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Effects of Olfactory Bulb Section on Brain Noradrenaline, Corticosterone and Conditioning in the Rat[1]

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KING, M. G. AND K. D. CAIRNCROSS. *Effects of olfactory bulb section on brain noradrenaline, corticosterone and conditioning in the rat.* PHARMAC. BIOCHEM. BEHAV. 2(3) 347–353, 1974. – Following bilateral olfactory bulb section or sham surgery, rats were subjected to a complete counterbalanced design in which appetitive and aversive conditioning were tested. Olfactory bulb section produced no appreciable effect on a food rewarded bar press response. However, a performance deficit was apparent when animals were subjected to prior fear conditioning and tested with the CS alone. On the basis of these results, rats following olfactory bulb section were subjected to prior fear conditioning and tested on avoidance learning. Anosmia produced no appreciable effect on number of avoidances, but anosmic fear conditioned rats responded more slowly than sham-operated fear conditioned rats. In order to evaluate these findings physiologically, assays were undertaken for telencephalic and hypothalamic noradrenaline (NA) and plasma corticosterone. There was no significant difference in hypothalamic NA and corticosterone between the anosmic and sham-operated rats. However, telencephalic NA was significantly lower in anosmic animals.

Anosmia Conditioning Corticosterone Noradrenaline

MARKS, Remley, Seago and Hastings [16] reported that rats rendered anosmic following bilateral olfactory bulbectomy were superior in performance compared to controls on a positively reinforced operant response but showed inferior performance on avoidance tasks, both active and passive, and on an activity task. Though unable to account for all their findings they suggested that afferent input from the olfactory to the limbic system is necessary for the integration of sensory information involved in rodent learning.

Previous studies of appetitive learning in anosmic rats [12, 15, 22] have shown that only the early stages of learning are impaired. Prior to the studies by Cairncross and King [6] and by Marks *et al.* [16] aversive learning in anosmic rats had not been discussed in the literature although recent studies [14] have indicated that odor may play an important part in aversive learning in normal rats. The initial aim of the present studies was to determine whether, following bilateral olfactory bulb section, the acquisition of an appetitive and an aversive task was inferior to that of sham-operated controls.

It was proposed to examine concomitantly the changes in physiological function accompanying the behavioural alterations anticipated. Thus, recent studies by Weiss *et al.* [23] indicate that whole brain noradrenaline (NA) is significantly lowered in normal rats during acquisition of an avoidance task. However, NA is not distributed uniformly throughout the brain, concentrations being greatest in the hypothalamus and telencephalon.

Further, the work of Pohorecky *et al.* [19] is of significance in this study. These workers reported a reduction in telencephalic NA in rats following unilateral section of an olfactory tract in the side ipsilateral to the lesion. There was no concomitant reduction in hypothalamic NA. These findings suggest that following bilateral olfactory bulb section a reduction in endogenous NA levels should be evident in the telencephalon, but not in the hypothalamus.

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It follows therefore, that any differences demonstrated in the anosmic rat during the behavioural study regarding acquisition in an appetitive or aversive situation may be related to changes in hypothalamic function, or telencephalic function or to both of these systems.

EXPERIMENT 1

Watson [22], Honzik [12] and Lindley [15] demonstrated that anosmia retarded acquisition of appetitive learning on complex maze tasks. In contrast to this, Marks *et al.* [16] reported that anosmic rats performed better than normals on a positively rewarded bar press response, but unfortunately did not report results for the early stages of acquisition. In the present study the acquisition of a food-rewarded operant response was studied. In a counterbalanced design the same rats were tested on a conditioned fear procedure. Marks *et al.* [16] had observed slower acquisition by anosmic rats early in one-way avoidance but the difference was not significant.

METHOD

Animals

The animals were 24 naive male albino rats of the Wistar strain, aged 100–120 days at the beginning of the experiment.

Apparatus

Appetitive conditioning was carried out in a Skinner Box (Davis Scientific Instruments) on a CRF schedule using 45 mg Noyes pellets. The box was housed within a soundproofed, airconditioned cubicle.

