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Effects of Nicotine, Mecamylamine, and Hexamethonium on Shock-Induced Fighting, Pain Reactivity, and Locomotor Behaviour in Rats

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Abstract. Three series of experiments were performed to evaluate possible nicotinic cholinergic influences on fighting behaviour in rats. Each series consisted of three tests (naive animals in each test); shock-induced fighting, pain threshold estimation and locomotor activity. In the first series, nicotine (0.25–1.00 mg/kg) was found to produce a dose-dependent inhibition of fighting without altering shock thresholds. However, the highest dose used also significantly reduced rearing in the activity test. In the second series, mecamylamine (a centrally active antinicotinic) produced a facilitation of fighting at low doses (2.5 mg/kg) and an inhibition at higher doses (10 mg/kg). Whilst these effects were unrelated to changes in shock thresholds, the high dose resulted in a reduction in both horizontal activity and rearing. Finally, as a control for possible peripheral effects of nicotinic blockade, a third series examined the behavioural effects of hexamethonium. Low doses of this compound (2.25–4.5 mg/kg) had little effect on fighting whilst higher doses (9–18 mg/kg) attenuated these responses. Interestingly, although hexamethonium had no effect on shock thresholds, the highest dose (18 mg/kg) produced a facilitation of horizontal activity. Results are discussed in relation to the hypothesis of central nicotinic cholinergic inhibition of agonistic behaviour.

Key words: Fighting – Pain thresholds – Locomotor activity – Nicotine – Mecamylamine – Hexamethonium – Rats

Much of the current evidence favouring central cholinergic mediation of agonistic behaviours directly implicates the involvement of muscarinic receptors (Allikmets, 1974; Avis, 1974; Reis, 1974 for reviews). For example, it has been reported that predatory attack in both rats (McCarthy, 1966) and cats (Berntson et al., 1976) can be induced by muscarinic agonists such as pilocarpine and arecoline. Conversely, centrally active muscarinic antagonists such as atropine have been found to inhibit these induced responses (Vogel and Leaf, 1972; Berntson and Leibowitz, 1973). Isolation-induced fighting in mice (DaVanzo et al., 1966; Karczmar and Scudder, 1969) and shock-induced fighting in both mice (Lapin, 1967; Petersen and Dren 1969) and rats (Powell et al., 1973; Rodgers and Brown, 1973) are also inhibited by centrally active antimuscarinics. It should be noted that these findings suggest central muscarinic involvement since quarternary analogues of these drugs (not readily penetrating the blood-brain barrier) do not produce similar behavioural effects. Finally, such potent inhibitory actions of antimuscarinic drugs have been confirmed in studies employing microinjections into various limbic brain structures (Leaf et al., 1969; Bandler, 1970; Bell and Brown, 1976; Rodgers and Brown, 1976).

In contrast to this wealth of information on muscarinic mechanisms, very few studies have directly examined possible nicotinic influences on agonistic behaviour. For example, nicotine has been reported to reduce intraspecific fighting in rats (Silverman, 1971), inhibit predatory attack in cats (Berntson et al., 1976) and to suppress shock-elicited biting in squirrel monkeys (Hutchinson and Emley, 1973). The aim of the present series of experiments was to further clarify nicotinic influences on agonistic behaviour by extending the above studies to an examination of shock-induced fighting in rats. In the experiments to be reported, the effects of nicotine, mecamylamine and hexamethonium on shock-induced fighting were evaluated. Since non-specific drug action can readily affect responding in this test paradigm, two control tests (within each experiment) were performed to assess possible treatment-induced alterations in pain reactivity and locomotor behaviour.

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Materials and Methods

Subjects

Adult male Sprague-Dawley rats (200–300 g) from the Bradford University colony were used as subjects. Animals were group housed (six/cage) with food and water avilable ad libitum, and were maintained on a 12-h light-dark cycle (7 a.m.–7 p.m.). All testing was performed under red light between 9 a.m.–1 p.m.

