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Effects of Nicotinic and Muscarinic Compounds on Biting Attack in the Cat[1]

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BERNTSON, G. G., M. S. BEATTIE AND J. M. WALKER. *Effects of nicotinic and muscarinic compounds on biting attack in the cat.* PHARMAC. BIOCHEM. BEHAV. 5(3) 235–239, 1976. – Predatory-like biting attack on a rat, as well as hissing, growling, and other threat behaviors, could be induced in normally non-aggressive cats by systemic administration of the muscarinic agonist, arecoline (7–12 mg/kg). In contrast to arecoline, nicotine was found to suppress aggressive behaviors. Systemic administration of nicotine (0.5 mg/kg) prior to arecoline injection resulted in a significant reduction in elicited attack and threat behaviors. Furthermore, nicotine (0.075–0.500 mg/kg) was found to produce a dose-dependent suppression of natural predatory behavior as well. This nicotine-produced suppression of attack did not appear to be due to the induction of general malaise, since attack suppression could be seen in the absence of general behavioral inhibition, and doses of nicotine resulting in complete suppression of attack had little effect on food intake. Results indicate that muscarinic and nicotinic compounds can exert antagonistic control over some types of aggressive behaviors.

Aggression Predatory behavior Threat Nicotine Arecoline Muscarinic Nicotinic Cholinergic

CONSIDERABLE evidence suggests that cholinergic systems may play a significant role in the control of some aspects of aggressive behaviors. For example, central or systemic administration of a variety of cholinergic agonists can facilitate or induce predatory-like biting attack or threat behavior in a number of species [3, 6, 10, 16, 21, 26, 27, 29, 32]. Such facilitatory effects on aggressive behaviors appear to be mediated, at least in part, through central muscarinic receptors. Relatively pure muscarinic agonists, such as arecoline, pilocarpine, or oxotremorine, can induce attack or threat in rats and cats; and these effects can be blocked by administration of centrally active, but not quaternary, muscarinic antagonists [3, 6, 10, 16, 27, 29]. Moreover, administration of centrally active muscarinic blockers has been reported to inhibit spontaneous predatory behavior and shock elicited aggression in rats [14, 23, 26], as well as attack and threat induced by hypothalamic or amygdaloid stimulation in the cat [15,28]. These findings strongly suggest the existence of a muscarinic link in central systems controlling some types of aggression.

In contrast to muscarinic compounds, nicotine may inhibit certain aggressive behaviors. For example, systemic administration of nicotine has been reported to suppress intraspecific fighting in rats [25] and reduce shock-elicited biting in monkeys [9]. Thus, it is possible that muscarinic and nicotinic cholinergic systems may exert antagonistic control over some aspects of aggressive behaviors.

To further determine the role of cholinergic systems in the control of aggressive behaviors, we examined the effects of systemic administration of muscarinic and nicotinic compounds on biting attack in the cat. We found that the muscarinic compound, arecoline, could induce vigorous predatory-like biting attack in the cat, while nicotine strongly suppressed both drug-induced attack and natural predatory behavior.

EXPERIMENT 1

Systemic administration of muscarinic agonists, such as arecoline or oxotremorine, has previously been shown to induce both biting attack and threat behavior in cats [6, 10, 16, 32]. Drug-induced threat consists of piloerection, hissing, growling, and clawing, resembling the natural defensive behavior of cats [17]. Drug-induced biting attack consists of approach to a rat or other suitable attack object and repetitive biting, which is reminiscent of the natural predatory behavior of the cat [5,17]. Drug-induced attack can often be seen in the absence of hissing, growling, clawing or other threat behaviors, suggesting that attack is not merely an additional manifestation of threat. Further, attack is highly directed towards a rat over similarly sized objects such as foam or wood blocks [6], and consequently is not a reflection of nonspecific biting behavior. While muscarinic compounds appear to facilitate both biting attack and threat behavior in the cat, evidence suggests that nicotinic cholinergic compounds may inhibit some aspects of aggression in the rat [25] and monkey [9]. To further

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examine the potential antagonistic effects of nicotinic and muscarinic compounds on biting attack, we (a) reexamined the effects of systemic administration of arecoline on biting attack in the cat, and (b) determined the effects of nicotine pretreatment on aggressive behaviors induced by arecoline.

Method

Animals. Ten adult cats (4 male and 6 female) which did not spontaneously attack rats were used. Animals were housed individually, and were maintained on cat chow and water.

