cages after recovery from surgery: Trial 1 and Trial 2 occurred on consecutive days, and Trial 3 occurred three days after Trial 2.

On each of the conditioning trials each rat had a 1 M length infusion hose connected to its cannula. The rats then received a 5 ml intraoral infusion of 0.5% saccharin solution over a 5 min period at a rate of 1 ml/min. Immediately after the saccharin infusion, each rat in the CS + group received a 15 mg/kg (2 ml/kg) intraperitioneal (IP) injection of apomorphine in solution with physiological saline (7.5 mg of apomorphine/ml of physiological saline), and each rat in the CSc group received a 2 ml/kg IP injection of physiological saline. Following the injections, the rats were immediately returned to their home cages.

To ensure equal exposure to apomorphine between groups, rats in the CSc group received 15 mg/kg (2 ml/kg)

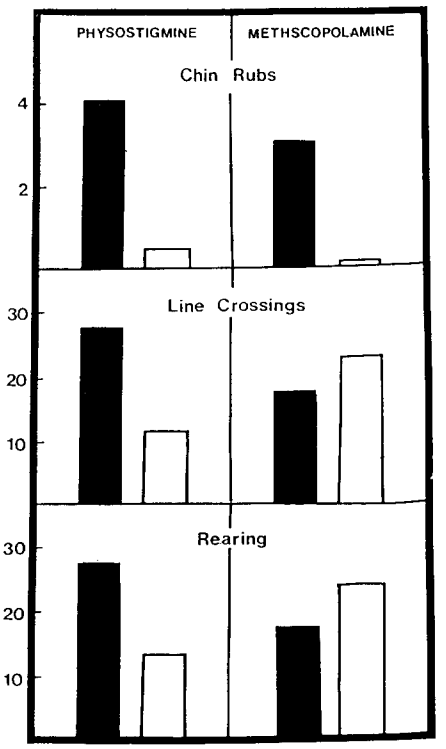

FIG. 2. Mean frequency of each somatic CR which showed evidence of conditioning in Experiment 2 with the US drugs of physostigmine and methscopolamine. The solid bars represent the CS + groups and the open bars represent the CSc groups.

IP injections of apomorphine in solution with saline, but these injections were not paired with the saccharin exposure. These injections occurred 24 hr before exposure to saccharin on Conditioning Trials 1 and 3, and 24 hr after exposure to saccharin on Conditioning Trial 2. The injections were matched by 2 ml/kg IP saline injections in the CS + group.

Adaptation trials. Twenty-four hours after the final conditioning trial, the rats received an adaptation trial on each of three consecutive days prior to the test trials. During each adaptation trial, each rat was removed from its home cage and placed in the glass test chamber. The test chamber, which was an aquarium-like structure (45 × 25 × 20 cm), sat on a metal stand in a darkened room. Both the ceiling and floor of the chamber were constructed of wire mesh, the floor being raised 2 cm from the glass bottom of the aquarium. The chamber was illuminated by two 25 W bulbs situated 30 cm from either side of the chamber and a mirror was situated behind the chamber to facilitate observation.

Each rat was placed individually into the test chamber and a 1 M length infusion hose was connected to its cannula through the wire mesh ceiling. Immediately after being placed in the chamber, the rats received 5 ml of water through the intraoral cannula for 5 min at a rate of 1 ml/min. After an infusion, the rat was removed from the chamber and the chamber was cleaned of any fecal matter.

On the third adaptation trial, the behavior of each rat during the intraoral infusion was videotaped. A Hitachi HV-62 videocamera transmitted the image through a videocassette recorder (JVC-CR6060U) in an adjacent room to an Electrohome, 17 inch, black and white monitor. As in the procedure described by Parker [16], in order to later determine whether a conditioned thermic response occurred,

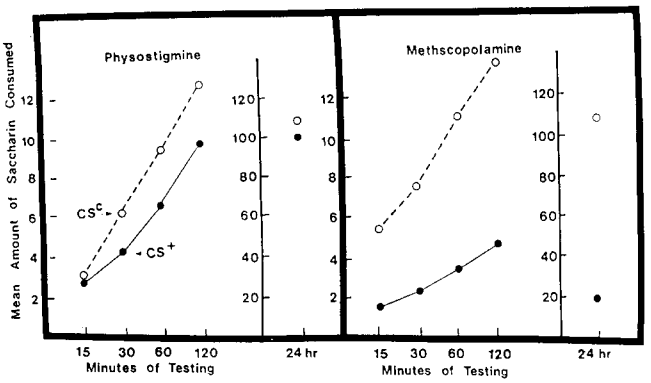

FIG. 3. Mean cumulative (ml) amount of saccharin solution consumed by the CS + groups and the CSc groups at each interval of testing in Experiment 2.

the body temperature of each rat was measured by means of a YSI-45 TUC Telethermometer immediately after the intraoral infusion.