Apparatus

Shock-Induced Fighting and Flinch-Jump Tests. A modified rat operant station measuring 23.5 × 22 × 22 cm served as the test chamber. The chamber was housed within a sound-attenuating enclosure and observations were made via a small perspex window in the front of the enclosure. An Aim Bioscience shock generator (model 507) supplied electric shock of specified intensity, duration and frequency to the grid floor of the test chamber.

Activity Test. A square box with white floor and walls (90 × 90 × 30 cm high) was used. Embedded in two adjacent walls were two banks of six light sources (red). The lower bank was positioned 3 cm above the floor level (to monitor horizontal activity) with the upper bank at 12.5 cm (to monitor rearing). On opposing walls, two banks of six sensors were arranged to receive light beams from the corresponding sources. Sensors from upper and lower banks were connected to separate counters which registered one count each time an appropriate light beam was interrupted.

Procedures

Shock-Induced Fighting. Weight-matched pairs of animals (one injected and one non-injected stimulus opponent) were placed in the test chamber and allowed 2 min habituation. The animals were then exposed to 60 electric shocks delivered to the grid bars (2 mA intensity; 0.5 s duration and 6/min frequency). Attack responses were recorded when one animal made a directed forward lunge either with forepaws or whole body. The upright boxing posture itself did not constitute an attack response. Only the behaviour of the injected animals was used in the data analysis.

Aversive Thresholds. Pain reactivity was measured using a modification of the flinch-jump test (Evans, 1961; Rodgers, 1977). Individual animals were placed in the test chamber where they received six series of eight electric shocks (0.5 s duration) delivered at 10 s intervals to the grid floor. Shock series were administered in alternating ascending and descending order with intensities ranging 0.1–1.0 mA in eight steps. Jump thresholds (the intensity at which the animals hind feet leave the grid floor) were recorded for each series and an overall mean value calculated to provide an estimate of pain reactivity.

Locomotor Activity. In this test, individual animals were placed in the activity box and, over a 10 min observation period, horizontal activity and rearing were recorded.

In all behavioural tests, the apparatus used was cleansed thoroughly after each session to as far as possible eliminate any olfactory cues from preceding subjects.

Drugs. The drugs used in this series of experiments were nicotine hydrogen tartrate, mecamylamine hydrochloride and hexamethonium bromide. Compounds were dissolved in physiological saline which alone served as vehicle control. All drugs were injected IP (volume 1 ml/kg) 15 min prior to testing. The doses cited in all cases refer to the salt.

Statistics. Results were initially analyzed using one-way analysis of variance (ANOVA; independent). In cases where overall significance was obtained, further analysis was performed using Duncan's multiple range tests.

Results

Experiment 1. This experiment examined the effects of various doses of nicotine on shock-induced fighting and the two control tests.

Eighty rats were used in this study. In the shock-induced fighting test, 40 animals were randomly assigned to two equal groups (experimental and stimulus opponent). The experimental group was further subdivided into four equal treatment groups (saline and 0.25, 0.50 and 1.00 mg/kg nicotine hydrogen tartrate); these subgroups were then weight-matched with non-treated stimulus opponents. Two naive groups (N in each = 20) were used in the flinch-jump and activity tests, following the above treatment design. Since any observed behavioural change in these tests may have reflected peripheral autonomic effects of nicotine administration, all experimental animals were pretreated (10 min prior to main treatment) with 0.2 mg/kg hexamethonium. Pilot studies had indicated that this dose of the quarternary antinicotinic drug is without effect on all three tests.

Shock-induced fighting was significantly inhibited by nicotine [$F = 26.87\,(3, 16)$, $P > 0.001$]. Further analysis revealed that whilst the lowest dose (0.25 mg/kg) was without effect compared to control values, significant decrements in fighting were produced by both 0.50 mg/kg ($P < 0.05$) and 1.00 mg/kg ($P < 0.01$) doses. The dose-dependent action of nicotine was further indicated by the finding that the highest dose used induced effects significantly different to all other treatments ($P < 0.01$). Figure 1 summarizes these results.