Aversive conditioning was carried out in a fully automated shuttlebox. The two compartments, of clear Plexiglas, were balanced on a fulcrum with an electrically operated guillotine door separating the arms. The grid floor on both sides was of stainless steel bars, each 0.32 cm in dia. and spaced 0.78 cm apart. The UCS was a constant voltage 100 V a.c. shock (0.2 mA approx.) delivered by means of a Davis Scientific Instrument shock generator (Model 250). The CS was an 88 db noise emanating from a Federal buzzer. Fear conditioning parameters and stimuli were controlled by a minicomputer.

Surgical Procedures

Rats were randomly allocated to two groups, one of which underwent bilateral olfactory section (A), and the other underwent a sham operation (S). Prior to surgery, animals were anesthetised with ether and the head shaved. A midline incision 2 cm long was then made caudad from the rim of the orbit. Burr holes were drilled through both frontal bones, 2 mm lateral to the frontal suture and 4 mm caudad to the posterior rim of the orbit, thus maintaining the integrity of the intracranial venous sinus. A probe was introduced through the burrhole and the corresponding olfactory bulb sectioned. The holes were plugged with gel foam and the wound sutured. Olfactory bulb section was confirmed post-mortem on completion of the behavioural experiment when animals were sacrificed by decapitation. The brain was removed from the skull by making a midline split from the foramen magnum to the frontal suture. Retraction of the split exposed the brain in situ, enabling visual inspection of the operated olfactory bulbs. Damage to the frontal pole was not observed. Experimental animals in which the tract was not completely sectioned from the bulb were excluded from the sample. The confirmation was done using a blind technique.

Surgery and post-mortem examination in the sham-operated animals were indentical to that for the anosmic (A) group except that the lateral olfactory tracts were not sectioned. No damage to intracranial structures was observed.

Behavioral Training

The S group was subdivided into (i) S–+ in which fear conditioning preceded appetitive conditioning and (ii) S+– in which the order was reversed. The A group was similarly subdivided into A–+ and A+–.

All groups were allowed 2 weeks for postoperative recovery during which food and water were available ad lib. In S–+ and A–+ groups, exploration of the aversive conditioning apparatus was begun. On Day 1 each animal spent 30 min per day in either arm of the shuttlebox with the guillotine door down. The procedure was repeated until Day 4 when the animals were fear conditioned; the CS was of 6 sec duration the last 2 sec of which was overlapped by foot-shock. Conditioning trials were repeated every 95 sec for 1 hr. Following conditioning 25 test trials were given in which the rat was placed in the conditioning chamber in darkness. The CS automatically onset after 10 sec and the guillotine door went up simultaneously with CS onset. The latency of the rat in crossing over to the second chamber was electronically recorded and printed out by a modified Sodeco timer. If the rat did not move within 25 sec the door was lowered, the CS offset. At the end of each test trial the animal was returned to a holding cage for an ITI of 90 sec. At no stage was the UCS delivered during testing i.e. animals were tested in extinction.

Following fear conditioning the rat was rested for 1 week on ad lib food and water. On Day 12, food deprivation was begun. Animals were fed wet mash for 90 min per day at the same time each day for the remainder of the experiment. On Day 14 each animal had 30 min alone in the Skinner box. On Day 15, magazine training took place for 30 min. Bar press training began on Day 16 and was repeated on Day 17. Cumulative records of bar press were taken on Days 16 and 17.

For the S+– and the A+– groups the procedure was as above with the appetitive conditioning preceding the aversive training.

RESULTS

Appetitive Conditioning

Mean bar press frequencies during the first 12 min of the 2 test sessions as shown in Fig. 1. Only the first 12 min were analysed as animals began to satiate thereafter. For each test day performance in the 4 treatments was subjected to a repeated measures analysis of variance. On Test Day 1 the effect due to order of appetitive and aversive conditioning (+– or –+) was not significant within the A or S groups. The effect due to A and S treatments was not significant but a significant Treatment × Trial Blocks effect occurred. Further testing of individual means using the Scheffé Test was carried out to determine where the significant trial effect within A and S groups occurred. The differential effect due to trial blocks arises from both S groups

