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Phenylethylamine-Induced Taste Aversion in Rats and Mice[1]

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KUTSCHER, C. L. *Phenylethylamine-induced taste aversion in rats and mice.* PHARMACOL BIOCHEM BEHAV **29**(2) 287–293, 1988.—Phenylethylamine (PEA) has the same structure as amphetamine (AMP) except that PEA lacks a methyl group at the alpha carbon. Although these analogues produce many similar neurobehavioral actions, a previous study found that PEA did not support formation of conditioned taste aversion (CTA). Using somewhat different procedures, in the present study a transient taste aversion was seen in rats. Use of noradrenergic blocking agents to attempt to pharmacologically tailor PEA action to make it more like that of AMP did not improve efficacy to form CTA. A robust PEA-induced CTA was seen in mice even when PEA produced multiple seizures.

Amphetamine Mice Phenylethylamine Rat Stereotypy Taste aversion

MANY drugs of the phenylethylamine structure (one ring separated from a terminal amine group by two carbons) have strong neurobehavioral actions [42]. Fenfluramine, phentermine, phenylpropanolamine and diethylpropion are anorectics [19]. Epinephrine, dopamine and norepinephrine are endogenous phenylethylamines which serve as neurotransmitters. Their hydroxylated rings produce strong affinity for receptor sites in the nervous system [42]. The parent compound, β-phenylethylamine (PEA) has been found in the brains of humans [20,35], rats [13,35] and rabbits [34], however, the function of the endogenous compound has not yet been clarified. Considerable attention has been devoted to the neurobehavioral action of exogenous PEA [10–12, 22, 30].

The amphetamine (AMP) molecule is constructed on the PEA skeleton by substituting a methyl group at the alpha carbon [42], a change which retards degradation by monoamine oxidase. Recently Greenshaw and Dourish [17] found a marked difference between these two analogues in ability to elicit conditioned taste aversion (CTA); a moderate dose of AMP produced robust, enduring CTA, but PEA did not, except for a weak and transient aversion produced by a near-lethal dose. This outcome was apparently not related to expected differential durations of drug action of the analogues [18]. The finding is important not only because it indicates that PEA should be considered to be a member of a restricted group of drugs which do not produce CTA, or produce it weakly—cocaine [15], strychnine [31], cyanide, pyrrolopyrimidine, gallamine, malonate [21] and heroin [40]—but also because it suggests that the efficacy hinges upon a single structural substitution in the molecule.

The purpose of this research is threefold: (1) to determine if PEA produces sequalae which are incompatable with acquiring CTA; (2) to determine if PEA can be made to produce CTA if the drug is administered after other drug pretreatments which should tailor PEA action to make it more like AMP action; (3) to examine the ability of PEA to produce CTA in another species.

EXPERIMENT 1

The ability of AMP to support CTA has been often observed [5]. In this experiment PEA was given concomitantly with AMP to see if PEA could prevent or diminish the magnitude of AMP-induced CTA. Stereotypy profiles were observed and quantified following injection as verification that PEA was given in a dose sufficient to interact with AMP in the modification of behavior.

METHOD

Animals

Thirty, naive, Long Evans hooded rats, 15 males and 15 females, 170–210 days old at the start of the experiment, were subjects. Rats were bred in the Behavioral Neuroscience Laboratory of Syracuse University from stock obtained from Charles River. Rats were gentled by being handled and stroked for one min before the beginning of solution discrimination training trials.

