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Facilitation of Muricide in Rats by Cholinergic Stimulation of the Lateral Hypothalamus

BYRON C. YOBURN, MURRAY GLUSMAN, MICHAEL POTEGAL AND LUDMILA SKAREDOFF

Department of Psychiatry, College of Physicians and Surgeons, Columbia University and Department of Behavioral Physiology, New York State Psychiatric Institute, New York, NY 10032

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YOBURN, B. C., M. GLUSMAN, M. POTEGAL AND L. SKAREDOFF. *Facilitation of muricide in rats by cholinergic stimulation of the lateral hypothalamus.* PHARMAC. BIOCHEM. BEHAV. 15(5) 747–753, 1981.—The effect of cholinergic stimulation of the lateral hypothalamus on muricide in rats was evaluated in two experiments. In Experiment 1, injections of the cholinergic agonist carbachol (5.0–20.0 μg) were found to facilitate muricide in rats that spontaneously killed mice. In Experiment 2, rats were induced to kill mice by food deprivation and then stimulated with carbachol (2.5–5.0 μg). Facilitation of muricide was found to be coincident with increased scores on a handling difficulty (irritability) scale for the majority of rats. These results suggest that facilitation of muricide by cholinergic stimulation of lateral hypothalamic areas may be related to increases in irritable aggression.

Aggression Cholinergic stimulation Lateral hypothalamus Interspecific aggression Muricide Handling Irritability Carbachol Rats

LATERAL hypothalamic cholinergic systems have been implicated in the mediation of muricide in the rat [3, 4, 5, 6, 9, 14, 24]. These studies have shown that intrahypothalamic administration of the cholinomimetic drug carbachol (7 μg) will facilitate aggressive behavior in rats which normally kill mice, and that a much larger dose (20–50 μg) will induce killing in nonkillers. However, careful consideration of the data suggests that cholinergic stimulation of hypothalamic structures may not specifically activate neural systems for predatory aggression. The conversion of nonkillers to killers and the facilitation of muricide in natural killers by cholinergic stimulation of the lateral hypothalamus have been accompanied frequently by motor seizures as well as signs of profound autonomic arousal [4, 14, 24]. Moderate doses of carbachol which would minimize these problems, were not effective in inducing killing by nonkillers [3,4] and lower doses (2 μg) have been reported to inhibit killing in natural killers [15]. Furthermore, it has been found that the aggressive behavior of nonkillers that are induced to kill differed from that of spontaneous killers in that they attacked rat pups and adult rats and their bites on mice were more widely distributed over the target, rather than being confined to the cervical region of the spine [9].

Taken together, these results have led to questions concerning the presumed cholinergic substrate for predatory aggression in the hypothalamus [3, 4, 5, 6]. Several investigators [9,15] have suggested that carbachol-elicited and facilitated muricide are actually due to increases in irritable aggression [17,18] related to aversive aspects of the stimulation (e.g., seizures) and not to activation of a system for predatory aggression. However, it is possible that cholinergic stimulation may concurrently activate specific systems for both irritability and predation, and that each one could be modulated independently. The present experiments sought to replicate some of the previous findings of facilitation of muricide by cholinergic stimulation of the lateral hypothalamus. In Experiment 1, we evaluated the effects of various doses of carbachol on the latency to attack and kill in order to establish an effective dose to facilitate muricide. In Experiment 2, this dose and a lower dose were used to examine the effects of cholinergic stimulation on muricide and irritability.

EXPERIMENT 1

METHOD

Subjects

Subjects were 59 male, experimentally-naive, Long-Evans rats that were between 2.5 and 9 months of age. They were individually housed in 21×24×20 cm clear plastic cages with metal tops. The bottom of the cage was filled with a thin layer of wood chips which was changed regularly, but never within 24 hours before a test session. Free access to water and food was provided at all times. Male and female white mice of various ages and sizes were used as targets.