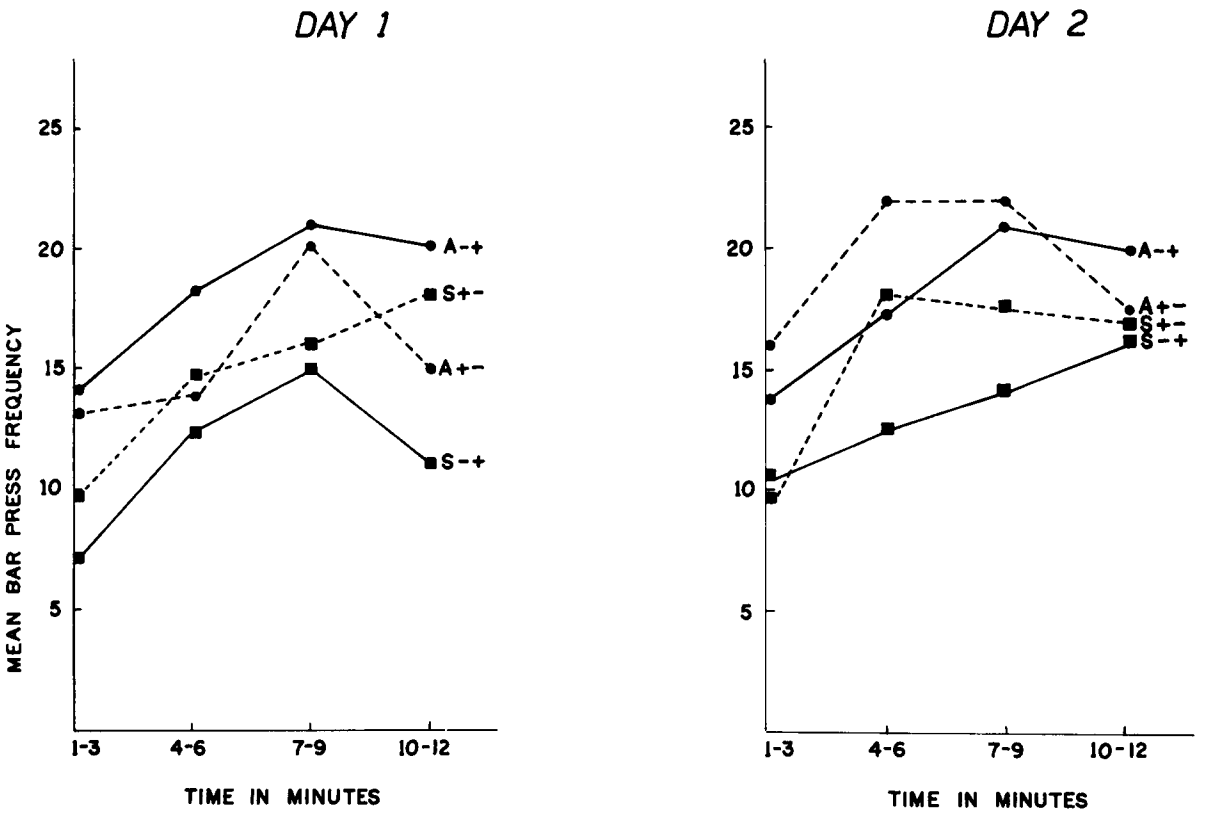

FIG. 1. Mean bar press frequency for the groups (A+−, A−+, S+−, S−+) over 3 min intervals on each test day.

having a lower score than the A groups during the first 3 min of the first test session. This suggests that olfaction may have retarded early acquisition of the food-rewarded bar press response but not later performance.

The analysis was repeated on the Day 2 scores (Fig. 1). Only the Trial Blocks effect proved significant. Thus all groups showed equivalent performance on the second test day.

Aversive Conditioning

The measure of fear conditioning was the latency of the crossover response to the CS. Each latency for each rat was inverted (sec^{-1}) and averaged over blocks of 5 trials. This score was the basic datum used in the repeated measures analysis of variance. Performance curves for the treatment groups, A+−, A−+, S+− and S−+, are shown in Fig. 2. Similar to the appetitive treatment the effect due to order of appetitive and aversive conditioning was not significant. The effects due to Treatments, to Trials and Treatment × Trials were significant. The trial effect in each S group was highly significant but not significant in either A group. Further testing of individual means using the Scheffé Test showed that significant learning occurred in each S group but in neither A group.

