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Potentiation of Odor by Taste and Odor Aversions in Rats are Regulated by Cholinergic Activity of Dorsal Hippocampus

FEDERICO BERMÚDEZ-RATTONI,* KERRY LEE COBURN,† JUAN FERNÁNDEZ,* A. FRANCISCO CHÁVEZ† AND JOHN GARCIA†

**Instituto de Fisiología Celular, Universidad Nacional Autónoma de México Apartado Postal 70-600, México, D.F. México 04510 and †Department of Psychology and the Mental Retardation Research Center University of California at Los Angeles, Los Angeles, CA 90024*

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BERMÚDEZ-RATTONI, F , K L COBURN, J FERNÁNDEZ, A F CHÁVEZ AND J GARCIA *Potentiation of odor by taste and odor aversions in rats are regulated by cholinergic activity of dorsal hippocampus* PHARMACOL BIOCHEM BEHAV **26**(3) 553–559, 1987 —Limbic cholinergic activity is critically involved in the retention of learned aversions tasks The purpose of these experiments was to assess the role of cholinergic mechanisms of the dorsal hippocampus in the acquisition of both odor and potentiated odor aversions through taste aversion Cholinergic activity was increased by physostigmine (Phys) When Phys was applied before the presentation of an odor-taste compound during acquisition, the potentiation of odor-aversion was disrupted, while taste aversion was left intact When hippocampal cholinergic activity was reduced with the muscarinic antagonist scopolamine (Scop), enhancement of potentiated odor aversion was observed, again with no effect on taste aversion Moreover, when Phys was applied before an odor alone it also disrupted odor avoidance in two different odor tests conditioning situations, i e , odor was followed immediately by lithium chloride or foot shock Neither Scop nor Phys had any effect on taste or potential odor aversions when applied to fronto-parietal cortex These results suggest that cholinergic activity of the hippocampus is involved in the acquisition of odor aversion conditioning

Conditioned taste aversions Odor Taste Aversive conditioning Cholinergic activity Limbic system Hippocampus Parietal cortex

PREVIOUS results have shown that odor and taste play different temporal roles in toxiphobic conditioning. The temporal gradient for odor is steep, odor must be followed immediately by poison to produce strong odor-aversion learning. The temporal gradient for taste, on the other hand, is shallow, strong taste aversions may be conditioned even when poison administration is delayed several hours. When odor and taste are combined to produce a compound ("flavor") CS, the conditionability of the odor component changes markedly, switching from the steep gradient characteristic of odor alone to the shallow gradient characteristic of taste alone. This "potentiation" of odor by taste is a robust phenomenon [26,29], depending critically on the temporal contiguity between the odor and taste CS components at acquisition [6]

In the presence of taste, odor information appears to be selectively gated out of an external defense system (characterized by steep temporal gradients and preferential place-avoidance learning) and into an internal defense system (characterized by shallow temporal gradients and preferential taste-avoidance learning). Presumably such an internal defense system integrates information from olfactory, gustatory, and visceral sources to mediate taste-potentiated odor aversions [11,12]

Anatomical studies indicate that a convergence of olfactory, gustatory and visceral information is to be expected at a number of loci within the CNS. For example, the ascending gustatory system carries with it visceral information. The nucleus solitarius (the first gustatory relay) receives heavy visceral input from the hepatic branch of the vagus (sensitive to stomach irritating toxins) as well as input from the area postrema (sensitive to blood-borne toxins) and the vestibular system (sensitive to nausea-inducing motion). Neurons responding to both gustatory and visceral stimuli are found in the pontine taste area of the parabrachial complex (second gustatory relay), these neurons project to the limbic system [12].