Muricide Screening

Following a minimum of one week of individual housing, the 59 rats were tested for spontaneous mouse-killing. A

TABLE 1
MEAN LATENCY TO ATTACK AND KILL (sec) FOR EACH SUBJECT IN EXPERIMENT 1

	Attack				Kill			
		Carbachol				Carbachol		
Subject	Buffer	5.0 μg	12.5 μg	20.0 μg	Buffer	5.0 μg	12.5 μg	20.0 μg
43	171.30	4.48	25.88	56.32	288.31	12.22	48.09	100.59
3	11.32	1.84	1.20	3.29	70.86	11.25	8.29	20.14
64	86.37	1.91	1.32	95.49	95.90	8.96	6.13	304.03
30	15.30	90.01	1.0	144.30	42.82	600.00	7.46	575.48
45	8.74	6.17	4.95	S	24.19	20.16	21.21	S
4	3.91	2.08	4.07	S	34.76	11.96	16.39	S
Mean	49.49	17.75	6.40	74.85	92.81	110.76	17.93	250.06

S=Seizure.

mouse was placed in the rat's homecage and 24 hours later the cage was checked. Ten of the 59 animals (17%) exhibited muricide and only these subjects were included in subsequent stages of the experiment.

Surgery

Each of the ten killers were stereotaxically implanted under anesthesia (50 mg/kg sodium thiopental, IP; 0.4 mg/kg atropine sulfate, SC) with a 22-ga guide cannula aimed at the right lateral hypothalamus. Nine of the ten animals were implanted with a second cannula aimed at the ventral tegmentum to be used in a later experiment. Animals were allowed to recover for at least 6 days following surgery before testing began.

Drug Injection Procedure

Rats were injected using a 28-ga internal cannula inserted into the implanted guide cannula and connected by polyethylene tubing to a 10 μl syringe mounted on a microdrive. The tip of the internal cannula extended approximately 0.5 mm beyond the tip of the guide cannula. Injections of 0.1 M phosphate buffer, and 5, 12.5 and 20 μg of carbachol dissolved in buffer were given to each subject in a counterbalanced order with a minimum of 48 hr elapsing between injections. Injection volume was 0.5 μl infused at a rate of 0.5 μl/min. The injection cannula was left in place for 1 min following the infusion. In most cases, animals were tested at least twice at each condition.

Muricide Testing

Ten minutes following an injection, subjects were exposed to five successive, ten-minute muricide tests in which a mouse was introduced into the homecage and the latency to attack and kill was recorded. Mice were removed from the cage immediately upon being killed. If the rat failed to attack or kill during a trial, a latency of 600 sec was recorded and the mouse was removed from the cage and immediately replaced with another mouse for the next trial. The session was terminated and maximum latencies were recorded if the rat did not kill on two successive trials, since pilot experiments indicated that muricide rarely occurred following two successive trials without muricide. Testing was terminated and the data were excluded from the anlaysis if seizures were apparent during aggression testing. Subjects that failed to kill at least once during all tests were also excluded from the data analysis. Latency scores were converted to common log values prior to statistical evaluation.

Histology

At the end of testing animals were sacrificed by an overdose of thiopental and perfused with 10% Formalin. The brains were removed and 40 micron sections were cut on a freezing microtome. Sections were stained with neutral red and luxol fast blue and examined to determine the location of the cannula tips.

RESULTS

Of the ten animals that were implanted, three were excluded from the experiment due to nonfunctional cannula or post-operative complications and one was excluded from data analysis due to failure to kill during any session. Attack and kill measures were positively correlated across conditions for the remaining group of six subjects (Pearson $r=.885$, $t(20)=8.49$, $p<0.001$), and, in general, the two measures were similarly affected by carbachol. The mean latencies to attack and kill over all trials in each condition are presented in Table 1. A repeated-measures, two-factor, analysis of variance indicated that there was a significant effect of dose on the latency to attack and kill, $F(3,13)=4.76$, $p<0.025$, but that there was no difference between the dose-response functions for attack and kill, $F(3,13)=1.44$, $p>0.05$. The calculations were accomplished using Li's [13] method for analysis of variance with missing observations. Analysis of orthogonal components revealed a significant quadratic component, $F(1,15)=24.74$, $p<0.005$, which reflects the facilitation of muricide by the 5.0 μg and 12.5 μg doses relative to the buffer and 20.0 μg conditions. Two-tail a posteriori tests (Least Significant Difference) indicated that the 12.5 μg condition differed from the buffer and 20 μg condition ($p<0.05$) and the 5.0 μg condition differed from the 20.0 μg condition ($p<0.05$). Finally, rats that showed facilitation of muricide by carbachol compared with buffer (Table 1) generally had reduced latencies to attack and kill on the first and all subsequent aggression tests following a carbachol injection.