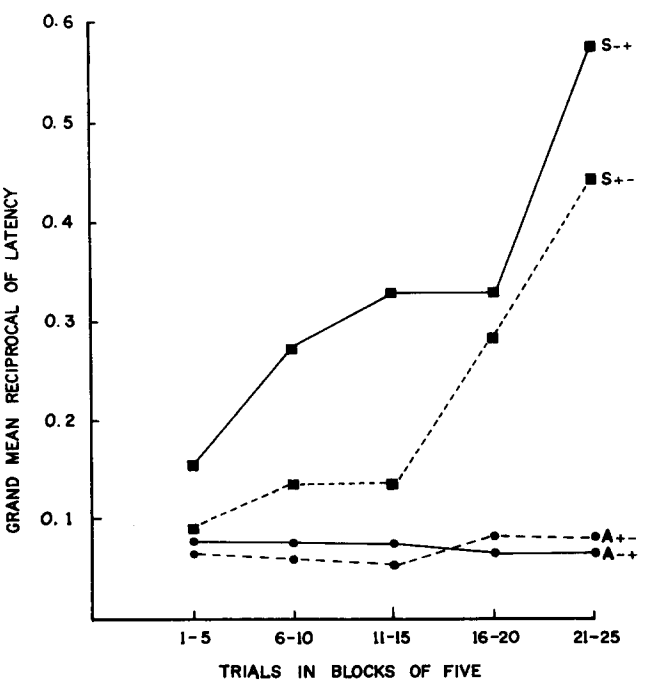

FIG. 2. Escape from CS following fear conditioning by A+−, A−+, S+− and S−+.

DISCUSSION

Comparison of the present findings with those of Marks *et al.* [16], Watson [22] and Honzik [12] reveals two major differences.

In the first place there appears to be a reversal of performance superiority depending upon whether the task is an operant or run-way task. In operant conditioning both Marks *et al.* [16] and the present study found superior performance by anosmic rats on a positively reinforced bar press response. In the Marks [16] study anosmic rats were given 25 CRF, then 225 VI-1 min, and 400 VI-2 min responses before testing on a VI-2 min schedule. Superior performance was found for anosmic rats. In the present study, the A groups performed on a CRF schedule for 2 daily sessions but superior performance was apparent only in the early stages of Day 1. However, it is not surprising that on the simplest of acquisition schedules (CRF) used in the present study, the performance differences between A– and S– operated rats would diminish. It was observed that sham-operated rats spent more time on Day 1 in sniffing around the food-cup than did the A group. On the basis of these observations, it would seem premature to attribute the poorer performance of the S groups to anything but competing responses.

Combining the results of the Marks study with the present findings, it would appear that anosmic rats acquire the bar press response more quickly than sham-operated rats, but the difference diminishes unless the schedule is made more complex. Thereupon the superiority of the anosmic animals again emerges.

By contrast with their superiority on positively reinforced operant tasks, the literature indicates poorer performance on maze tasks. On complex mazes Watson [22] and Honzik [12] found anosmic rats to be poorer in initial acquisition but no differences were observed once the task had been mastered. However, Lindley [15] reports anosmic rats to be poorer in all stages which is consistent with the Marks finding that, after 40 trials of food-reward on a one-way crossover response in a hurdle box, sham-operated and normal rats ran significantly faster than anosmic animals.

In the aversive situation, Marks *et al.* [16] subjected anosmic and sham-operated rats to extended one-way avoidance training followed by testing in extinction (CS alone). They reported that anosmic rats were slower in the early stages of acquisition. The present results show that by use of the conditioned drive procedure an extreme difference can be obtained between sham-operated and anosmic rats in the acquisition of an aversively motivated response (Fig. 2).

In Stage I (one-way avoidance training) of the procedure used by Marks, rats learn both conditioned fear and an avoidance response. Several recent reports by Di Giusto and King [8], and Di Guisto, Cairncross and King [9] have pointed out that indices of conditioned fear diminish as avoidance improves. Thus in Stage II of the procedure used by Marks (testing with CS alone) conditioned fear would be low since the avoidance response had been acquired in Stage I. In the present procedure however, Stage I of training comprised conditioned fear in which no escape or avoidance was possible and only fear could have been acquired. Thus when the rats (anosmic or sham-operated) entered Stage II of the experiment (testing with CS alone) conditioned fear should have been high since no avoidance response was previously learned. Consequently, the present procedure is far more sensitive to the initial slowness of the anosmic group in acquiring an aversively motivated task.