Apparatus

At the beginning of the experiment, rats were removed from the breeding colony and housed in stainless steel cages in groups of 5–6. Drinking boxes were plastic, 17×26×12 cm with steel covers. Drinking fluids during drinking tests were given in 100 ml gas-measuring tubes with stainless steel sip tubes. Stereotypy observation chambers were 58×53×43

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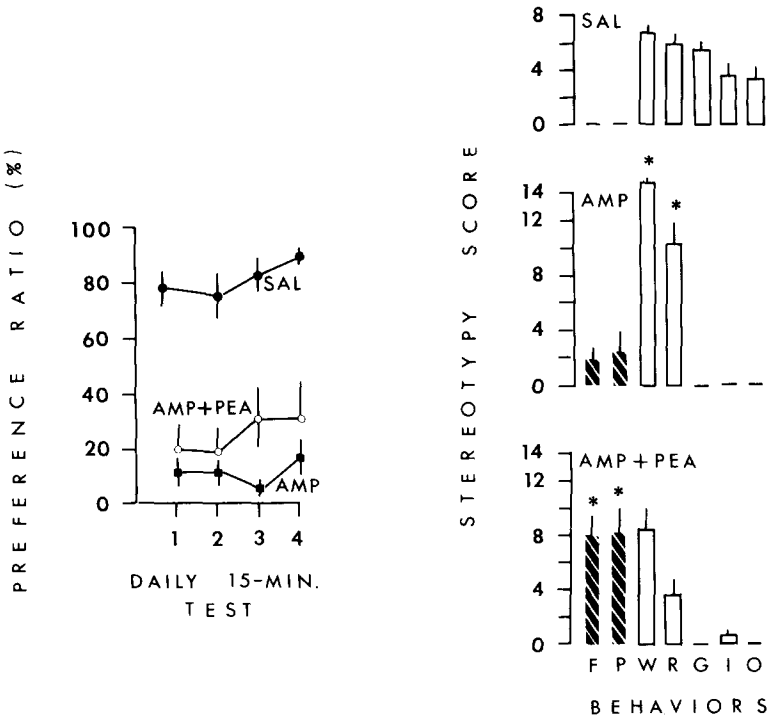

FIG. 1. (Left) Saccharin preference ratios (% of total intake which was 0.1% saccharin) over 4 consecutive tests days for rats given saline (SAL), amphetamine (AMP) or combined amphetamine-phenylethylamine (AMP + PEA) immediately after saccharin drinking on conditioning day. (Right) Stereotypy scores (periods out of 15 in which behaviors were observed) for these groups during 45 min after injection. Abbreviations are: F, forepaw padding; P, piloerection; W, walking; R, rearing; G, grooming; I, inactive; O, oral activity. Asterisks indicate scores significantly different from SAL group.

cm, constructed of plywood painted medium gray with a front panel of Plexiglas. Floors were covered with wood chips. Chambers were illuminated by a 15 W light bulb and were surrounded by a 5 cm layer of Styrofoam to attenuate sound. In the holding room and the test room temperature was maintained at 21±1°C. Lights were on for 14 hr/day.

Procedure

Rats were given 6, 15-min, training trials for drinking fluid selection on 6 consecutive days with the following order of drinking fluids, each mixed with demineralized water and paired with demineralized water: 1.0% NaCl, 0.5% KCl, 0.01% quinine HCl, water, water. Following each session in the drinking boxes, rats were returned to group cages where tap water was available for one hr. Food was always available in the home cage. After the 6 drinking box sessions, rats were maintained on a 22-hr deprivation schedule for 9 days with water bottles placed on the home cage for 2 hr/day.

On the CTA conditioning day, rats were placed in drinking boxes where only 0.1% sodium saccharin was available for 15 min. Immediately after drinking, rats were injected with one of these fluids: 0.9% NaCl (SAL); 2.4 mg/kg AMP; 55 mg/kg PEA + 2.4 mg/kg AMP. Drugs were mixed as salts in saline vehicle. AMP was a gift of Smith, Kline and French. PEA was obtained from Sigma. Injections were given IP, 1 ml/kg. Immediately after injection, rats were placed in individual observation cages for 45 min. Each rat was observed for 10 sec during each 3-min interval. Behaviors observed were recorded on a checklist.