The 20.0 μg dose induced severe seizures in two animals

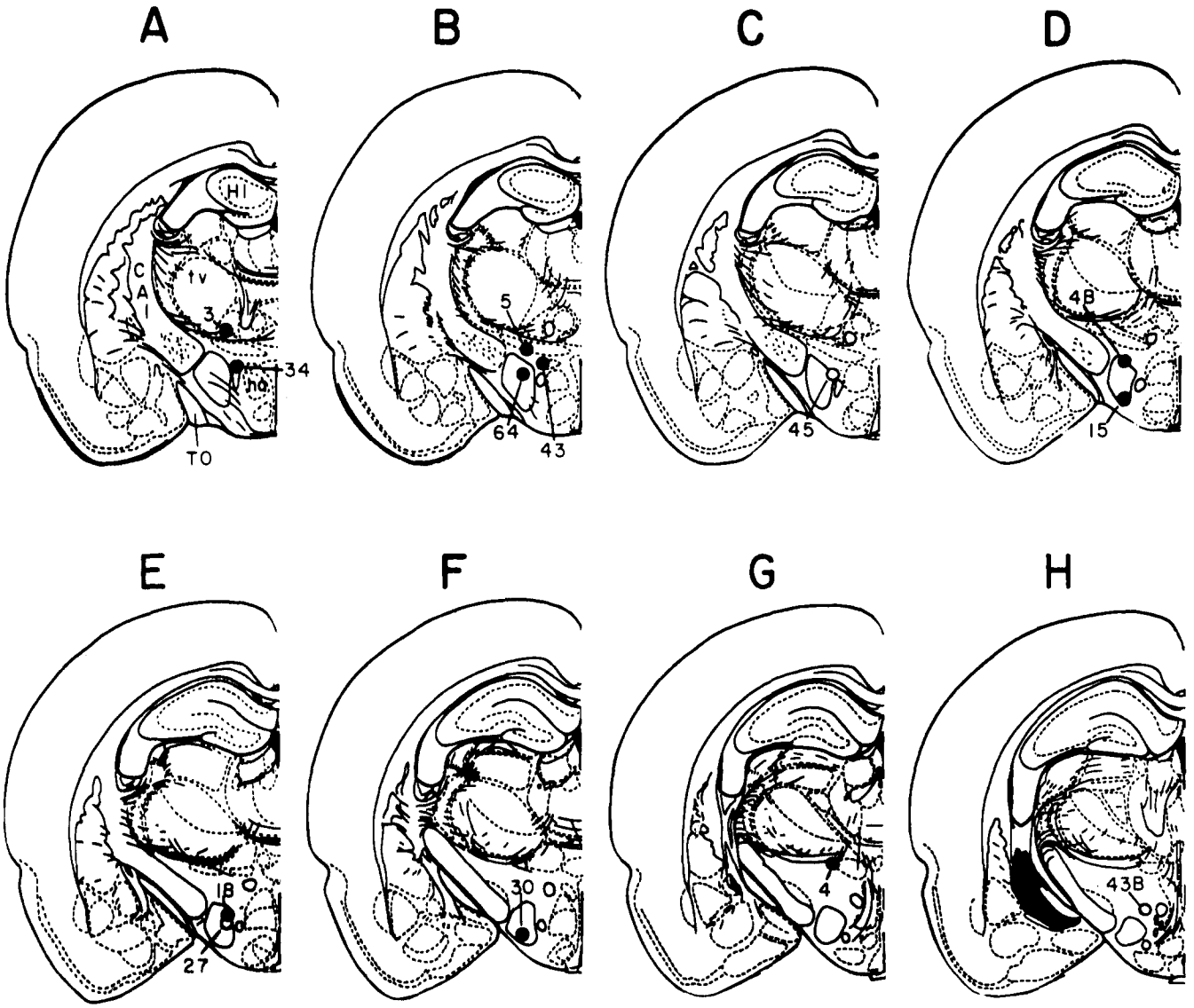

FIG. 1. Location of cannula tips from histological analysis for rats in Experiments 1 and 2. Sections A–D and E–F correspond to Figs. 31b–34b and 36b–39b, respectively, from König and Klippel [11]. Filled circles represent points at which facilitation of aggression by carbachol was found. Open circles represent points at which very weak or no facilitation of aggression was found (see Tables 1 and 2). CAI=internal capsule, HI=hippocampus, TO=optic tract, ha=anterior hypothalamic nucleus, tv=ventral thalamic nucleus.

(4,45) during the first test and therefore this dose was not repeated in these rats. This dose also induced seizures in one animal (43) during one of the two sessions at that dose. All but two animals (4,30) exhibited seizures during one of the sessions following injection of the 12.5 μg dose. The 5.0 μg dose of carbachol did not induce seizures in any animal.

Figure 1 is a reconstruction of the location of the cannula tips. Most injection sites were lateral to the fornix. Three of the sites (30,45,64) were in the lateral hypothalamic area, two sites (3,4) were in the area of the zona incerta, and the reamining site (43) was on the border of the caudal pole of the magnocellular paraventricular nucleus. Histological damage was minimal and confined to the cannula tips in all cases. Visual inspection of the sections showed that damage was less than 1mm in diameter at the end of the cannula track for all rats.

DISCUSSION

The results of this experiment are consistent with previous reports of facilitation of muricide in rats by cholinergic stimulation of the hypothalamus and surrounding structures [3, 4, 5, 6]. As has been reported before, we found that doses of carbachol that induced seizures in several animals were effective in facilitating aggression in the same animals. However, the 5 μg dose which did not elicit observable seizures also was effective in facilitating aggression. The absence of observable signs of convulsion does not rule out the