EXPERIMENT 2

Experiment 1 demonstrated that anosmic rats with high levels of acquired fear, but no avoidance response, did not acquire an avoidance response when exposed to the CS alone. In the present study rats were tested on one-way avoidance following either prior fear conditioning or no prior fear conditioning. As a consequence of the results obtained in Experiment 1 the question arose as to whether rats, following prior fear conditioning, would perform as well as sham-operated rats if punished for not responding to the CS.

There is some conflict of data which bears on the present methodology. Some doubt exists as to whether prior fear conditioning facilitates or depresses subsequent avoidance learning. Most of the disparate results however, relate to two-way rather than one-way avoidance; the data of one-way avoidance, Baum [3], Bresnahan and Riccio [4] and Slotnick [21] generally show a facilitatory effect. De Toledo and Black [7] report that if preshocks are paired with stimuli that signal danger, rats subsequently learn a one-way avoidance task faster than controls receiving no preshock. Thus, in the present study it is predicted that fear conditioning with delayed CS-UCS pairings should lead subsequently to enhanced acquisition of one-way avoidance in sham-operated and probably in anosmic rats. This would assume however, that the degree of aversiveness of the one-way avoidance task would be the same for the sham-operated as for the anosmic group of animals. One parameter of measurement for such an assumption [5,14] would be to measure the elevation of circulating 11-hydroxycorticoids in both experimental groups in the aversive situation. For a predictable aversive situation Bassett, Cairncross and King [2] reported a rise in 11-hydroxycorticoids to about 60 μg/100 ml plasma.

METHOD

Animals and Apparatus

Forty-eight male albino rats of the Wistar strain, aged 90–110 days at the beginning of the experiment were used. The apparatus was the automated shuttlebox described in the previous experiment.

Surgery

Animals were randomly allocated to two groups for surgery. The procedure for bilateral olfactory bulb section and sham surgery was the same as in Experiment 1.

Behavioural Tests

Two weeks were allowed for post-operative recovery, after which half the anosmic rats were allocated to an experimental fear conditioning (AE) procedure and half to a control procedure (AC). The sham-operated rats were similarly allocated to experimental fear conditioning (SE) or control (SC) procedures. The fear conditioning procedure for both AE and SE groups was the same as that used in Experiment 1. In the control groups, AC and SC, the rats were confined in one arm of the shuttlebox for 1 hr. At the conclusion of its pretest treatment the animal was returned to its home cage for 23 hr.

In testing, all groups received 25 one-way avoidance learning trials 23 hr after their pretest treatment. On each trial the CS onset was simultaneous with the opening of the guillotine door. If the animal did not cross over within 8 sec after CS onset, a constant voltage 100 V a.c. shock (0.2 mA approx.) was delivered through the grids; CS and shock

remained on until the rat crossed to the other side, whereupon CS and shock terminated and the door automatically lowered. After crossing, the rat remained in the safe arm for 10 sec and was then returned to a holding cage for an ITI of 40 sec.

Biochemical Procedure

Animals were sacrificed by decapitation and the olfactory tracts inspected as in Experiment 1. Experimental animals in which the tract was not clearly sectioned were excluded from the sample. The inspection was done using a blind technique.

Immediately after avoidance training the rats were decapitated and exsanguinated, apart from one AE group which was sacrificed 24 hr later. Blood was collected in a heparinized tube, each blood sample was centrifuged at 3,000 rpm for 10 min to obtain the plasma which was stored at 4°C for subsequent 11-hydroxycorticoid estimation. The procedure was undertaken spectrofluorimetrically by the method of Mattingley [17].

The brain was removed from the skull immediately after decapitation, chilled, and dissection performed on an ice-cooled plate following the method of Glowinski and Iverson [10] except that the brain, posterior to the transverse section at the level of the optic chiasm, was stripped of telencephalon as described by Pohorecky [19]. The NA was extracted after the method of Anton and Sayre [1] and assayed spectrofluorimetrically as described by Haggendahl [11].