Behavior categories were: *forepaw padding*, rhythmic lateral movement of forepaws usually right and left, but sometimes only in one direction; *walking*, normal locomotion; *rearing*, two forepaws lifted off the floor; *grooming*, licking and stroking fur; *inactive*, not exhibiting any other type of behavior; *oral activity*, biting while holding object (usually a wood chip) in forepaws, biting without forepaw involvement, and licking; and *piloerection*.

At the end of the 45-min period, rats were returned to home cages and food and water were given ad lib for two days. In order to measure degree of CTA rats were deprived of water and allowed to drink in the drinking box for 15 min each day, for 4 consecutive days, where they were given demineralized water and 0.1% saccharin. On return to the home cage they were given water for 60 min. Food was always available in the home cage.

RESULTS

The score for each behavior is the number of 3-min observation periods (out of the 15) in which that behavior was seen, sometimes accompanied by other behaviors. Scores for each type of behavior were analyzed in separate analyses of variance using a completely-randomized design to determine if scores differ as a function of injection—SAL, AMP or AMP + PEA. Post hoc comparisons were made with Tukey tests ($p<0.05$) [26]. As shown in Fig. 1, forepaw padding, $F(2,27)=14.91$, $p<0.0001$, and piloerection,

$F(2,27)=12.30$, $p<0.0002$, differed with injection, but were significantly different from the SAL group only following the AMP + PEA injection. Both walking, $F(2,27)=17.88$, $p<0.0001$, and rearing, $F(2,27)=8.04$, $p<0.002$, were affected by injection. The AMP injection increased behaviors compared to the SAL injection, but the AMP + PEA injection produced scores no different from the SAL group. Grooming, inactivity and oral activity were precluded by both the AMP injection and the AMP + PEA injection.

The preference ratio data were analyzed by a split-plot factorial design in order to determine the effect of consecutive test days and injection on the preference ratio [26]. Saccharin preference differed as a function of injection, $F(2,27)=37.97$, $p<0.0001$, but not as a function of test day (no extinction of the aversion occurred). The interaction was also not significant. Tukey tests performed by collapsing over test days showed that both AMP and AMP + PEA injections depressed preference scores relative to the SAL control group, but the two drug groups did not differ from each other; PEA did not interfere significantly with CTA formation.

EXPERIMENT 2

Experiment 1 showed that the powerful action of AMP to produce CTA was not significantly compromised by a dose of PEA high enough, when superimposed on the AMP dose, to introduce forepaw padding and piloerection and to reduce the AMP-induced increase in walking and rearing. In Experiment 2, a PEA treatment was given over a pharmacological pretreatment in an attempt to fashion the neurobehavioral action of PEA to make it more like that of AMP. Except for the short duration of action of PEA compared to AMP, there are very few neurobehavioral differences between the two analogues, however, oral activities—biting and licking—commonly seen after AMP injection [29] and apparently dependent upon dopamine activity in the basal ganglia [36] are not observed after PEA injection even when very high doses are given [29]. Mogilnicka and Braestrup [29] showed that when rats were pretreated with phenoxybenzamine, clonidine and FLA-63, drugs which interfered with noradrenergic transmission, oral activity was produced in PEA-injected rats. They suggested that even though both AMP and PEA have dopaminergic and noradrenergic action, in the case of PEA the noradrenergic component may dominate and inhibit oral activity. If this difference in behavioral action of the two analogues correlates with neural events which have an impact on CTA formation, then the pharmacologic shaping of the PEA action to make it more like that of the AMP action should improve PEA's ability to form CTA. Stereotypy immediately after the injection was monitored to verify that drug pretreatments were adequate in dose to alter behavioral response to PEA. Pilot studies showed that doses of drugs used in the taste aversion paradigm must be lower than those used by Mogilnicka and Braestrup in order to be safely combined with a PEA dose (both were injected into water deprived animals) and to be compatible with vigorous drinking of saccharin on the conditioning day. Consequently no oral activity was seen.