Taste reactivity test. The rats were tested on the day following the final adaptation trial. On the test day, each rat was placed in the test chamber where it received an immediate intraoral infusion of 0.5% saccharin solution for 5 min at a rate of 1 ml/min. The rat's somatic behaviors exhibited during the intraoral infusion were videotaped and its body temperature was recorded as on the final adaptation trial.

A rater who was blind to the experimental conditions scored the videotaped records using a keyboard connected to a 20 channel Esterline-Angus event recorder. The following behaviors, described by Parker [16] and presented in Table 1, were scored: line crossing, rearing, stretching, face washing, body washing, limb flicking, scratching, shaking, freezing and chin rubbing.

Flavor avoidance test. On the day after the taste reactivity test, each rat was deprived of water for 2 hr before being presented with a weighed water-bottle filled with 0.5% saccharin solution. The amount of saccharin that each rat consumed was measured at 15, 30, 60, 120 min and at 24 hr.

RESULTS

The only somatic behavior which showed evidence of being conditioned on the test trial was that of chin rubbing, $t(17) = 1.9$, $p<0.05$. The CS + group showed significantly more chin rubs (mean=6.1) than did the CSc group (mean= 0.1). No significant differences existed between the groups for any of the behaviors measured during the final adaptation trial. Also there were no significant differences for the body temperature data on either the test day or the adaptation day.

Figure 1 presents the mean cumulative amount of 0.5% saccharin solution consumed during the flavor avoidance test by the CS + and the CSc group at each interval of testing. As is evident from the figure, the CS + group drank significantly less saccharin solution than did the CSc group at the 24 hr interval of testing, $t(17) = 3.74$, $p<0.01$. A 2×4 Unweighted Means Repeated Measures ANOVA, across intervals 15–120 min, revealed a significant CS condition effect, $F(1,17) = 6.42$, $p<0.025$; the CS + group drank less saccharin solution across the 120 min of testing than did the CSc group. Additionally, both the Minutes effect, $F(3,51) = 44.6$, $p<0.001$, and the CS Condition × Minutes effect, $F(3,51) = 10.8$, $p<0.001$, were significant. The CS + group drank less saccharin solution than did the CSc group at each of intervals 15–120 min (p's<0.05).

DISCUSSION

Apomorphine, a classic emetic agent, was effective in producing avoidance of a saccharin flavored solution as well as producing chin rub CRs. Chin rub CRs are a component of a sequence of responses elicited by aversive tastes [9, 11, 12]. Since both lithium chloride- and apomorphine-paired flavors elicit chin rub CRs, the avoidance of tastes produced by these two drugs may be mediated by a shift in the palatability of the flavor. On the other hand, since amphetamine-paired flavors do not elicit chin rub CRs [16,17], avoidance produced by this drug is probably not mediated by such a palatability shift.

EXPERIMENT 2

Experiment 2 used the taste reactivity test and the flavor avoidance test to measure the effects of two drugs which act upon the cholinergic system that are not specifically emetic agents. Physostigmine, a cholinergic agonist, is a centrally and peripherally acting anticholinesterase agent. Methscopolamine, a cholinergic antagonist, is a peripherally acting cholinergic blocking agent. Even though these agents have opposing effects upon the cholinergic synapse, each drug has been shown to effectively produce avoidance of a flavored solution (e.g., [18]).

METHOD

Thirty-two male Sprague-Dawley rats, weighing from 218 to 299 g, served as subjects in Experiment 2. As in Experiment 1, all subjects were implanted with intraoral cannulae and maintained on ad lib access to food and water. Except where specified below, the procedures used for conditioning, and testing were identical to those of Experiment 1.