possibility that the stimulation may be noxious and that increased irritability may play a role in the facilitation of aggression by the 5.0 μg dose. In fact, casual observation indicated that animals were more difficult to handle and more likely to bite following all of the carbachol stimulation tests, regardless of dose. The next experiment addresses some of these issues by using low doses of carbachol and formally evaluating irritability by the use of a handling difficulty scale.

EXPERIMENT 2

In the previous experiment, cholinergic stimulation of the hypothalamus was effective in facilitating muricide in rats that spontaneously killed mice. As in previous experiments [7,10], we found that approximately 20% of our rats would spontaneously attack and kill mice when allowed free access to food. Unfortunately, the consequence of this low incidence of spontaneous muricide was that 49 of the 59 animals were discarded from the experiment prior to surgery. A number of experiments have shown that food deprivation increases the proportion of rats exhibiting muricide [1, 16, 20, 21, 23, 26]. In order to increase the number of killers in our colony, rats in this experiment were exposed to a cyclic food deprivation schedule prior to testing [1,21]. The effects of cholinergic stimulation of the lateral hypothalamus of food deprived rats can be compared to that of nondeprived animals since one of the doses of carbachol (5 μg) used in Experiment 1 was employed in this experiment.

METHOD

Subjects

Forty-eight, male, experimentally-naive, Long-Evans rats between 3.5 and 5 months of age were housed individually in 24.1×20.3×17.8 cm metal hanging cages. Male and female white mice of various ages and sizes were used as targets.

Food Deprivation and Muricide Screening

All animals were placed on a 23-hr food deprivation schedule in which they were allowed ad lib access to food at the same time each day for one hour. Water was present at all times throughout the experiment.