Drugs. The drugs used in the present study were atropine methyl nitrate (Sigma), arecoline hydrochloride (Sigma), and nicotine hydrochloride (K & K Laboratories). All drugs were dissolved in a normal saline vehicle. Drug doses are expressed in terms of the base.

Apparatus. The testing chamber was a sound attenuated box 68 × 30 × 45 cm, with a one-way viewing screen for observation. Stopwatches and timers were used to measure latencies and durations of induced behaviors. Since drug-induced attack on live or dead prey is essentially comparable [6], dead rats were used as prey-objects in the present study to eliminate variability due to a rat's defensive behavior, and to avoid injury to the cats.

Procedure. Each cat was first given a formal one-hour screening test in the presence of a dead rat, to determine whether the animal would attack rats spontaneously. Since none of the animals evidenced any biting or threat behavior, all 10 were included in the present experiment. A previous report indicated some interanimal variability in the arecoline dosage required to induce attack or threat behavior [6]. Consequently, all animals were given one or more preliminary arecoline tests, in the presence of a rat, to determine an effective dose for inducing biting attack. In these preliminary tests, arecoline was injected intraperitoneally (in 1 ml volumes), the cats were placed into the testing chamber with the rat, and the experimenter noted the presence of any biting of the prey in the subsequent one-hour period. Five minutes prior to arecoline injections in this and all subsequent arecoline tests, animals received subcutaneous pretreatment with the quaternary muscarinic blocker, atropine methyl nitrate (1 mg/kg), to minimize the peripheral parasympathomimetic effects of arecoline [6]. The arecoline dosage for the initial preliminary test was 7 mg/kg [6]. If arecoline failed to induce attack at the 7 mg/kg dosage, an additional test was given at a higher dose (10–12 mg/kg) at least 48 hr after the first.

Following preliminary testing, each cat was given two formal attack tests with arecoline, according to the procedures outlined above. Prior to one of these tests, the cat received an injection of nicotine, and prior to the other test, a control injection. The arecoline dose for each cat (7–12 mg/kg) was that found to be effective in inducing attack in preliminary tests. Nicotine dissolved in normal saline, or the normal saline vehicle alone, was administered subcutaneously (1 ml volumes) 5 min after atropine methyl nitrate injections, and 10 min prior to arecoline. The nicotine dosage (0.5 mg/kg) was that found in pilot studies to be effective in suppressing attack. Tests were separated by 48 hours; half the cats received the nicotine test first, and half, the saline test first. On all tests, the experimenter recorded, by means of switch closures, the latencies and cumulative durations of prey-biting as well as two predominate features of threat behavior, hissing and growling. Biting was scored whenever the cat bit or grabbed the rat in its teeth, and the duration of biting was taken as the time the cat's teeth were in actual contact with the rat. Hissing was scored only when the animal emitted a clearly audible hiss, accompanied by elevation and retraction of the upper lip. Growling was scored when the animal emitted a clear, low pitched growling vocalization; meowing and screaming were excluded.

Results and Discussion

All ten cats tested demonstrated short latency biting attack on the rat following arecoline injections while none evidenced any attack in formal control tests. Six of the ten cats evidenced attack at the 7 mg/kg dose, while four required higher doses (10–12 mg/kg). Following administration of arecoline, the cats appeared restless and agitated, and evidenced intermittent tremorous and unsteady locomotion. They generally hissed or growled, and occasionally evidenced piloerection. During this period, the cats showed repeated episodes of biting attack on the rat, ranging from an isolated bite, up to two or three minutes of virtually continuous attack. The forepaws were often used to hold or pin the prey for biting, but were virtually never used to rake or claw the prey. Prey-kicking, which has previously been described as a component of natural predatory behavior [5,17], was also frequently seen during drug-induced attack in the present study. Following a number of bites, the cat would seize the rat in the mouth and forepaws, roll on its side, and repeatedly kick and tear at the rat with its hindpaws.

While arecoline was highly effective in inducing attack, as illustrated in Fig. 1, nicotine pretreatment strongly inhibited this attack. Pretreatment with nicotine led to a significant increase in the latency to attack following arecoline (Wilcoxin T, $p<0.02$), and a significant decrease in the cumulative duration of attack (Wilcoxin T, $p<0.02$) as well as the overall duration of the attack period (Wilcoxin T, $p<0.02$). Further, consistent with a previous report that nicotine can inhibit threat responses elicited by hypothalamic stimulation [28], nicotine also reduced the amount of hissing and growling induced by arecoline on the formal tests (mean number of hisses on arecoline + saline trials = 24.4, on arecoline + nicotine trials = 6.3, Wilcoxin T, $p<0.02$; mean duration of growling on saline trials = 27.2 sec, on nicotine trials = 10.8 sec, $p<0.02$). These reductions in aggressive behaviors were seen, in most cases, in the absence of other apparent behavioral effects of the nicotine. In some cases, however, the animals appeared somewhat less agitated under the influence of nicotine. In addition, a few animals evidenced signs of peripheral autonomic activation, such as salivation or retching, immediately following nicotine injections. These effects were transient when they occurred, however, and in all cases had disappeared before arecoline injections.