METHOD

Eighty naive Long Evans hooded rats, 40 males and 40 females, were used in the experiment. Each of the following treatment groups contained four males and four females. Gentling, housing, preference training, and the conditioning day procedure were the same as in Experiment 1, except that a pharmacologic pretreatment was injected 22 hr (immediately after water drinking) and $3\frac{1}{2}$ hr before saccharin drinking on the conditioning day. Drugs which were injected at these times were: clonidine (Boehringer Ingelheim) 0.15 (22 hr) and 0.15 mg/kg ($3\frac{1}{2}$ hr); phenoxybenzamine (Smith, Kline and French), 8 and 4 mg/kg; diethyldithiocarbamate (Fluka) 300 and 300 mg/kg; and 0.9% NaCl. The fifth group was given a single injection of p-chloroamphetamine (Sigma) 4 mg/kg, 72 hr before saccharin drinking in an attempt to manipulate brain serotonin. All injections were made IP in a volume of 2 ml/kg. Doses were calculated as salts and were mixed in a 0.9% NaCl vehicle. Immediately after drinking the 0.1% saccharin, rats were injected IP with either 65 mg/kg of PEA (in a SAL vehicle) or SAL (injection volume was 1 ml/kg) and were transferred immediately to the observation chambers where behavior was monitored for 45 min. Behavioral categories and preference testing procedure were the same as in Experiment 1.

RESULTS

The behavioral impact of the pharmacologic pretreatments was monitored in two ways: either by the action of these drugs in the groups injected with SAL on the conditioning day (action of drugs alone) or in those animals receiving PEA injections (interaction of pretreatment with PEA). Stereotypy scores within each behavioral category were analyzed with a completely-randomized model analysis of variance with Tukey tests used for post hoc testing [26] to see if behavioral frequencies for drug-pretreated groups differed from those of the SAL-pretreated group. Stereotypy scores are shown in Fig. 2.

For groups which were drug-pretreated and SAL-treated, type of drug pretreatment produced a significant action on walking, $F(4,35)=6.81$, $p<0.0004$, rearing, $F(4,35)=9.32$, $p<0.0001$, grooming, $F(4,35)=7.55$, $p<0.0002$, and inactivity, $F(4,35)=15.73$, $p<0.0001$. Walking was depressed from that of the SAL-pretreated group for rats pretreated with clonidine, diethyldithiocarbamate and phenoxybenzamine. Rearing and grooming were depressed and inactivity scores were increased in groups pretreated with clonidine or diethyldithiocarbamate.

For drug-pretreated and PEA-treated rats, the only category altered was piloerection, $F(4,35)=7.34$, $p<0.0002$; phenoxybenzamine completely blocked this response. The robust forepaw padding considered to be serotonergically mediated [16] was not altered by any of these drug pretreatments, not even by p-chloroamphetamine which was expected to reduce brain serotonin levels.

Saccharin preference ratios over four test days are shown in Fig. 3. A split-plot factorial analysis of variance model [26] was used within each drug pretreatment condition to determine effect of treatment (PEA or saline) and test days on preference. Statistical comparisons among the various drug pretreatment groups were not considered feasible because, in some cases, drug pretreatments influenced amount of saccharin consumed on the conditioning day, a condition which could bias the amount of aversion established. The PEA treatment lowered saccharin preference (produced CTA) in groups pretreated with SAL, $F(1,14)=19.82$, $p<0.0005$, clonidine, $F(1,14)=8.97$, $p<0.01$, and p-chloroamphetamine, $F(1,14)=4.61$, $p<0.05$. Saccharin preference was altered by test day for SAL-, $F(3,42)=8.60$, $p<0.0001$, and clonidine-, $F(3,42)=3.08$, $p<0.04$, pretreated animals. A significant day