ANOVA revealed no overall significance on jump thresholds [$F = 1.56\,(3, 16)$, NS]. Table 1 (panel A) gives the mean values (± SEM) for the various treatment conditions. Whilst horizontal activity was not significantly altered by nicotine [$F = 1.71\,(3, 16)$, NS], vertical activity was significantly depressed [$F = 7.08\,(3, 16)$, $P < 0.01$]. Subsequent analysis indicated that

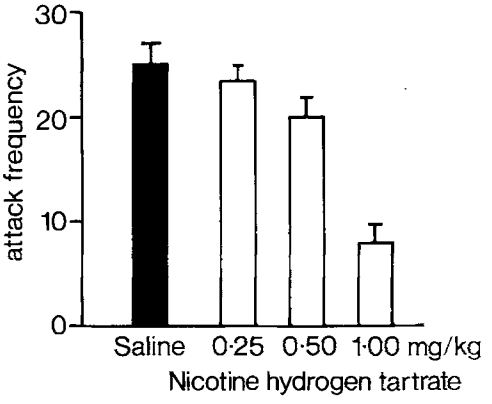

Fig. 1. Effects of nicotine hydrogen tartrate on frequency of attack ($\bar{X}$ ± SEM) in the shock-induced fighting test

Table 1. Effects of nicotine (panel A), mecamylamine (panel B) and hexamethonium (panel C) on aversive thresholds (mA)

Panel A		Panel B		Panel C	
Nicotine (mg/kg)	mA ($\bar{X} \pm$ SEM)	Mecamylamine (mg/kg)	mA ($\bar{X} \pm$ SEM)	Hexamethonium (mg/kg)	mA ($\bar{X} \pm$ SEM)
Saline	0.38 ± 0.01	Saline	0.37 ± 0.03	Saline	0.38 ± 0.02
0.25	0.41 ± 0.04	1.25	0.32 ± 0.03	2.25	0.37 ± 0.01
0.50	0.44 ± 0.03	2.50	0.35 ± 0.04	4.50	0.39 ± 0.03
1.00	0.42 ± 0.05	5.00	0.35 ± 0.02	9.00	0.37 ± 0.01
		10.00	0.34 ± 0.04	18.00	0.36 ± 0.01

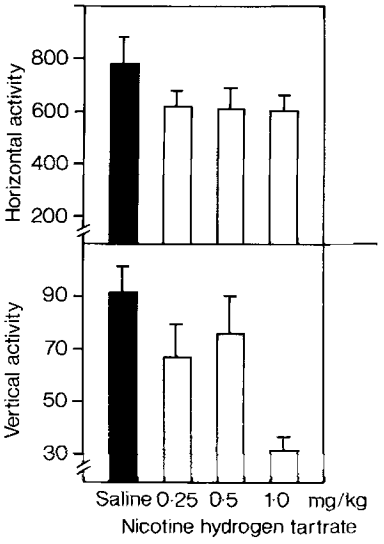

Fig. 2. Effects of nicotine hydrogen tartrate on horizontal and vertical activity ($\bar{X} \pm$ SEM)

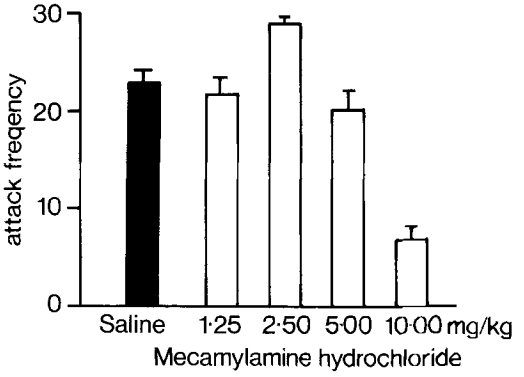

Fig. 3. Effects of mecamylamine hydrochloride on frequency of attack ($\bar{X} \pm$ SEM) in shock-induced fighting test

only 1.00 mg/kg nicotine produced a significant reduction when compared to control ($P < 0.01$). These results are presented in Fig. 2.