RESULTS

Both speed of response (Fig. 3) and successful avoidances (Fig. 4) were analysed as each brings out a different aspect of the avoidance behaviour.

As in Experiment 1 the response latency of each animal on each test trial was inverted (sec $^{-1}$) and averaged over blocks of 5 trials. The group means are shown in Fig. 3. An analysis of variance for repeated measures was carried out on the mean reciprocals of latency over blocks of 5 trials.

The following effects were significant: Treatment Groups ($F(3,44) = 9.63$, $p<0.01$), Trial Blocks ($F(4,176) = 25.97$, $p<0.01$) and the Group x Trial Blocks effect ($F(12,176) = 3.36$, $p<0.02$). Further testing of the Trial Blocks effect within each treatment group was carried out using the Scheffé Test. The results showed a very marked increase in speed of response in the SE group, strong increments in SC and AC groups, and a null effect in the AE group.

The effect due to treatment groups was significant on all Trial Blocks except the first. Further testing of the treatment groups effect was carried out within Trial Blocks 2–5 using the Scheffé Test. Within Trial Blocks 2 and 3 the significant effects ($p<0.05$) arise from SE performing faster than AC and in Trial Block 4 and Trial Block 5, from SE performing faster than AC. In Trial Block 4 and Trial Block 5, SE performed faster ($p<0.01$) than all other groups.

Prior to analysing the number of avoidance responses the number of successful avoidances for each rat was calculated within each block of 5 avoidance learning trials. The avoidance means for each treatment on each block were plotted against the corresponding variance and the ensuing binomial distribution indicated that the arcsin transformation was necessary in order that the avoidance data be analysed by a parametric analysis of variance. Accordingly the number of successful avoidances by each animal within each trial block was converted to a proportion, the square root found and its inverse sine taken. An analysis of variance for repeated measures was carried out, but only the first 4 trial blocks could be included as there was no variance in the SE group on Trial Block 5. The following effects were significant (over the first 4 Trial Blocks); Treatment Groups ($F(3,44) = 6.03$, $p<0.01$) Trial Blocks ($F(3,44) = 42.23$, $p<0.01$) and Groups x Trial Blocks ($F(9,144) = 2.68$, $p<0.05$).

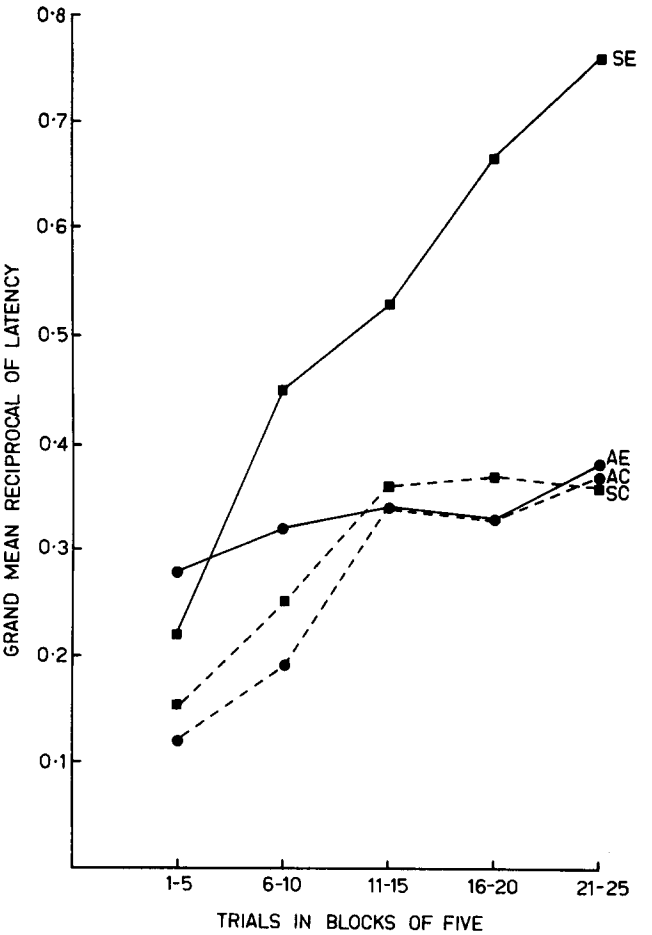

FIG. 3. Speed of performance (in sec^{-1}) on 1-way avoidance learning following either fear conditioning or a control procedure in anosmic and sham operated rats.