Olfactory input reaches the amygdala from the accessory olfactory bulbar formation and olfactory cortex, and the amygdala thus appears to receive the three modality inputs necessary for the mediation of taste-potentiated odor-illness conditioning [11,12] Initial work in our laboratories indi-

cated that lesions restricted to the lateral portions of the amygdaloid complex impair the potentiation of odor by taste [12] Later work using local microinjections of novocaine to produce "reversible lesions" revealed that local anesthesia of the dorsolateral region of the amygdala preferentially suppresses the potentiation of odor by taste, while leaving odor-shock and taste-illness learning intact [4]

Moreover, another limbic structure that receives olfactory inputs through the entorhinal cortex is the dorsal hippocampus [17] This limbic structure has long been implicated in integrative processes such as learning and memory [24,25]. However, some studies have failed to find deficits on the acquisition of taste aversions with hippocampal lesions [22,23] Nevertheless, it has recently been reported that hippocampal lesions produce a significant disruption of neophobia, and odor and taste aversion conditioning [2,23] In the latter study large bilateral electrolytic hippocampal lesion were made in rats The animals were exposed to an odor conditioned stimulus or a compound odor-taste CS followed by LiCl The results showed that the lesioned animals did not acquire the odor or the potentiated odor by taste aversion learning [23]

It is well known that there is a high content of acetylcholine in the hippocampus [19,30] and Douglas [8] has shown that the hippocampal cholinergic activity is strongly involved in the acquisition of conditioned alternation behavior The purpose of the present series of experiments was to determine if the hippocampal cholinergic activity is involved in the potentiation of odor by taste aversions

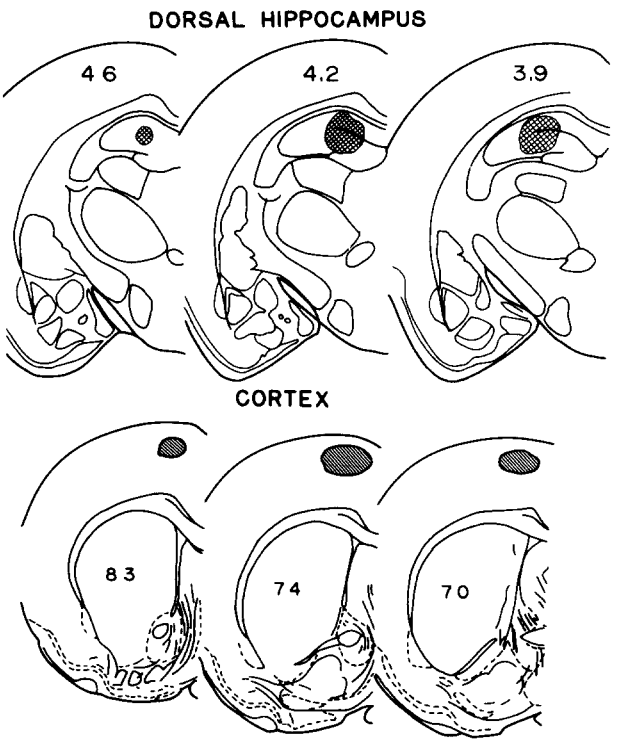

FIG 1 Diagramatic representation of histology sections The stippled areas represent the range of cannula tip locations taken from 69 rats of the dorsal hippocampus (Experiments 1, 2 and 3 above), and 24 of the cortical group of Experiment 4 (below) Only cannula placements of the right hemisphere are represented

GENERAL METHOD

Subjects

Subjects were male Sprague-Dawley albino rats, weighing 250–350 g at the beginning of the experiments Subjects were individually housed under standard laboratory conditions with ad lib food. Drinking was restricted to a 5 minute period in the experimental apparatus, and 10 minutes of supplemental home-cage water

Procedure

Training and testing for all experiments were carried out in 20×23×25 cm clear plastic drinkometer boxes with floors composed of two metal plates. A hole (1 cm dia.) provided access to a stainless steel drinking spout fitted with an "odor disc" and connected to an electronic contact sensor (Grason Stadler, E4690). The drinking boxes were kept in sound attenuated chambers, each equipped with a 7 5-watt wall light and a speaker for white masking noise. The total number of licks were recorded daily as a baseline consumption measure [26,28]