Experiment 2. To further examine nicotinic influences on shock-induced fighting behaviour, a second experiment assessed the behavioural effects of the centrally active nicotinic antagonist mecamylamine hydrochloride.

One-hundred animals were used in this study. In the shock-induced fighting test, 50 rats were randomly allocated to two equal groups (experimental and opponent). The experimental group was further subdivided into five equal treatment conditions (saline and 1,25, 2.50, 5.00 and 10.00 mg/kg mecamylamine hydrochloride). Two naive groups (N in each = 25) were used in the flinch-jump and activity tests. In each of these tests, animals were randomly assigned to treatment groups identical with the above design.

ANOVA revealed a significant overall effect on fighting behaviour [$F = 39.09$ (4, 20), $P < 0.001$]. Statistical follow-up indicated that, compared to controls, fighting was significantly increased by 2.5 mg/kg ($P < 0.05$) and depressed by 10 mg/kg ($P < 0.01$) mecamylamine. No other drug versus control comparisons were significant. Results are summarised in Fig. 3.

In the flinch-jump test, mecamylamine failed to alter aversive thresholds [$F = 0.54$ (4, 20), NS]. Mean values (± SEM) are presented in Table 1 (panel B). Horizontal activity was significantly altered by mecamylamine treatment [$F = 7.31$ (4, 20), $P < 0.01$], an effect that was attributable to a large reduction in this behaviour produced by 10 mg/kg ($P < 0.01$). On vertical activity, ANOVA also revealed significance [$F = 5.9$ (4, 20), $P < 0.01$], which upon statistical follow-up could be attributed to a dose-dependent decrease in rearing produced by 2.5 mg/kg ($P < 0.05$), 5.0 mg/kg ($P < 0.05$) and 10 mg/kg ($P < 0.01$) mecamylamine. Figure 4 summarises these results.

Experiment 3. The results of experiment 2 suggested that, at low doses, a centrally active nicotinic antagonist produces a significant facilitation of fighting behaviour. To control for the possibility that this observation may merely have reflected a peripheral action of this drug, experiment 3 examined the behavioural ef-

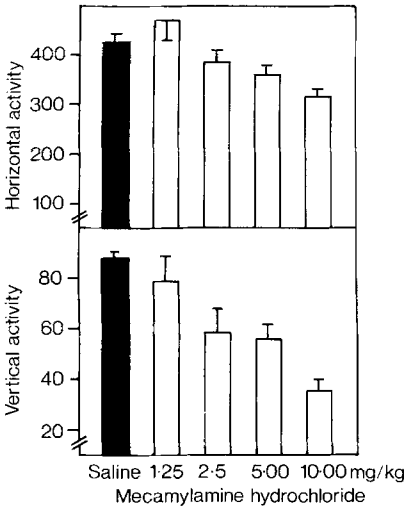

Fig. 4. Effects of mecamylamine hydrochloride on horizontal and vertical activity ($\bar{X} \pm$ SEM)

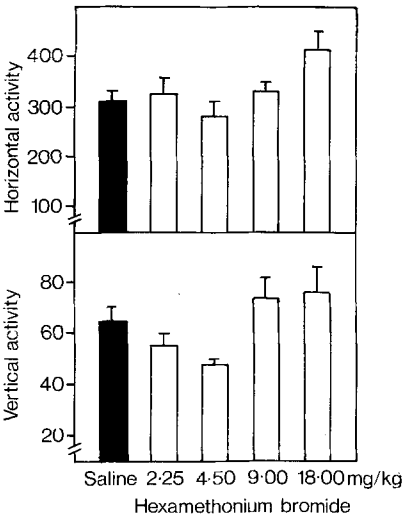

Fig. 6. Effects of hexamethonium bromide on horizontal and vertical activity ($\bar{X} \pm$ SEM)