These results are consistent with previous reports of reduced aggressive behaviors following nicotine administration, and suggest the possibility of a nicotinic link in the systems controlling some types of aggressive responses. However, an important question arises as to the behavioral specificity of the suppression, and it is not entirely clear whether such findings with drug-induced attack can be extended to natural attack behavior. These questions are addressed in Experiment 2.

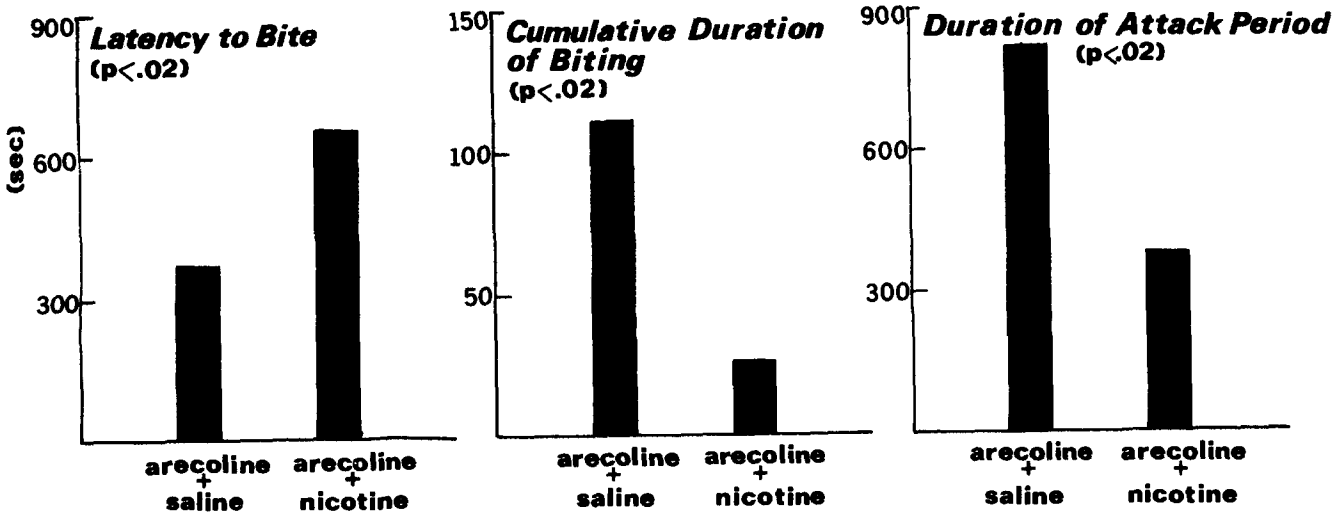

FIG. 1. Effects of nicotine pretreatment (0.5 mg/kg, subcutaneous) on biting attack induced by arecoline (7–12 mg/kg). (Probability values based on Wilcoxin *t*-tests.)

EXPERIMENT 2

Results outlined above indicate that nicotine can strongly inhibit muscarinically-induced biting attack in the cat. In the present experiment, we examined the effects of nicotine on the natural predatory behavior of cats which demonstrated spontaneous mouse-killing.

Method

Animals. Animals were 8 adult female cats which demonstrated spontaneous attacking of mice. All cats were housed individually, and were maintained on cat chow and water.

Drugs. The drugs used in the present study were nicotine (supplied by Philip Morris) and hexamethonium chloride (Sigma). All drug doses are expressed in terms of the base. Drugs were dissolved in a normal saline vehicle, and administered in 1 ml volumes.

Apparatus. The testing chamber was a sound attenuated box, 73 x 54 x 48 cm, with a one-way viewing screen. Solid state programming equipment was used to record response occurrences, latencies, and durations.