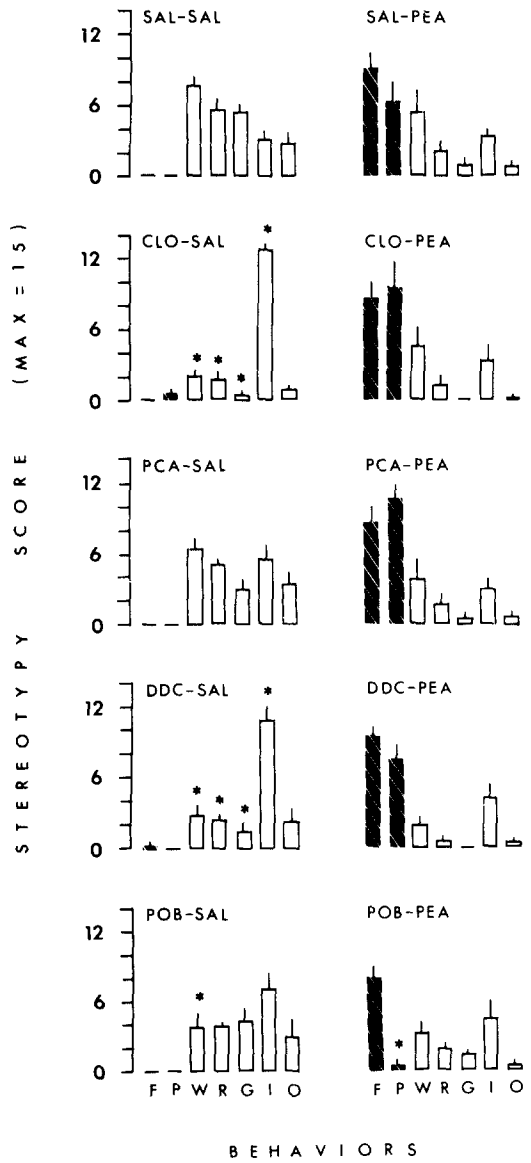

FIG. 2. Stereotypy scores for rats pretreated with various drugs and then treated with SAL (left) or PEA (right). Drug abbreviations are: clonidine (CLO), p-chloroamphetamine (PCA), diethyldithiocarbamate (DDC), and phenoxybenzamine (POB). Asterisks indicate scores significantly different from SAL-preinjected group.

× treatment interaction occurred only for the phenoxybenzamine-pretreated groups, $F(3,42)=3.43$, $p<0.03$.

EXPERIMENT 3

In this experiment, an attempt was made to establish PEA-induced CTA in mice. Rats and mice are the two most widely-used species in research on the neurobehavioral action of PEA [30]. PEA responsiveness varies with genotype in mice and was found to have 80% heritability [24].

METHOD

Animals

Forty-four female CD-1 mice bred in the laboratory from

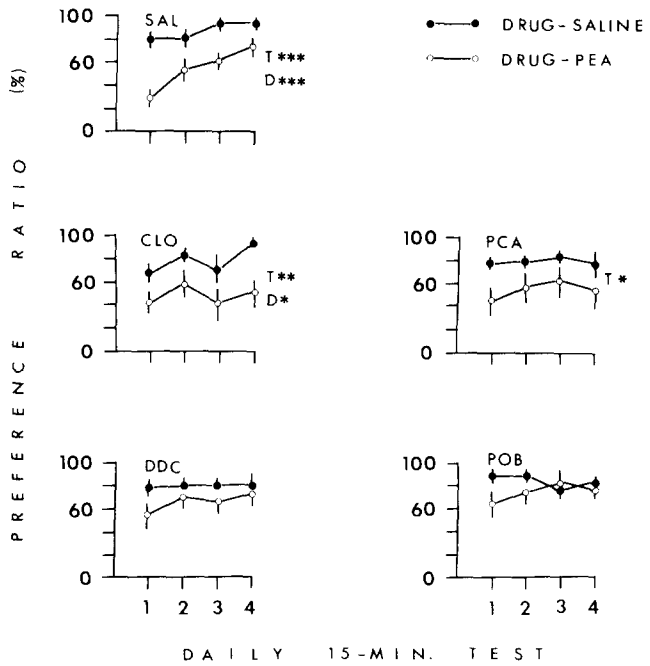

FIG. 3. Saccharin preference for preinjected rats on 4 consecutive test days after SAL or PEA injection. Asterisks indicate a significant difference for drug treatment (T) and test days (D). *=$p<0.05$; **=$p<0.01$; ***=$p<0.001$.