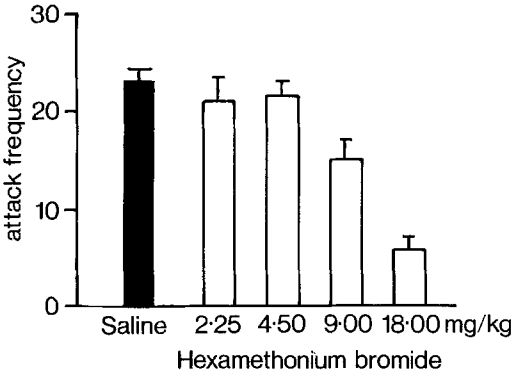

Fig. 5. Effects of hexamethonium bromide on frequency of attack ($\bar{X} \pm$SEM) in the shock-induced fighting test

fects of equimolar doses of the quarternary anti-nicotinic hexamethonium bromide.

One-hundred rats were used in this study. These animals were randomly allocated to various test and treatment groups in accordance with the design of experiment 2. However, in this case the treatment conditions were saline and 2.25, 4.50, 9.00 and 18.00 mg/kg hexamethonium bromide.

ANOVA revealed overall significance on fighting responses [$F = 14.47\ (4, 20)$, $P < 0.01$]. Duncans' tests indicated that, compared with controls, fighting was significantly reduced by both 9 mg/kg ($P < 0.05$) and 18 mg/kg ($P < 0.01$) doses of hexamethonium. Figure 5 summarises these results.

Jump thresholds were unaffected by the administration of hexamethonium [$F = 0.31\ (4, 20)$, NS]. Mean values ($\pm$ SEM) for the various conditions are summarised in Table 1 (panel C).

Horizontal activity was significantly altered by hexamethonium [$F = 3.46\ (4, 2020)$, $P < 0.05$], an effect that was attributable to increased activity levels with 18 mg/kg dose ($P < 0.05$). On vertical activity, ANOVA failed to yield significance [$F = 2.34\ (4, 20)$, NS]. Figure 6 summarises these results.

Discussion

The present studies provide at least partial support for the suggestion that central nicotinic and muscarinic cholinergic systems play antagonistic roles in the mediation of agonistic behaviours (Berntson et al., 1976). Muscarinic facilitation of shock-induced fighting has previously been reported in both peripheral (Powell et al., 1973; Rodgers and Brown, 1973) and central (Bell and Brown, 1976; Rodgers and Brown, 1976) injection experiments. In contrast, current data suggest an inhibitory role for central nicotinic systems in this form of fighting behaviour.

In experiment 1, nicotine (0.25 – 1.00 mg/kg) produced a dose-dependent suppression of shock-induced fighting, thus supporting previous evidence for nicotinic inhibition of other agonistic response patterns (Silverman, 1971; Hutchinson and Emley, 1973; Berntson et al., 1976). Within the dose range employed, nicotine failed to alter shock thresholds thus eliminating a possible indirect effect on fighting via changes in pain reactivity. This finding confirms earlier reports on the ineffectiveness of nicotine in modifying aversive thresholds (Oliverio, 1966; Houser, 1976). However, whilst horizontal activity remained unchanged under all doses, vertical activity (rearing) was greatly reduced by the highest dose of nicotine (1 m/kg). Thus, the possibility exists that the potent inhibitory action of 1 mg/kg nicotine on fighting was secondary to altered patterns of activity.

Interestingly, these activity results both confirm and fail to confirm previous studies. The inhibitory action of high nicotine doses on rearing confirms the findings of Morrison and Lee (1968). In contrast, our failure to find effects of nicotine on horizontal activity is at variance with the literature. At low doses (0.2 mg/kg), nicotine has been found to increase activity (Averett, 1967; Driscoll and Battig, 1970; Battig et al., 1976) and at higher doses (0.4–2.0 mg/kg) to decrease activity (Averett, 1967; Stolerman et al., 1974; Fleming and Broadhurst, 1975). A possible reconciliation of these contradictory findings may be found in the work of Morrison and Lee (1968) who reported that nicotine facilitates activity in animals with low basal activity levels and suppresses activity in animals with high basal activity. It seems possible that, in the current experiment, these opposing effects of nicotine were cancelled out through intra-group variability in basal activity levels. It is pertinent to note that Pryor et al. (1978) have also recently failed to find significant effects on horizontal activity with a similar dose range of nicotine to that used here.