Following one week of 23-hr food deprivation, all animals were tested for mouse-killing. A mouse was placed in the animal's homecage and the cage was checked 5, 15, 30, and 60 min later. Dead mice were removed as soon as they were discovered. Seventy one per cent of the rats killed the mice in 30 min or less and 11 of these were randomly selected to be included in subsequent stages of the experiment.

Surgery

Each of the 11 killers was allowed free access to food for a minimum of one week prior to surgery. Rats were implanted with one cannula (as described in Experiment 1) aimed at the right lateral hypothalamus. Following surgery animals were housed individually in clear plastic cages as described in Experiment 1.

Drug Injection Procedure

The injection apparatus and procedure were identical to that used in Experiment 1. Injections of 0.1 M phosphate buffer, and 2.5 μg and 5.0 μg of carbachol dissolved in buffer were given to each subject in a counterbalanced order with a minimum of 48 hr elapsing between injections. Animals were tested once at each condition.

Muricide and Handling Testing

Following at least three days post-operative recovery with free access to food, rats were food-deprived to 80% of their free-feeding weight. Testing was conducted only if subjects were within 20 g of their 80% deprivation weight.

Each session consisted of a pretest, an injection, and three posttests. The pre- and posttests were identical and involved a muricide test and a handling test. Five minutes following a pretest an injection was given and posttests were conducted 10, 20 and 60 min following an injection. Aggression tests were the same as in Experiment 1 except that they were of 5 min duration. If the mouse was not attacked or killed in 5 min it was removed and a latency of 300 sec was recorded. Two minutes following termination of the aggression test (either by a kill or removal of the live mouse), animals were rated for handling. The test consisted of four trials: (1) picking up the rat by the base of the tail with tongs; (2) picking up the rat by the nape of the neck with tongs; (3) probing the mouth area of the rat with tongs; (4) picking up the rat with a gloved hand.

For each trial the rat was scored as follows: 0=no vocalization; 1=vocalization; 2=escape attempt with or without vocalization; 3=bite attempt with escape attempt, with or without vocalization; 4=bite attempt without escape attempt, with or without vocalization. Only one number was assigned for each trial and the sum of the numbers for each of the 4 trials was the handling score for that test. The mean handling score was computed for the three posttests within a condition and the three pretests across conditions.

Animals which did not kill during any test were excluded from the data analysis as were sessions in which seizure activity was present during testing. All latency scores were converted to common log values prior to statistical evaluation.

Histology

At the end of testing animals were sacrificed and histology was obtained as described in Experiment 1.

RESULTS

Of the eleven animals implanted, three were excluded from the experiment due to post-operative complications or nonfunctional cannula assemblies. Of the remaining eight animals, five completed testing, two animals lost their cannula assemblies prior to the last test session, and one animal's data are not presented since it had seizures during testing at both drug doses. Table 2 presents the mean latencies to attack and kill for all pre- and posttest trials for all rats. As in Experiment 1 the attack and kill measures were positively correlated across conditions for the group (Pearson $r=.934$, $t(28)=13.79$, $p<0.001$) and both measures were similarly affected by carbachol. Statistical tests were calculated using Li's [13] method for analysis of variance with missing observations. A repeated-measures, two-factor, analysis of variance indicated that there was a significant effect of treatment on the latency to attack and kill, $F(3,16)=6.57$, $p<0.005$. However, there was no difference between the dose-response functions for attack and kill, $F(3,16)=2.28$, $p>0.05$. The analysis for orthogonal components revealed a significant linear component, $F(1,6)=12.56$,