Prior to surgery, rats were habituated to the drinkometer boxes for 9–10 days where they received access to water during a daily 5 min session, a 10 min supplement of home-cage water was given 2 hr later. Animals were anesthetized with pentobarbital (Nembutal, 50 mg/kg, IP) and implanted bilaterally with double-walled cannulae (hypodermic needle tubing of 31 and 25-ga) aimed at the dorsal hippocampus via stereotaxic coordinates A-P −3 3 from bregma, L ±2.0, H −3 2 from skull level [16] Subjects were allowed to recover for 7 days on ad lib food and water Water deprivation was then reinstated and subjects were habituated to being handled and restrained in holding cages for 3 min prior to drinking One acquisition trial and six testing trials were conducted every fourth day with baseline access to distilled water on the intervening days Immediately prior to acquisition, the animals were restrained while receiving 3 μl of saline, scopolamine, or physostigmine infused at a speed of 2 μl/min, in each brain side The infusion needle protruded 0 5 mm beyond the guide cannula tip Acquisition involved presentation of an odor and/or taste CS during the trial followed by intragastric infusion of 0 15 M LiCl (190 mg/kg) 30 min later The odor CS was 0 2 ml of almond extract (Schilling) on the "odor-disc", the taste CS was 0 1% sodium saccharin dissolved in distilled water presented in the drinking spout Three days after acquisition all subjects were tested with the taste component alone or odor component alone in three extinction trials for each component The odor or taste was tested every fourth day in alternation, test odor being counterbalanced within groups Simple ANOVA was done on percentage from previous day baseline for each extinction trial of number of licks during the 5 min trial with post hoc group comparisons where appropriate using the Sheffe test

Histology

After completion of the experiment, all animals were deeply anesthetized with barbiturate and perfused intracardially with isotonic saline followed by 10% formalin The brains were then removed and stored in formalin before being embedded in gelatin, sectioned coronally every 60 μm, Nissl stained, and examined microscopically to verify cannulae placement

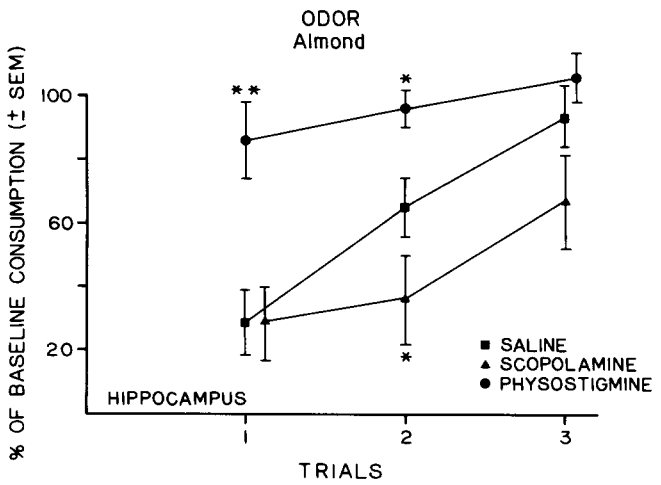

FIG 2 Results of Experiment 1 Water consumption in the presence of odor alone is shown The physostigmine group showed significantly reduced odor aversion, as compared to the saline control group The scopolamine group had significantly enhanced odor aversions in the second extinction day $^{**}p<0.01$, $^{*}p<0.05$

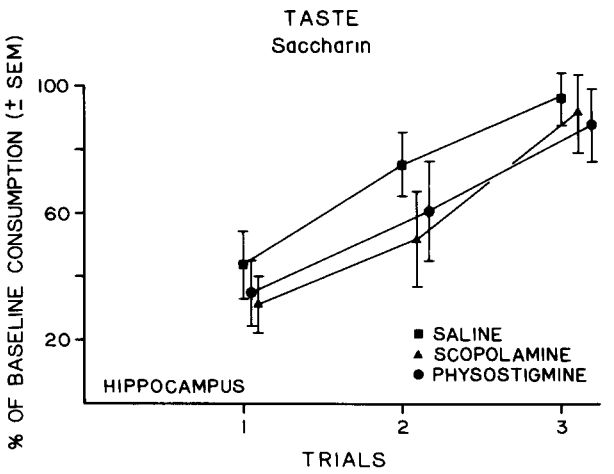

FIG 3 Results of Experiment 1 Consumption of saccharin solution on taste alone is shown for each of the extinction tests No statistically significant differences were found among the groups