The rats were randomly assigned to one of four groups on the basis of CS Condition (CS + or CSc) and US drug condition (physostigmine or methscopolamine). Although there were initially 8 rats per group, loss of videotaped records due to malfunctioning equipment resulted in the following group compositions: CS + physostigmine, n = 8; CSc physostigmine, n = 6; CS + methscopolamine, n = 7; CSc methscopolamine, n = 7. During the three conditioning trials, the rats received appropriate IP injections of 2 ml/kg of either physostigmine (0.25 mg/kg eserine sulfate in solution with saline; 0.125 mg/ml) or methscopolamine (1 mg/kg of methscopolamine HBr in solution with saline; 0.5 mg/ml). These injections were given immediately following a 5 min intraoral infusion of 0.5% saccharin (1 ml/min). As in Experiment 1, control procedures were also conducted to ensure that the CSc and CS + rats received equivalent experience with the appropriate US drug, and to ensure that the CS + and CSc groups received an equal number of injections. Immediately after injections, the rats were returned to their home cages.

RESULTS

Taste reactivity test. Figure 2 presents the somatic be-

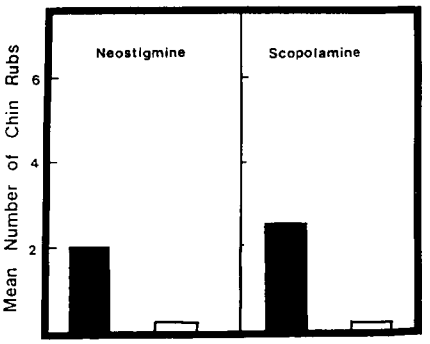

FIG. 4. Mean number of chin rubs shown by the CS+ groups (solid bars) and the CSc groups (open bars) in Experiment 3 when neostigmine and scopolamine served as the US drugs.

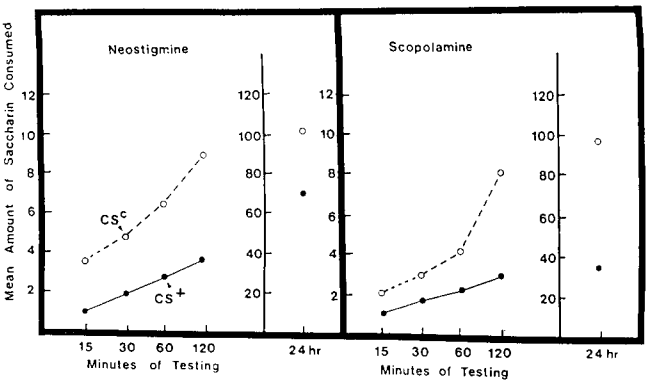

FIG. 5. Mean cumulative (ml) amount of saccharin solution consumed by the CS+ groups and CSc groups at each interval of testing in Experiment 3.

haviors which showed evidence of conditioning in Experiment 2 when either physostigmine or methscopolamine served as the US drug. Each of the behaviors described in Table 1, as well as the body temperature data for the final adaptation trial and the taste reactivity test, was analyzed using a 2×2 unweighted means ANOVA with the factors of CS Condition $\times$ US Condition. No significant effects were found for any behavior measured on the final adaptation trial. On the test trial the behaviors of chin rubbing, line crossing and rearing frequency showed evidence of conditioning.

As is evident from the first panel in Fig. 2, analysis of the chin rub behavioral data revealed a significant CS Condition effect, $F(1,24) = 10.2$, $p<0.005$; the CS+ groups (mean = 3.5) showed a significantly greater number of chin rubs than the CSc groups (mean = 0.3), regardless of the US drug condition.

The line crossing and rearing (frequency) data analyses revealed significant CS Condition $\times$ US Condition effects (line crossing: $F(1,24)=10.8$, $p<0.005$, rearing frequency: $F(1,24) = 7.5$, $p<0.05$). As is suggested by Fig. 2, when physostigmine served as the US drug, the CS+ group line crossed ($p<0.01$) and reared ($p<0.025$) significantly more frequently than did the CSc group; however, when methscopolamine served as the US drug there were no differences between the CS Conditions.

Flavor avoidance test. Figure 3 presents the mean cumulative amount of saccharin solution consumed by each group during the flavor avoidance test in Experiment 2. A $2 \times 2 \times 4$ unweighted means repeated measures ANOVA for intervals 15–120 min revealed a CS Condition Effect, $F(1,24) = 7.7$, $p<0.01$; the CS+ groups drank less than did the CSc groups. Additionally, a CS Condition $\times$ Minute interaction, $F(3,72) = 5.4$, $p<0.01$, was evident which indicated that, the difference between the CS groups increased across the first 120 min of testing. Although there was no significant CS Condition $\times$ US Condition interaction, inspection of Fig. 3 suggests that the saccharin aversion produced by physostigmine was not as strong as the saccharin aversion produced by methscopolamine. In order to compare the strength of the avoidance response produced by both drugs, we used different scores between the CS Conditions (CSc-CS+) as input into t-tests (using the pooled error term) which compared the two US drug conditions at each interval of testing (15–120 min). By these comparison tests, the difference between CSc and CS+ was greater for the methscopolamine US drug condition at each of intervals 15–120 min (p's<0.01). Although the methscopolamine-based avoidance response was stronger than the physostigmine-based avoidance response, physostigmine did produce a flavor avoidance response. When the US drug was physostigmine, the CS+ groups drank less saccharin than the CSc groups at intervals 30 min, 60 min, and 120 min (p's<0.05), but not at interval 15 min. The CS+ rats conditioned with methscopolamine drank less than the CSc rats at each interval tested.