However, the finding that a lower dose of nicotine (0.5 mg/kg) did not produce changes in either horizontal or vertical activity suggested a more selective action of nicotine on fighting behaviour. This suggestion was supported by the results of experiments 2 and 3. At low doses (2.5 mg/kg), the centrally active nicotine antagonist mecamylamine facilitated fighting, an effect not observed with equimolar dose of hexamethonium (quarternary antinicotinic). Although this dose of mecamylamine resulted in a small (but significant) depression of rearing, it seems unlikely that this change could account for enhanced levels of fighting behaviour. At higher doses, both compounds severely depressed fighting but, interestingly, exerted opposite effects on activity measures. Mecamylamine (10 mg/kg) depressed both horizontal and vertical activity whilst hexamethonium (18 mg/kg) facilitated horizontal activity without altering vertical behaviour. Although it is possible to equate both of these activity effects with decreased fighting it does not seem possible to ascribe the action of mecamylamine on activity to peripheral nicotinic blockade. Of course, the possibility needs to be considered that other peripheral ganglionic-blocking actions common to both drugs may have significantly contributed to the observed behavioural effects. For example, ptosis was observed with the highest dose of each compound. However, it is unlikely that impaired visual function alone could explain decreased fighting since visual integrity appears to be relatively unimportant in shock-induced fighting (Flory et al., 1965; Bugbee and Eichelman, 1972; Ghiselli and Thor, 1975). An alternative suggestion would appear to be that the potent inhibitory effects of 10 mg/kg mecamylamine on both fighting and activity relate to comparatively non-specific actions on central mechanisms.

The behavioural effects of hexamethonium also require further comment. As mentioned above, the facilitation of activity produced by 18 mg/kg hexamethonium may explain the observed decrement in fighting at this dose. This interpretation cannot, on the other hand, account for the inhibitory action of 9 mg/kg hexamethonium on fighting behaviour. Nor can this effect be related to altered shock thresholds since these responses were unaffected by both drugs in the dose ranges used. One possible interpretation of these findings is that hexamethonium, normally considered peripherally active only, actually penetrated the blood-brain barrier. In fact Asghar and Roth (1971) have reported that within 5 min of systemic injection, hexamethonium (10–30 mg/kg) can be detected in the basal ganglia and cerebral cortex. In this context, it is interesting to note that Driscoll (1976) has recently reported that very small doses of mecamylamine (0.25 mg/kg) can affect avoidance behaviours in a manner very similar to nicotine (0.1 mg/kg). It seems possible that in the present experiment, the high doses of hexamethonium, by penetrating the blood-brain barrier, may have yielded low levels of the drug in brain tissue and that this contributed to nicotine-like effects on fighting behaviour. A similar suggestion has been made concerning the similarity between the effects of nicotine and hexamethonium on avoidance behaviour in rats (Evangelista et al., 1970). However, the actual mechanism whereby central hexamethonium exerts its effects on fighting (and possibly activity) remains to be elucidated.

Whilst present data are consistent with the hypothesis of central nicotinic cholinergic inhibition of fighting in rats, further studies are required to determine the precise nature of this influence. Although current findings may reflect direct action on nicotinic systems, an alternative possibility is that the observed effects relate to an indirect action on other neurotransmitter systems. For example, nicotine has been shown to affect both catecholaminergic (Westfall, 1974) and serotonergic (Balfour, 1973) function, both of which have been implicated in the regulation of shock-induced fighting (Reis, 1974).

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