The effect due to Trial Blocks was significant in three treatment groups: in SE, ($F(3,144) = 13.96$, $p<0.01$) in SC, ($F(3,144) = 14.49$, $p<0.01$) and in AC, ($F(3,144) = 20.71$, $p<0.01$). Further testing of the effect due to Trial Blocks was carried out within each treatment group using the Scheffé Test. The results showed significant increases in successful avoidance in the SE, SC, and AC groups with SE reaching a plateau earlier in training. The AE group did not improve over trials, despite a comparatively high performance level early in training.

The effect due to treatment groups was significant in 3 Trial Blocks: in Trial Block 1, ($F(3,44) = 6.92$, $p<0.01$); in Trial Block 2, ($F(3,44) = 3.96$, $p<0.05$) and in Trial Block 3, ($F(3,44) = 3.13$, $p<0.05$). Further testing of the treat-

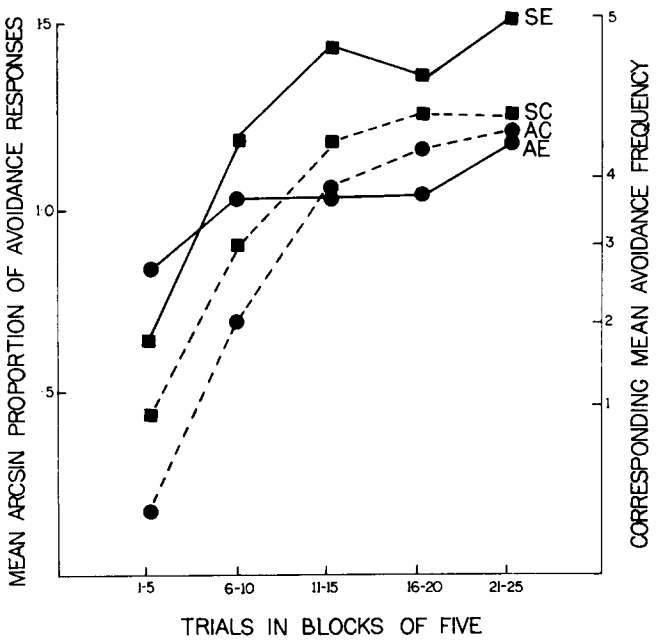

FIG. 4. Avoidance responding on a 1-way task following fear conditioning or a control procedure in anosmic and sham operated rats.

ment groups within Trial Blocks 1, 2 and 3 was carried out using the Scheffé Test. In Trial Block 1 where the effect of prior fear conditioning might be expected to be greatest, the AE group performed significantly more avoidances than the AC ($p<0.01$) and the SC group ($p<0.05$). The SE group gave significantly more avoidances ($p<0.05$) than the AC group. Within subsequent Trial Blocks the treatment group effect diminished; in Trial Block 2 and Trial Block 3, the SE group had significantly more avoidances ($p<0.05$) than the AC group. No significant differences occurred in Trial Block 4.

Corticosterone levels in blood plasma were determined fluorimetrically; no significant differences ($p<0.05$) occurred between the levels which were (in μg/100 ml of plasma): AE = 58.8 ± 8.7, SE = 58.2 ± 6.7, AC = 54.7 ± 10.2 and SC = 53.8 ± 7.2. In the AE group sacrificed 24 hr after the last training session the plasma level was 16.1 ± 3.6, indicating that corticosterone concentrations in the plasma have returned to the normal range within 24 hr.

Brain noradrenaline following avoidance training was assayed also. The results obtained showed no difference in the assay level of NA for either of the sham-operated groups, or for the anosmic groups. Consequently, the assay results were pooled within the anosmic group and within the sham group. The following concentrations of NA were obtained (in ng/g of wet tissue): in sham-operated rats (SC, SE) the hypothalamic level was 996 ± 7 and the telencephalic level was 106 ± 4, in anosmic rats (AC, AE) the hypothalamic level was 1020 ± 3 and the telencephalic level was 60 ± 9. The difference between the S and the A groups was significant for the telencephalon ($p<0.01$) but not for the hypothalamus ($p<0.05$).