stock obtained from Charles River were used in the experiment. Mice were 95–115 days old at the beginning of the experiment and were housed in groups of 10–12 in plastic cages with stainless steel tops, 43×23×15 cm. Mice were maintained on Purina Chow and tap water. Lights were on for 14 hr/day.

Apparatus

Drinking boxes were 18×12×13 cm and were constructed of galvanized steel with wire mesh tops. Drinking fluids were given in 100 ml gas-measuring tubes with stainless steel sip tubes. Following PEA injection, behavior was observed in 20×14×26 cm Plexiglas chambers with glass floors covered with wood chips.

Procedure

For mice the best water-deprivation schedule, one which yielded vigorous drinking and minimized weight loss, was found to be 22–26 hr of water deprivation followed by 2–3 days of water ad lib. Twice each week mice were water deprived and placed in drinking boxes for 10 min. Each of these drinking fluids, mixed with demineralized water, was paired with demineralized water and was given in this order: water, 0.5% NaCl, 0.1% KCl, 1.0% NaCl, 0.5% KCl and 0.02% quinine HCl. Food was continuously available except in the drinking box. Water was available except where otherwise specified. Three or four days after the last training trial, mice were allowed to drink 0.5% sodium saccharin (mice accepted this higher concentration more readily than rats) and were injected immediately IP with 0, 25, 50 or 100 mg/kg PEA calculated as salt and given in an injection volume of 10 mg/kg in a 0.9% NaCl vehicle. Mice were placed into Plexiglas observation chambers for 60 min before they were re-

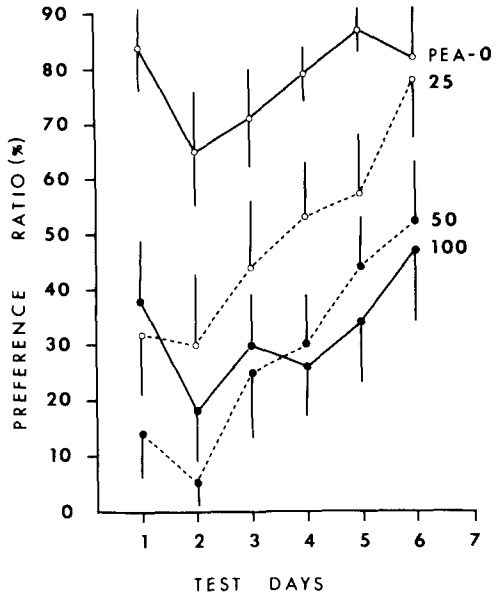

FIG. 4. Saccharin preference for mice on tests given twice each week. Mice were given SAL (open symbols, solid lines) or PEA doses (25, 50, or 100 mg/kg) immediately after saccharin drinking on the conditioning day.

turned to the home cage. Food and water were returned to the home cage two hr after the injection. Twenty-four hr after the injection, mice receiving 0 mg/kg PEA were injected with 100 mg/kg PEA and other groups were injected with the SAL vehicle. During 6 biweekly tests, mice were offered water and 0.5% saccharin and were allowed 10 min to drink.

RESULTS

Preference ratios were calculated (Fig. 4) and were subjected to the analysis of variance using a split-plot factorial model to determine the effect of injection and test days. Tukey tests were used for comparisons of group means [26]. Preference for saccharin differed as a function of PEA injection, $F(3,40)=9.39$, $p<0.001$, and test days, $F(5,200)=11.89$, $p<0.001$. There was no interaction. Mean preference ratios for each dose group (25, 50 or 100 mg/kg) collapsing over trials were significantly different from the control group (0 mg/kg), but were not different from each other; PEA produced clear CTA, but did not do so in a significant dose-dependent manner over the dosage range used here.