TABLE 2

MEAN LATENCY TO ATTACK AND KILL (sec) FOR EACH SUBJECT IN EXPERIMENT 2

	Attack				Kill			
		Posttests				Posttests		
Subject	Pretest	Buffer	2.5 μg Carbachol	5.0 μg Carbachol	Pretest	Buffer	2.5 μg Carbachol	5.0 μg Carbachol
18	12.07	8.45	12.74	1.62	22.72	29.31	24.65	8.33
27	3.80	3.68	3.53	2.06	10.19	8.56	8.42	7.25
5	138.95	48.04	32.32	8.32	259.21	101.02	145.18	22.51
15	18.12	10.41	7.27	1.10	63.23	45.92	29.10	6.34
4B	48.10	12.20	1.26	2.80	92.17	21.48	8.94	9.57
34	48.86	NA	21.11	2.00	173.98	NA	300.00	5.91
43B	2.45	1.82	NA	3.80	8.22	8.05	NA	10.98
Mean	38.91	14.10	13.04	3.10	89.96	35.72	86.05	10.13

NA=Not available.

TABLE 3

MEAN HANDLING SCORE FOR EACH SUBJECT IN EXPERIMENT 2

		Posttest		
Subject	Pretest	Buffer	2.5 μg Carbachol	5.0 μg Carbachol
18	2.33	3.00	3.33	3.00
27	4.33	7.67	4.00	9.00
5	0.33	2.00	4.67	8.00
15	0.33	0.67	2.67	5.33
4B	0	0.33	5.33	5.33
34	0.50	NA	1.33	5.33
43B	12.00	11.33	NA	10.67
Mean	2.83	4.17	3.56	6.67

NA=Not available.

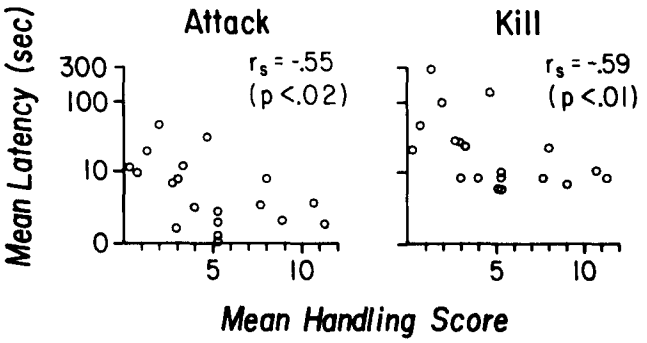

FIG 2. Scattergrams of mean latency (logarithmic scale) to attack (left panel) and latency to kill (right panel) plotted against the mean handling score. The data are from the posttest values in Tables 2 and 3. The Spearman rank-order correlation coefficients (r_s) are shown above each graph.

$p<0.025$ which reflects the generally decreasing latencies for the buffer, 2.5 μg, and 5.0 μg conditions, relative to the pretest. Two-tail a posteriori tests (Least Significant Difference) indicated that the 5.0 μg condition differed from the pretest, buffer, and 2.5 μg conditions ($p<0.05$). In addition, the pretest differed from the buffer condition ($p<0.05$) which suggests that the injection procedure or the pretest itself facilitated aggression.

Table 3 presents the mean handling scores over all trials for each animal for each condition. A Friedman two-way analysis of variance by ranks for the five animals with complete data revealed a significant effect of treatment on the handling score, $\chi^2=140.7$, $df=3$, $p<0.001$. In general, the handling score was higher during the posttests than during the pretest. Out of 19 possible comparisons the pretest handling score exceeded a posttest score for the same animal only three times ($p<0.005$, two-tail binomial test). These findings suggest that the injection procedure or the pretest heightened irritability in a similar manner to the facilitation of muricide during posttests. However, there was a trend for animals which showed facilitation of aggression by carbachol relative to the buffer to also show an increase in the handling score. For the ten possible comparisons (animals which showed facilitation of attack or kill or both by carbachol relative to buffer), the mean handling score for the 2.5 and 5.0 μg doses exceeded that for the buffer in all but two cases ($p<0.06$, one-tail binominal test). In addition, there was a significant negative correlation between the posttest handling score (pretest scores were not included) and latency to attack (Spearman $r_s=-.554$, $t(17)=-2.74$, $p<0.02$) and kill (Spearman $r_s=-.592$, $t(17)=-2.93$, $p<0.01$). Figure 2 presents scattergrams that plot the mean handling score against the mean latency to attack (left panel) and kill (right panel) for the buffer, 2.5, and 5.0 μg posttests for all animals. In general, facilitation of aggression was accompanied by increases in the handling score. Inspection of Tables 2 and 3 will show that this relationship is due to within subject modulation of both aggression and handling. Finally, by 20 min following an injection, the 5.0 μg dose of carbachol had facilitated muricide and irritability in all but one animal.