EXPERIMENT 1

In order to assess the role of dorsal hippocampus cholinergic mechanisms in the formation of potentiated odor aversions, bilateral cannula were implanted During acquisition, three groups of subjects were given a single 5 min exposure to the odor-taste (OT) compound followed 30 min later by LiCl One group (Scop; n=9) was given scopolamine (10 μg/ml) 15 min prior to the presentation of the odor-taste compound, a second group (Phys, n=9) received physostigmine (3 μg/μl) 30 min prior to the compound CS A third group (Sal, n=9) received isotonic saline 15 min prior to the compound CS, the differences in time injections were selected from our own pilot studies and experience (see [1])

Results and Discussion

From the histological inspection of the dorsal hippocampus groups, most of the infusion needle tips were located in the dentate region (Fig 1). However, in three subjects the needle tips were more anterior and lateral, directly above the lateral ventricles One of these animals received scopolamine and the other two received physostigmine Inspection of the individual responses indicated that these animals were not particularly different from the mean of the control group in the odor or taste tests, thus, these animals were not included in the analysis of the data

Figure 2 shows the effects of the treatments on the odor component Simple ANOVA comparing scores of each group on extinction tests 1 and 2 showed reliable group differences, $F's(2,23)>7.0$, $p's<0.005$. The group receiving physostigmine showed a reliable disruption of odor aversion both on test day 1 ($p<0.01$) and on test day 2 ($p<0.05$) when compared to the saline control group The Phys group showed extinction to the level of water baseline on day 3 The group receiving scopolamine showed the opposite effect, i e , it significantly enhanced potentiated odor aversion on day 2 with ($p<0.05$) and showed no significant differences with the saline group during the first and the third extinction days

Figure 3 shows the extinction curve of taste aversion for the three groups. Inspection of the curve shows a strong taste aversion for all the groups. However all groups were homogenous and did not present any significant differences along the three extinction days, $F's(2,23)<0.97$ $p's>0.50$.

The cholinergic manipulation of the hippocampus affected the potentiation of odor by taste. The saline control subjects formed the expected potentiated odor aversion, which extinguished over repeated tests Enhancement of hippocampal cholinergic activity by physostigmine prior to acquisition produced a marked attenuation of odor potentiation, but essentially normal extinction. Blockade of hippocampal cholinergic activity with scopolamine produced no effect on odor potentiation on the first day of testing, but significantly retarded extinction during the second test day.

While hippocampal cholinergic manipulation greatly affected potentiated odor aversions, it was without effect on simultaneously conditioned taste aversions. Drugged and saline control subjects showed strong taste aversions on the first day of testing which extinguished over subsequent test days

EXPERIMENT 2

Procedure

From the results of Experiment 1, it can be concluded that the physostigmine significantly disrupted the odor aversion and left unaffected the taste aversion, while the scopolamine produced enhanced potentiated odor aversions Therefore, it is possible that a direct odor-illness process could be affected in the same fashion by the cholinergic agents used in Experiment 1 We tested the same agents with a direct odor-illness procedure Since odor-illness conditioning does not tolerate delays, it was necessary to use odor alone followed immediately by poison [4,28]. Each of three groups of rats were infused with physostigmine (Phys, n=6), scopolamine (Scop; n=6), or physiological saline (Sal, n=8), before the almond-extract odor exposure The temporal parameters for microinjections were similar to those of Experiment 1 An intragastric load of LiCl (190 mg/kg, 0.15 m) was delivered 1 min after the odor trial.