EXPERIMENT 4

Observations of behavior immediately following the PEA injection revealed that a few mice in the 100 mg/kg group had seizures. Because seizures may have an amnesic action [8] and thus interfere with the learning of the CTA, the impact of seizures on CTA in mice was examined.

METHOD

Forty-two female CD-1 mice, 95–110 days old at the start of the experiment were used. They were bred in the Behavioral Neuroscience Laboratory and were housed as previously described. The procedure used in Experiment 3 was repeated here except that immediately following the saccharin consumption on the conditioning day, 12 mice were injected with 0 mg/kg PEA, 14 received 125 mg/kg and 16 received 150 mg/kg PEA. The two doses were chosen because they were found by pilot studies to be slightly below or slighly above, respectively, seizure threshold. Immediately following injection, mice were observed for 60 min in the observation chambers and every incidence of seizure was recorded. Mice were then transferred to the home cage. Two hr after injection, food and water were returned. There was no second injection on the following day. Six biweekly test sessions were run with 0.5% saccharin and water presented.

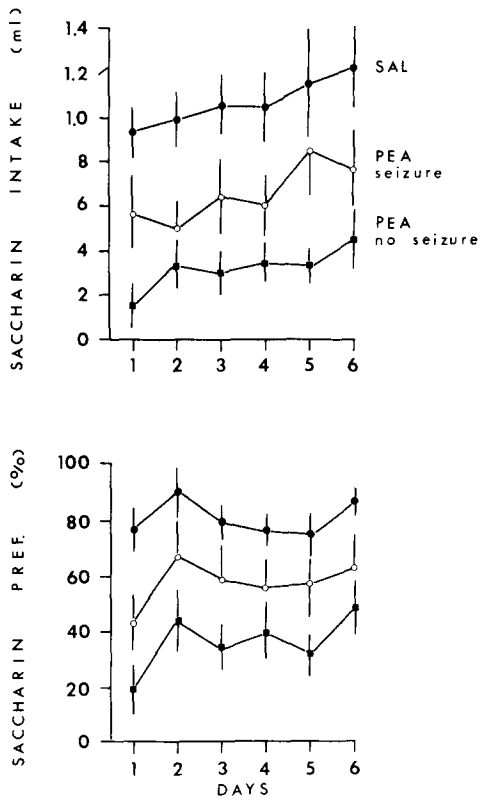

FIG. 5. Saccharin intakes and saccharin preference for mice injected with SAL or PEA. The latter group is divided on the basis of seizure incidence.

RESULTS

Figure 5 shows saccharin intake (ml) and saccharin preference (%). Clearly, the pattern of outcome was the same for both measures. The statistical outcomes were congruous. PEA-injected mice were grouped on the basis of seizure incidence. Of the PEA-injected mice, 15 had seizures and survived; 12 did not have seizures. Three mice were randomly eliminated from the former group in order to equalize group size. Saccharin intake (ml) varied with group: SAL, PEA—Seizure, PEA—No Seizure, $F(2,23)=11.83$, $p<0.0001$, and with test day, $F(10,165)=2.68$, $p<0.03$, but there was no interaction. Saccharin preference also varied with group, $F(2,33)=9.42$, $p<0.006$, and with test day, $F(5,165)=3.54$, $p<0.005$, but there was no interaction. Post hoc tests on both sets of data collapsing over test days showed that all treatment groups differed from each other, indicating that (as seen in both consummatory measures) the presence of seizures reduced the level of CTA formed by PEA, but did not prevent it from occurring.