Procedure. Each cat was given five attack tests with a mouse, 10 min after subcutaneous administration of nicotine or the saline vehicle. Each cat received two saline control tests and three nicotine tests at different doses (0.075, 0.200, and 0.500 mg/kg). Tests were separated by 48 hours. On the first and last tests cats received saline injections, while on intermediate tests, animals received nicotine treatments. The order of testing with the three doses of nicotine was counterbalanced across animals, according to a Latin square design. Pilot experiments had indicated that some cats evidence transient salivation and/or vomiting following the higher doses of nicotine, and that such autonomic effects could be blocked by the quaternary nicotine antagonist, hexamethonium. In order to minimize the peripheral autonomic effects of nicotine, animals were routinely given hexamethonium pretreatment (0.2 mg/kg, subcutaneously), 10 min prior to the nicotine or the saline control injections. (Pilot experiments had shown that such hexamethonium treatment has little effect on spontaneous attack, or on nicotine produced changes in attack.)

On all tests, a mouse was introduced ten min following nicotine or saline injections, and the experimenter measured the latency to bite the mouse, the number of bites, and the number of pawing and cuffing responses, as well as recording the animal's general behavioral reactions to the drug treatments. Biting was scored whenever the cat grabbed or bit the mouse with its teeth. Pawing/cuffing was scored whenever the cat tapped or swatted the mouse with its paw; pinning of the mouse with the paw during biting was not counted. The mouse was removed upon being killed, or if not killed, at 10 min following introduction. In order to determine the effects of the drug treatment on food intake, cats at this time were given access to tuna fish for 5 min, and the amount of food eaten was recorded. If the cat had not bitten the mouse in the formal attack test, a second mouse was introduced after the food test, in order to determine the approximate duration of attack suppression.

Results and Discussion

Results of the present study (Fig. 2) demonstrate that systemic administration of nicotine can strongly inhibit spontaneous biting attack in a highly dose-dependent fashion (Friedman's Anova on latency to bite, $\chi^2 = 13.5$, $df = 4$, $p<0.01$). Considerable interanimal differences existed, however, in the nicotine dosage required for attack suppression. One cat showed complete suppression of attack, for the duration of the formal ten min test, at the lowest nicotine dose tested; three evidenced complete suppression at the intermediate dose; and six at the highest dose; while two cats never showed complete suppression. Further testing revealed that the attack suppression produced by nicotine had generally declined and disappeared within 60 min following drug treatment (at the highest dose, the median time to the reappearance of biting following injection was 33.5 min).

While some animals appeared somewhat less active at the highest dose of nicotine, suppression of biting did not appear to be secondary to the induction of general malaise or to general behavioral depression. This is suggested by the following observations. First, with hexamethonium pretreatment, 7 of the 8 animals evidenced no signs of

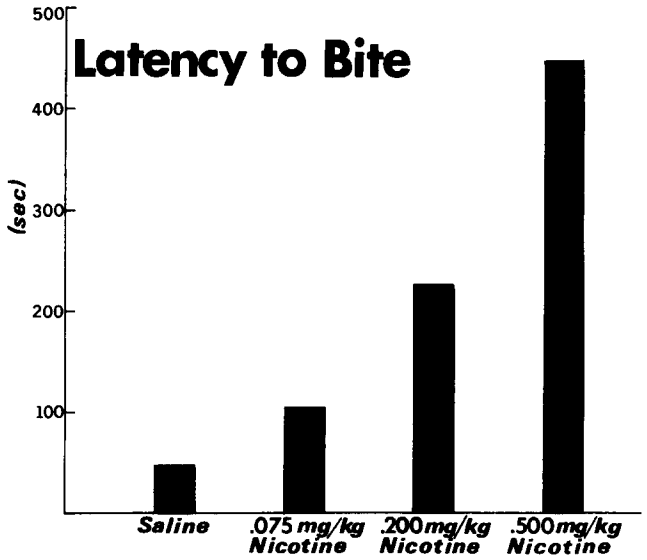

FIG. 2. Effects of different doses of systemically administered nicotine on spontaneous mouse-biting. Saline control tests were given both before and after the nicotine series, but are averaged and represented as one test for comparison. (Prior to all tests cats received 0.2 mg/kg hexamethonium, subcutaneously, to minimize peripheral autonomic effects of nicotine. In cases where no attack was seen in the ten minute test, cats were given the maximum latency of 600 sec).