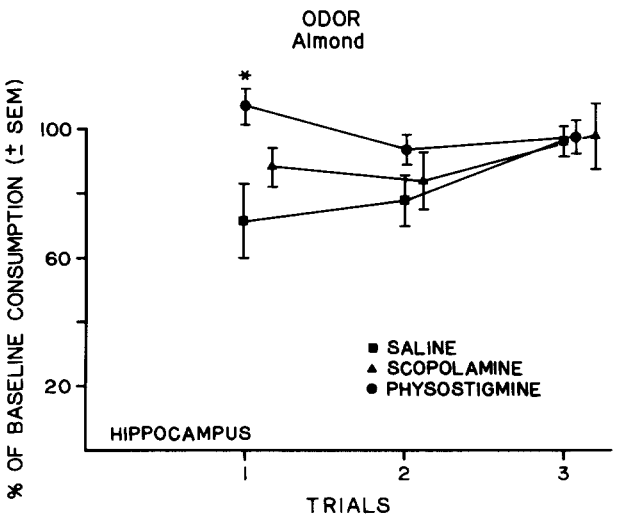

FIG 4 Results of Experiment 2 Water consumption in the presence of odor alone is shown After odor-LiCl conditioning The physostigmine group significantly reduced the odor aversion *$p<0$ 05

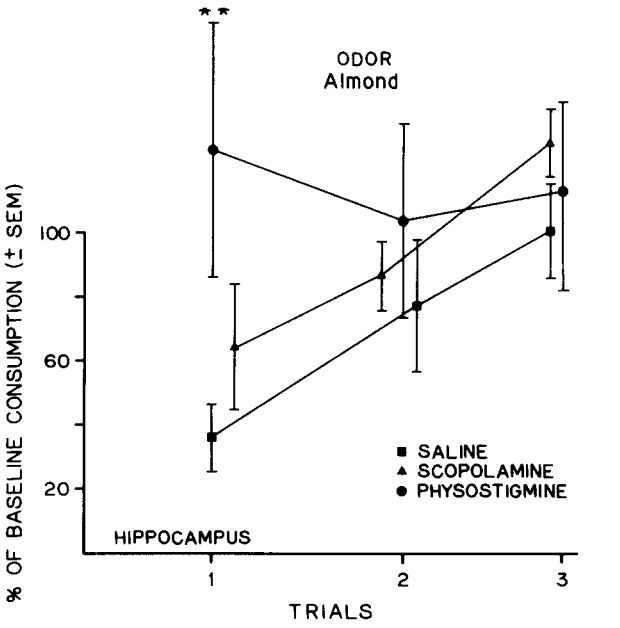

FIG 5 Results of Experiment 3 After odor-shock conditioning Group physostigmine significantly reduced the odor aversion **$p<0$ 01

Three repeated extinction tests to odor were then given All other procedures, including dosage and volume of injections, were the same as in Experiment 1

Results and Discussion

As shown in Fig. 4, the group that received saline showed a slight aversion to the odor in the first test day, and extinguished very fast during the second and third test days As mentioned in the Introduction, it is difficult to produce strong direct odor illness conditioning. Nevertheless there were significant group differences during the first test day, $F(2,19)=3$ 64, $p<0.05$ The physostigmine microinjection significantly disrupted the direct odor aversion only during the first extinction day. The three groups did not differ from each other on the second and the third test days, F's$(2,19)<1.90$, p's>0.20

EXPERIMENT 3

Despite the fact that there was a weak direct odor aversion conditioning, the microinjection of physostigmine significantly reduced the acquisition of odor aversion This result is in agreement with those found in Experiment 1 However, we were unable to find any clear scopolamine effects on direct odor-illness

These results suggested that odor-illness processes were affected specifically by increases of the cholinergic activity in the hippocampus Consequently, it is possible that cholinergic agents may affect all of the conditioned procedures where the odor is used as a CS

Therefore, the third experiment tested the effect of physostigmine, scopolamine and saline upon direct odor-foot shock conditioning. Three groups received the same odor used in Experiments 1 and 2 followed immediately by foot shock on one acquisition trial inhibitory avoidance. The groups received physostigmine (Phys, n=7), scopolamine (Scop, n=7), or physiological saline (Sal, n=11) as was described in Experiments 1 and 2.