The 24 hr intake scores, also presented in Fig. 3, were analyzed in a 2×2 unweighted means ANOVA. A significant CS condition $\times$ US Condition effect, $F(1,24) = 11.0$, $p<0.01$, was the result of a significant difference between CS+ and CSc when methscopolamine was the US drug, $t(24) = 5.6$, $p<0.01$, but not when physostigmine was the US drug.

DISCUSSION

In Experiment 2, the centrally and peripherally acting cholinergic agonist, physostigmine, and the peripherally acting cholinergic antagonist, methscopolamine, were both effective in conditioning chin rub CRs. Although the results clearly demonstrated chin rub CRs, the mean number of chin rubs supported by physostigmine (mean=4.0) and methscopolamine (mean=3.0) tended to be lower than the mean number of chin rubs supported by apomorphine (mean = 6.1) in Experiment 1 or by lithium (mean = 6.4) in our previous work [17]. Additionally, although physostigmine produced a weaker conditioned flavor avoidance response, it alone supported enhanced rearing and line crossing activity.

EXPERIMENT 3

In Experiment 3, we measured somatic CRs and the flavor avoidance response elicited by neostigmine, a peripherally acting cholinergic agonist, and scopolamine, a centrally and peripherally acting cholinergic antagonist. These drugs were selected to complete an appraisal of the somatic CRs elicited by cholinergic and anticholinergic agents which act peripherally and/or centrally.

METHOD

Thirty-two rats weighing between 260–323 g were treated

identically as in Experiment 2 except that the drugs employed were 0.25 mg/kg of neostigmine methyl sulphate in solution with physiological saline (0.125 mg/ml) and 1 mg/kg of scopolamine HBr in solution with physiological saline (0.5 mg/ml).

RESULTS AND DISCUSSION

Of all behaviors measured, the only somatic behavior which showed evidence of conditioning was that of chin rubbing. Figure 4 presents the mean number of chin rubs supported by the CS+ and CSc group conditioned with either neostigmine or scopolamine. The 2 × 2 ANOVA revealed a significant effect of CS Condition, $F(1,28) = 7.4$, $p<0.01$; the CS+ groups showed more chin rubbing activity than did the CSc groups. Again, however, fewer chin rub CRs tended to be conditioned with neostigmine (mean = 2.0) or scopolamine (mean = 2.6) than with apomorphine (mean = 6.0) or with lithium (mean = 6.1) [17].

The mean amount of 0.5% Saccharin Solution consumed by each group in Experiment 3 is depicted in Fig. 5. The 2 × 2 × 4 Repeated Measures ANOVA across intervals 15–120 min revealed a significant CS Condition effect, $F(1,28) = 13.1$, $p<0.01$, and a significant CS Condition × Intervals interaction, $F(3,84) = 6.3$, $p<0.01$. Overall the CS+ groups drank less saccharin during each of intervals 15–120 min than did the CSc groups (p's<0.05). The 24 hr consumption scores are also presented in Fig. 5. The 2 × 2 ANOVA for the 24 hr scores revealed only a significant CS Condition effect, $F(1,28) = 9.9$, $p<0.01$; the CS+ groups drank less than the CSc groups.

Both the peripherally acting cholinergic agonist neostigmine, and the centrally and peripherally acting cholinergic antagonist, scopolamine, supported both a conditioned flavor avoidance response and chin rub CRs. The quantity of chin rubs CRs elicited by these agents, however, was less than the quantity of chin rub CRs supported by lithium [16] apomorphine (Experiment 1). These data represent the first demonstration of a conditioned flavor avoidance response with neostigmine. The results of Experiments 2 and 3 suggest that chin rub CRs are not the result of agents which specifically act upon the CNS, because the CRs were effectively elicited by flavors paired with the peripherally acting agents of methscopolamine and neostigmine.