peripheral autonomic activation on nicotine tests, and the salivation and retching shown by the eighth animal shortly after injection had disappeared by the time behavioral testing began. Secondly, nicotine produced only a small and nonsignificant decrease in eating (mean food intake in the five minute test on control trials = 44.7 g, on nicotine trials, 34.1 g; Friedman's Anova, $p>0.30$). These findings indicate that nicotine did not merely make the animal sick, secondarily resulting in reduced attack behavior. Thirdly, nicotine produced a relatively selective suppression of biting over the pawing and cuffing components of attack. Nicotine pretreatment resulted in only a small and nonsignificant decline in pawing (mean number of paws on saline trials = 22.4; on nicotine trials = 19.3). Indeed, for three of the five cats demonstrating pawing and cuffing of the prey-object, pawing remained stable or actually increased on nicotine trials, while biting was completely eliminated. In an additional animal not showing pawing on control tests, this response appeared on nicotine tests at a time when biting was suppressed. These findings suggest that nicotine did not invariably produce a general suppression of all behaviors, but rather more selectively reduced the biting component of attack.

GENERAL DISCUSSION

Consistent with previous reports [6, 10, 16], the present results indicate that systemic administration of muscarinic agonists in the cat can induce vigorous and short-latency biting attack on a rat as well as threat behavior. Biting attack consists of distinct components (biting, paw-holding, cuffing, and prey-kicking), which resemble the responses seen during natural predatory behavior [5,17]. These results together with the finding that centrally active muscarinic blockers can suppress both drug induced attack [6] and biting attack induced by hypothalamic stimulation in the cat [15], suggest the existence of a muscarinic (cholinergic) link in central systems for predatory behavior in the cat. Similar lines of evidence exist for predatory behavior in the rat [3, 14, 26, 29, 31].

In contrast to muscarinic compounds, nicotine was found to reduce both arecoline-induced biting attack and natural predatory behavior in the cat, a finding consistent with previous reports of reduced aggressive behaviors in the rat [25] and monkey [9] following nicotine administration. The nicotine-produced suppression of attack, observed in the present study, did not appear to result from the induction of general malaise or from general behavioral suppression, and food intake was only slightly reduced by the nicotine treatments. This latter effect is in contrast to the strong anorexic effects of similar doses of nicotine in the rat [20]. While it is possible that this reflects a species difference in the effects of nicotine, an alternate explanation for this disparity resides in the fact that animals in the present study were not food deprived, and were allowed access to a high incentive food (tuna fish) for only a short time (5 min). Under these conditions, eating may have been largely controlled by the incentive properties of the food, and may have been quite insensitive to potential nicotine effects on other aspects of food motivation. In any event, the minimal effects of nicotine on food intake suggest that the reduction in attack was not due to a generalized reduction in food-getting behaviors. Further, while hunger may potentiate biting attack, cats in the present study were not food deprived and consequently attack must have been motivated by factors other than hunger in the present experiment. In addition to having minimal effects on eating, nicotine produced no significant suppression of the pawing and cuffing components of attack. Rather, nicotine appeared to more selectively suppress the biting components of attack. Since an increase in pawing and cuffing responses, relative to biting, is a characteristic feature of weak predatory behavior [5], it appears that nicotine may reduce attack behavior along the natural dimension of attack strength, rather than generally suppressing all aspects of attack equally.

While the above findings demonstrate a degree of specificity in the behavioral effects of nicotine, the finding that nicotine also strongly inhibits muscarinically-induced threat behavior indicates that its effects are not restricted exclusively to biting attack. Thus, while the present results are consistent with the possible existence of antagonistic muscarinic and nicotinic systems controlling predatory behavior, further work is required to more precisely define the behavioral nature of the nicotine-produced suppression of attack. Similarly, the pharmacological actions of nicotine, with respect to attack behavior, remain obscure. Nicotine can have both excitatory and blocking actions on nicotinic receptors (e.g. [11, 18, 22]), and has also been shown to affect other central neurotransmitter systems as well [2, 7, 12, 13, 30]. While nicotine may suppress attack through a direct action on nicotinic systems, an alternate possibility is suggested by findings that nicotine can cause a marked central release of norepinephrine [7, 12, 13, 30]. Since central adrenergic systems appear to exert an inhibitory influence on predatory behavior [24] it is possible that nicotine suppresses attack through its effects on central catecholamine systems. Nicotine has also been shown to affect the uptake and release of serotonin [2],

which may play a role in the regulation of predatory behavior [8,19]. It is not clear at present which of these or other potential actions of nicotine is responsible for the suppression of attack, and further work will be required to resolve this question. Nevertheless, the present findings clearly document the antagonistic effects of nicotinic and muscarinic compounds on certain aspects of aggressive behaviors.

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