Training and testing procedures were modified for shock avoidance as follows. All animals were given 5 daily trials of habituation of 5 min each, followed by another 5 daily habituation trials of 1 min each. This schedule was followed by cannula implantation, a period of recovery (7 days) and rehabituation to the drinking schedule (10 days), then, all groups received one odor-shock acquisition trial On the acquisition trial, the almond extract was presented for one minute on the odor disk with distilled water on the spout, a 1 mA, 1 sec foot shock terminated the trial. During the next five days water was presented until consumption reached the previous (habituation) base line Subsequently, odor trial presentations were given for one minute, the sequence of presentations being similar to those previously described in Experiment 2 Three Phys and two Scop animals became either ill or the cannulae caps were dislodged. These animals were eliminated from the experiment

Results

Figure 5 shows the percentage from each previous day base line of number of licks across three odor-test trials.

The analyses of variance showed that there were significant differences among the groups during the first odor test trial, $F(2,19)=4$ 83, $p<0$ 05 and there were no significant differences during the last two odor-test trials, F's$(2,19)<0.90$. Inspection of Fig 5 shows that the saline and scopolamine groups showed a reduced consumption of water during the first odor-test trial. The aversion extinguished during the second and third odor-test trials However, the Phys group did not show any odor aversion during the first day as compared with the control group ($p<0.01$) The Phys group did not reduce the consumption of water in presence of odor in any of the three odor tests presentations.

As stated above, the significant difference in water intake with the control group shown by the Phys group disappeared

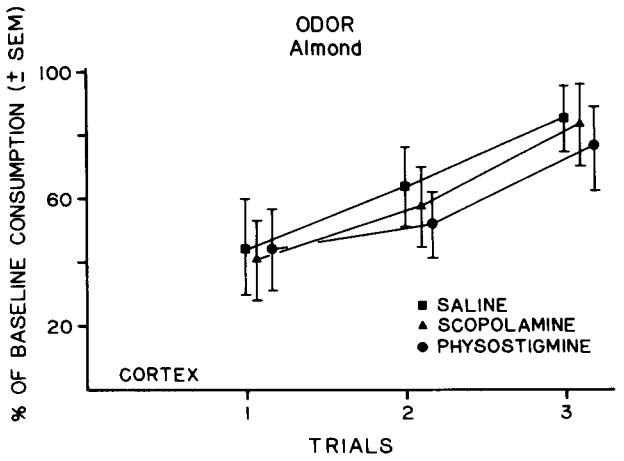

FIG 6 Results of Experiment 4 Water consumption in the presence of odor alone is shown No statistically significant differences were found among groups

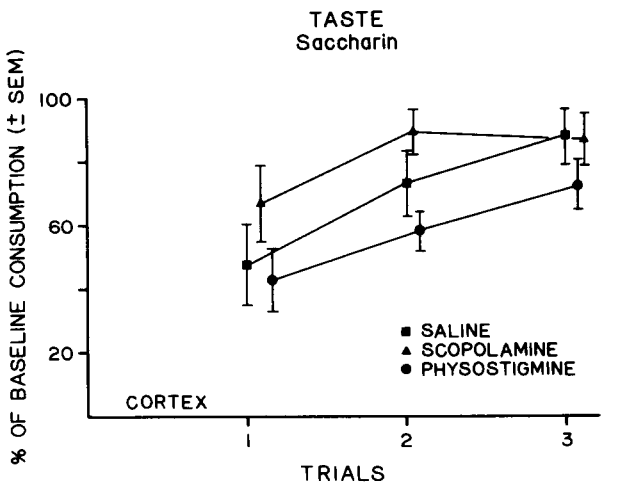

FIG 7 Results of Experiment 4 Consumption of saccharin solution on taste alone is shown Statistically significant differences were found only in the second day (see text)