Histological analysis (Fig. 1) showed that the cannula tips were in or on the borders of the anterior lateral hypothalamic nucleus (4B, 15, 18, 27). Other sites were in the rostral zona incerta (5), in the ventral border of the fornix (34) and lateral to the caudal portions of the mamillothalamic tract (43B). Histological damage was less than 1.0 mm in diameter at the cannula tip for all rats. Damage was confined to the area of the cannula tip in all animals except one (18) in which there was also a lesion in the dorsal thalamus along the cannula track extending approximately 1.0 mm medially and laterally.

DISCUSSION

Cyclic food deprivation was effective in inducing muricide in 71% of the rats in this experiment, whereas only 17% of satiated rats in Experiment 1 exhibited muricide. However, cholingeric stimulation of the hypothalamus facilitated muricide in both spontaneous killers in Experiment 1 and deprivation-induced killers in this experiment. Thus, the facilitating effects on muricide of carbachol applied to the hypothalamus are not confined to spontaneous killers.

The facilitation of muricide by carbachol in this experiment was accompanied by an increase in irritability as measured by the response to handling. It is possible that deprivation may have affected basal irritability, and that the effect of carbachol on irritability and muricide may have been related to an interaction between these two factors. In any case, the present results indicate that modulation of muricide is correlated with changes in irritability for rats induced to kill by food deprivation.

Muricide and irritability were both found to be greater following injections during the posttests than prior to injections. This finding may be related to the injection procedure itself, or to facilitating effects of the pretest on these behaviors. With regard to muricide, however, it is likely that the injection procedure was responsible for the facilitation during posttests, since prior mouse-killing experience apparently does not enhance immediately subsequent killing [22].

GENERAL DISCUSSION

Cholinergic stimulation of lateral hypothalamic areas resulted in facilitation of muricide in both Experiments 1 and 2. Regardless of whether rats are spontaneous killers or have been induced to kill by food deprivation, cholinergic systems in the hypothalamus seem to be involved in this form of interspecific aggression. However, it should be noted that the dose of carbachol required to enhance muricide generally was greater than that needed to affect drinking [12,25], temperature regulation [8], and other behaviors [19].

The results of Experiment 2 indicate that there is an increase in handling difficulty (irritability) coincident with more rapid mouse-killing in food-deprived rats. Although it is possible that this effect is confined to food-deprived animals, casual observation of increases in handling difficulty following carbachol stimulation of satiated rats in Experiment 1 suggests that the effect is general. These results indicate that although cholinergic stimulation of lateral hypothalamic areas clearly facilitated muricide, it did not do so in a specific manner. This finding is consistent with suggestions that carbachol-induced and facilitated muricide are related to increases in nonspecific irritability [9,15]. However, the coincident increases in irritability and muricide do not necessarily imply that facilitation of muricide is causally related to increases in irritability. Cholinergic stimulation may activate separate systems for muricide and irritability. In either case, the fact that facilitation of muricide and irritability occurred shortly after stimulation suggests a primary pharmacological effect of cholinergic stimulation.

The control of muricide by cholinergic systems in the hypothalamus also has been indicated by blockade of muricide by injection of a cholinergic antagonist [24]. However, it has been shown that the blockade occurs only at high doses which are accompanied by suppression of feeding [2]. Thus suppression of muricide by cholinergic antagonists does not affect muricide alone. In short, both facilitation and suppression of muricide by cholinergic drugs are accompanied by collateral behavioral effects. The degree to which the changes in muricide are due to general behavioral effects needs to be examined more closely.

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