GENERAL DISCUSSION

Testing with one-way avoidance, rather than the CS alone, revealed that in anosmic rats test performance was facilitated by the prior fear conditioning c.f. the performance of AE and AC in Fig. 4. Hence the failure of the A group in Experiment 1 to perform to the CS alone cannot be attributed to a failure in the prior fear conditioning phase, but rather to a failure in the test phase. However, the difference between the present results and those of Marks *et al.* [16] was that the performance in the anosmic rats depended in the present case upon the UCS being present during testing. Comparison of the two studies suggests that early in training the anosmic rats exhibit a performance deficit which can be remedied by use of the UCS, but after extended training anosmic rats perform as well as normals regardless of the UCS. These observations only apply however, where number of avoidances, rather than speed of avoidance, is the dependent variable.

Figure 3 in which speed measures are given, shows that later in learning several interesting differences emerge. In the first palce, prior fear conditioning facilitated the speed of avoidance of sham-operated rats c.f. SE and SC which is in keeping with the previous studies which reported that prior fear conditioning facilitates subsequent avoidance learning. On the other hand, performance by the anosmic groups (AE and AC) does not exhibit the same differentiation of speed scores. Both the AE and SE groups avoided at the same criterion level as AC and SC (in excess of 80 per cent) but the AE did not exhibit the great increase in speed shown in Fig. 3 by the SE group on later trials. Thus, in early learning, as distinct from the extended training used by Marks *et al.* [16], the AE group would be far less likely than the SE group to conserve anxiety by responding before UCS onset simply because of the slower speed of avoidance, as illustrated in Fig. 4. This could explain also the failure of the A group in Experiment 1 to perform to the CS alone.

The physiological implications associated with these conclusions are important. The findings of Pohorecky *et al.* [19] have been confirmed and extended to include totally anosmic animals; the results show a significant reduction in telencephalic NA without a concomitant reduction in hypothalamic NA. Further, histopathological evidence of Powell *et al.* [20] does not demonstrate a direct projection of primary olfactory neurones to hypothalamic nucleii. Instead following olfactory tract section, Pigache [18] reported that degeneration occurs in olfactory neurones passing to the allocortex. Following primary neurone degeneration, transneuronal degeneration occurs, involving the pyramidal cells of the allocortex, which according to Jones *et al.* [13] and White *et al.* [24] in the rat is characterised by a loss of dendritic proliferation. Thus, the anatomical and physiological evidence implicates the telencephalon as the functional centre in the changed response to an aversive CS. Such a conclusion is substantiated in that endogenous hypothalamic NA is not significantly reduced in the anosmic animal. Further, the corticosterone elevation to moderate levels occurs in both anosmic and sham-operated rats indicating that the stress response to the aversive situation is the same in both groups of animals.

Therefore, a possible explanation exists for the observed similarity between the anosmic and sham groups described for the appetitive situation (Experiment 1). The feeding response is a limbic phenomenon relating in particular to the ventro-medial nucleus of the hypothalamus, and results have been presented which show that disruption of the limbic system is minimal following olfactory tract section. The weight of physiological evidence would suggest there-

fore, that marked differences between control animals and those subjected to olfactory tract section would not emerge in an appetitive situation.

Of greater physiological significance is the need to explain why the anosmic group in Experiment 2 improved their performance over the A group in Experiment 1, when the UCS was introduced during testing. It is suggested that these differences in performance relate to the changes, both chemical and pathological, evident in the telencephalon following bilateral olfactory tract section. In the A groups, loss of dendritic proliferation in cortical pyramidal cells following olfactory tract section, would result in a reduced level of cortical synaptic activity. Such a conclusion is substantiated by the present finding of reduced NA availability in the telencephalon following olfactory tract section.

As a sequitur the physiological and behavioural results would suggest that the use of the UCS in testing leads to a greater afferent input into the ascending reticular formation which could well compensate for the reduced level of telencephalic activity induced by olfactory tract section.

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