by the second test trial. This lack of difference may be due to the variance characteristic of one-trial shock avoidance performance. With odor-foot shock conditioning we were unable to detect any reliable scopolamine effect Nevertheless, the effect of the microinjection of physostigmine into the hippocampus corroborates the disruptive effects upon the aversive conditioning when odor is used as a CS

EXPERIMENT 4

Results from the first experiment indicate a relationship between cholinergic activity of the hippocampus and the formation of potentiated odor and odor aversions However, it is possible that drinking performance may be affected by nonspecific (e g , motor) drug effects. However, the deep infusion sites and small drug volumes used in the first experiment make it unlikely that the results were due to diffusion of the drugs to the cortex or to other remote sites. Nevertheless, we addressed this question directly in a fourth experiment in which infusions were made into the fronto-parietal motor cortex

Procedure

The procedures for this experiment were the same as those for Experiments 1 and 2 Each of three groups of rats received microinjections of physostigmine (Phys, n=9), scopolamine (Scop, n=9), or saline (Sal, n=6) into the fronto-parietal cortex prior to acquisition (stereotaxic coordinates A-P, 0 0 mm from bregma, L, ±3 0 mm from midline, D-V, −1.5 mm from skull [16]

Results and Discussion

For the cortical group, the infusion needle tips were in the frontal-parietal cortex, always dorsal to the corpus callosum, and 8.2 to 9.2 mm anterior to the interaural plane (see Fig. 1).

In Fig. 6 the data from three days of odor extinction are presented No significant differences among the groups were found during the three extinction days, F's(2,23)<1.0. In Fig. 7 data from the three extinction days with taste as the conditioned stimulus are shown. All groups showed strong taste aversions and no significant differences were found among groups during the first and third test days, F's(2,23)<1.00. However during the second day there was a significant difference, $F(2,23)=6.56$, $p<0.0079$. Pair wise comparisons between the Phys and Scop groups showed a significant difference ($p<0.01$) However, none of them was significantly different from the control group. All the groups extinguished to baseline during the third extinction trial.

GENERAL DISCUSSION

For some time it has been evident that cholinergic mechanisms are involved in memory or associative processes [24, 25, 27]. Thus, when cholinergic activity is reduced with muscarinic antagonists of acetylcholine such as atropine or scopolamine, and exteronociceptive stimuli such as foot shocks are used, memory-like processes are disrupted. For example Deutsch [7] found impairment on a passive avoidance task when IP or intraventricular injections of atropine were delivered shortly before the acquisition trial, but not when the injections were made after the acquisition trial. Using interonociceptive stimuli in a taste aversion paradigm, however, cholinergic antagonists failed to disrupt conditioning when given immediately prior to the UCS Disruption of the conditioned taste aversions was seen only when the cholinergic drug was given immediately prior to the test trial [7, 10, 18].

Contradictory results have been reported when cholinergic activity is increased through the use of agonists of acetylcholine or antagonists of acetylcholinesterase. Goddard [13] found that the cholinergic agonist carbachol impaired passive avoidance but not active avoidance. Todd and Kesner [31] found that when physostigmine or carbachol were applied into the amygdala the retention of a passive avoidance task was impaired, but when the same drugs were applied to the hippocampus no impairment was produced Consistent results have been found when physostigmine is applied to the amygdala at the onset of apomorphine induced aversion to grape juice The results showed a significant disruption of the learned taste aversion [9]. Moreover, a previous experiment in our laboratories indicated that physostigmine infused into the amygdala before acquisition of

compound saccharin/almond produces a significant reduction of potentiated odor aversion, but leaves the taste aversion unalterated [1]. The same pattern of results was found when infusions of physostigmine were made into the hippocampus before acquisition using the OT compound. a reliable decrease of potentiated odor aversion (Experiment 1, Fig 1) with no effect on taste aversion (Fig 2)