GENERAL DISCUSSION

The three experiments reported above demonstrated that apomorphine, physostigmine, neostigmine, scopolamine and methscopolamine each are capable of supporting chin rub CRs. Apomorphine is a classic emetic agent which pharmacologically serves as a dopaminergic agonist. Each of the other four drugs are not specifically emetic agents and pharmacologically act on the cholinergic system. The cholinergic agonists used were centrally and peripherally active physostigmine and peripherally active neostigmine. The cholinergic antagonists used were centrally and peripherally active scopolamine and peripherally active methscopolamine. Although these drugs act on different pharmacological systems, each effectively conditioned chin rub CRs. Since neostigmine and methylscopolamine are ineffective at crossing the blood-brain-barrier, the peripheral activity of a US agent is sufficient to produce chin rub CRs. However, since all peripheral input may be acted upon within the CNS, we cannot be certain that an eventual central site of action may not be ultimately responsible for the establishment of chin rub CRs.

The behavioral response of chin rubbing is one component of an aversive ingestion sequence reported to occur to lithium-paired flavor solutions, as well as to bitter tasting quinine solutions (e.g., [9, 11, 12]). Presumably, the rat rubs its chin along the floor or wall of the cage in order to facilitate removal of the distasteful solution from its oral cavity. The chin rub CR, then, may reflect a shift in the hedonic value of a flavored solution such that the drug-paired solution becomes distasteful to the rat. Since our results indicate that apomorphine, physostigmine, neostigmine, scopolamine and methscopolamine, at the dosages tested, support chin rub CRs, conditioned flavor avoidance based on these drugs may be mediated by a shift in the hedonic rating of the flavored solution.

Parker [16] reported that lithium (3.0 mEq/kg of 0.15 M) paired flavors elicit chin rub CRs, but amphetamine (3 mg/kg) paired flavors do not elicit chin rub CRs even though both drugs produced equally strong avoidance of the flavored solution in the flavor avoidance test. Furthermore, a dose of amphetamine as high as 5 mg/kg given on each of three conditioning trials did not support the conditioning of chin rubs. Finally, Parker [17] demonstrated that even after nine saccharin (3 mg/kg)-amphetamine pairings, chin rubbing was only minimally elicited by the saccharin.

Since each of the drugs employed in the experiments reported above, as well as lithium chloride, supported chin rub CRs, we suggest that the presence of chin rub CRs reflects a common process among various drugs which produce conditioned flavor avoidance. Furthermore, since lithium and apomorphine tended to more effectively produce chin rub CRs than did the cholinergic and anticholinergic agents that we tested, we suggest that emetic agents may be especially effective in producing this hedonic shift. The conditioned flavor avoidance response produced by drugs which support chin rub CRs is probably mediated by a shift in the hedonic rating of the flavored solution. On the other hand, amphetamine based flavor avoidance is apparently mediated by a different mechanism than a shift in the hedonic rating of the flavor. It has been suggested that amphetamine-based conditioned flavor avoidance is based on a conditioned anorexic response. However, Stollerman and D'Mello [25] have reported, in a thorough review of the conditioned anorexia hypothesis, that there is little correlation between the dose-response effects of amphetamine on conditioned flavor avoidance and the dose-response effects of amphetamine on anorexia or hypodipsia. Furthermore, the amphetamine analog dl-cathinone is as potent as amphetamine as an anorexic agent, but is less potent than amphetamine in producing conditioned flavor avoidance [6].

Although, amphetamine-based conditioned flavor avoidance does not appear to be mediated by conditioned anorexia, the mediating mechanism appears to differ from that which induces conditioned flavor avoidance produced by each of the other drugs we have tested. One possibility that is currently being investigated relies on the paradox that some drugs, such as amphetamine and morphine, are positively reinforcing in some situations and yet produce avoidance of a flavored solution in the conditioned flavor avoidance test (e.g., [20, 21, 24]). It is possible that the flavor avoidance response supported by these "paradoxical" drugs is not mediated by a shift in the hedonic value of the drug-paired flavored solution. A second possibility is based on reports that amphetamine-based flavor avoidance is centrally

rather than peripherally mediated. Destruction of central catecholamine systems by 6-OHDA [26] or the reduction of catecholamine levels in the brain by AMPT [10, 13, 23] prevents the establishment of an amphetamine-based conditioned flavor avoidance response (see also [7]). It is, therefore, possible that chin rub CRs are supported by drugs which specifically act as peripheral US agents (e.g., via the area postrema) in the flavor avoidance learning situation.

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