DISCUSSION

It was previously reported [17,18] that, even though PEA produces many of the same neurobehavioral actions produced by AMP [1, 6, 10, 11, 22, 28, 30], only AMP supported CTA formation in rats even though a wide dosage range was used (12.5 to 100 mg/kg) including a near lethal dose [17]. (Mice were more tolerant of PEA and could withstand doses of 150 mg/kg in Experiment 4.) Vigorous stereotypy induced by PEA indicated that doses used were adequate to have a strong CNS action in rats [17,18]. By contrast, the findings reported above (Experiment 3 and 4) show that strong CTA was established in mice even in those in which PEA elicited multiple seizures. Also, using a different stock of rats and a different procedure than Greenshaw and Dourish [17,18], CTA was established under three different conditions of drug pretreatment (Experiment 2). There are procedural differences between the present study and the Greenshaw and Dourish study [17] which may influence the results obtained. The present study utilized more extensive pretraining in a 2-tube taste discrimination test, more time to adapt to the water deprivation schedule, a longer access to drinking fluids each day (less stringent water-deprivation schedule), two preinjections (drug pretreatment), and a different strain of animals (Syracuse University strain vs. Wistar strain) with differences in body weight (300–500 g for the Syracuse strain vs. 200–250 g for the Wistar strain). Rats in the Syracuse stock tend to accumulate fat throughout life. Drug doses calculated on body weight of obese rats are probably higher in relation to lean body weight (metabolically active tissue) than those calculated on weight of leaner animals. It should be noted, however, that the preference ratios for the SAL-preinjected rats injected with PEA are similar to those observed by Greenshaw and Dourish [17] in that weak aversion was seen on the first day, but subsequent test days showed rapid extinction.

A comparison of the magnitude of CTA attained in Experiment 1 using AMP to that attained in Experiment 2 with PEA suggests that even though PEA produced CTA, it was much less effective since AMP produced very low preference ratios (below 20) and no extinction during the 4 test days. It was previously shown that AMP induced CTA in rats in doses as low as 0.05 mg/animal [27].

A possible species difference in the efficacy of PEA to produce CTA is suggested by results in mice (Experiment 3, 4) in which PEA was seen to be a stronger elicitor of CTA in mice as indicated by two outcomes: (1) Significant CTA was formed with the lowest PEA dose used, 25 mg/kg of PEA, and this aversion was not significantly different from that produced by 50 or 100 mg/kg doses; (2) CTA was attenuated by PEA-induced seizures, but was not prevented by them even in cases when multiple seizures occurred during the observation period. It is well known that seizures induced either chemically or electrically can produce amnesia [7] depending upon the time interval between learning event and seizure and depending upon the type of learning. CTA learning may be different from other types of learning, however, because, when an effective US is used, CTA can be established even though altered states of CNS function are introduced into the CS-US interval or following presentation of the US. In studies using rats drinking saccharin (CS) and then injected with LiCl (US) spreading cortical depression induced by LiCl on the cortex initiated 5 min after LiCl injection did not prevent CTA formation [4], suggesting either rapid action of the memorial processes or limited participation of the cortex in this type of learning. CTA also occurred when cortical spreading depression [3], electroconvulsive shock [33] and general anesthesia [38] were introduced into the CS-US interval. In the case of general anesthesia the length of the CS-US interval over which CTA learning was possible was greatly extended by the anesthesia. Given this context, the failure of multiple PEA-induced seizures to prevent CTA formation in mice (Experiment 4) is not unusual, but only attests that PEA is an effective US in this species.

Seligman [39] has argued that all potential stimuli and responses are not equipotential in conditioning experiments, but organisms come to a learning situation with biological constraints which predispose them toward certain types of associations. The potency of PEA to support CTA may also vary with species or perhaps stock of animals, an hypothesis strengthened by the importance of genotype on PEA responsiveness in mice [24]. It is clear that PEA does not produce sequalae with amnesic actions when a moderate AMP dose was used as the US (Experiment 1). Also tailoring PEA action to make it more like AMP action either by suppressing noradrenergic function [29] (Experiment 2) or by extending duration of drug action [17] did not improve efficacy for CTA formation.

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