From the results presented in Experiments 1 and 2, it can be seen that microinjections of physostigmine into the dorsal hippocampus produce disruptive effects on odor and potentiated odor aversions These results are in agreement with those found by Miller *et al* with electrolytical hippocampal lesions [23]. Furthermore, results from Experiment 3 showed that cholinergic activity of the hippocampus is involved in the acquisition of odor-shock conditioning. On the other hand, the lack of effects of cholinergic drugs on taste aversions when applied in to the dorsal hippocampus (Experiment 1) are at variance with those found by Ellins and Kesner [9] (see above). However, it should be kept in mind that these authors used different conditioning procedures.

The enhancement of potentiated odor aversion in the group that received the microinjections of scopolamine (Experiment 1) was not replicated when odor was followed immediately by illness (Experiment 2) or with the use of a exteronociceptive foot-shock conditioning (Experiment 3). It has been reported that smaller doses of scopolamine applied into the hippocampus did not produce any disruptive effect on passive avoidance However, when the same drug is applied into the striatum, disruptive effects occur in passive avoidance [14]. Therefore, it is necessary to make a dose-response curve with scopolamine to clarify the effects of cholinergic antagonist drugs on odor aversions conditioning

Recently, it has been postulated (see the Introduction) that odors can be associated either with the external or the internal defense systems, depending on the stimulus context In the presence of taste, odor information appears to be selectively gated out of the external defense system and into the internal defense system, where it takes on parametric properties of taste [6, 11, 12, 28, 29] The anatomical localization of neurons performing gating and potentiating functions has been found in studies employing lesions in the gustatory neocortex [15,20] The magnitude of the disruptions on taste and odor functions depended on the lesion place. Kiefer, Rusiniak and Garcia [15] found that lesions in the dorsal somatic region of the anterior insular gustatory neocortex disrupted taste aversions but spared taste-potentiation of odor. Lasiter, Deems and Garcia [20] demonstrated that lesions in the ventral insular region disrupted both taste aversions and potentiated odor aversions

In this regard, within the limbic system, it has been demonstrated that lesions of the anterodorsal but not the posteroventral hippocampus produced disruption of conditioned taste aversions [5]. However, in a similar experiment, but using x-rays as an unconditioned stimulus, the results showed a lack of effect on the acquisition of taste aversions after dorsal hippocampal lesions. On the other hand, the same authors found substantial impairments on the same aversive conditioning with large amygdaloid lesions [21] Recently, it has been reported that selective electrolytical lesions of the lateral or basolateral nuclei disrupted the potentiated odor aversion but left intact the development of taste aversion after one trial of OT-toxin association [3]. The same was found in a previous study in which it was demonstrated that novocaine applied to the amygdala before acquisition had a selective effect on odor-toxin associations but not on taste-toxin or odor-shock avoidance [4] In contrast, large electrolytical amygdala lesions disrupted the acquisition of T, O and OT-illness associations [3] These results suggest that the limbic system is not a unitary structure regarding its involvement in the acquisition of odor, taste and potentiated odor by taste aversion learning. Nevertheless, the disruption of odor aversions (Experiments 1, 2 and 3) appear to be specific consequences of cholinergic alteration within limbic structures, since infusion of the same drugs into parietal cortex in Experiment 4 produced no changes in taste aversion or potentiated odor aversion

The limbic pharmacological manipulations reported here and elsewhere [1,4] have little or no effect on taste-illness associations but a significant effect on odor-illness and odor-shock associations Moreover, it appears that cholinergic activity of dorsal hippocampus is related to the potentiation of odor by taste, and to acquired odor aversion learning The present series of studies give further support to possible cholinergic mechanisms in limbic structures involved in the acquisition of odor aversion learning

ACKNOWLEDGEMENTS

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