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Characteristics of conditioned taste aversion produced by nicotine in rats

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1 Nicotine produced conditioned taste aversions in rats which were directly related to the dose of nicotine and to the number of conditioning trials.

2 The tobacco alkaloid (−)-nicotine was four to five times as potent as its stereoisomer, (+)-nicotine.

3 Mecamylamine but not hexamethonium blocked the development of taste aversions produced by nicotine.

4 Mecamylamine did not block the development of taste aversions produced by apomorphine.

5 Prolonged treatment with mecamylamine prior to conditioning did not produce supersensitivity to nicotine.

Introduction

Nicotine contributes to the maintenance of cigarette smoking through its positive reinforcing effects, whereas its possible aversive properties (perhaps linked with nausea, vomiting or dizziness) may set an upper limit to smoke intake (Kumar & Stolerman, 1977; Russell, 1979). Experiments in squirrel monkeys have confirmed both the powerful positive reinforcing effect and the aversive effect (Goldberg, Spealman & Goldberg, 1981; Goldberg & Spealman, 1982). Conditioned taste aversions (CTA) provide one possible approach for studying aversive effects of drugs in rats, although it is not certain that the effects of drugs studied by this method are equivalent to aversive effects which motivate conventional punished or negatively reinforced behaviour (Stolerman & D'Mello, 1981). This paper describes experiments aimed at characterizing the actions of nicotine in CTA procedures. Etscorn (1980) has reported briefly on CTA produced in mice by nicotine at the relatively large dose of 2 mg/kg. Possible aversive effects of other constituents of smoke (e.g. carbon monoxide) have not been studied yet.

In typical CTA experiments, rats learn to reject a distinctively flavoured solution when its consumption reliably precedes and thus signals exposure to putative aversive stimuli (Garcia & Ervin, 1968). Traditionally, such findings have been interpreted as evidence for the development of associations between flavour stimuli and noxious effects of drugs (e.g., nausea, gastrointestinal disturbance or other toxic effects). Emesis produced by nicotine is mediated at least partly through the *area postrema* (Laffan & Borison, 1957), and studies with nicotine might therefore help to clarify the role of emetic mechanisms in CTA. Coil, Hankins, Jenden & Garcia (1978) were able to attenuate CTA with some antiemetic drugs although Goudie, Stolerman, Demellweek & D'Mello (1982) were unable to obtain such effects.

The aim of the first experiments was to test whether nicotine could produce CTA in rats with a standardized procedure used previously in studies on amphetamine, apomorphine and related compounds (Booth, D'Mello, Pilcher & Stolerman, 1977; D'Mello, Goldberg, Goldberg & Stolerman, 1981). Dose-response relations for the CTA effect of nicotine were then studied with fewer conditioning trials in order to develop a more rapid method, better suited to further pharmacological analysis.

The stereospecificity of the nicotine-produced CTA was examined and the effects of pretreatment with two ganglion-blocking drugs (mecamylamine and hexamethonium) were determined to facilitate comparisons with other behavioural effects of nicotine. Mecamylamine is thought to penetrate readily to the central nervous system. In order to determine whether the block of the nicotine CTA had any pharmacological specificity, mecamylamine was also tested against the CTA produced by apomorphine. Pratt & Stolerman (1982) have given a preliminary account of some of these results.

Finally, the CTA produced by nicotine was examined after prolonged exposure to mecamylamine. Emmelin (1961) has reviewed evidence that chronically administering ganglion-blocking drugs can produce 'pharmacological denervation' supersensitivity in peripheral systems. It is not known whether comparable effects can be produced at central nicotinic sites.

Methods

Animals

Male, Lister hooded rats from a commercial supplier (Olac, Bicester) were used throughout. The overall range of weights was 240–340 g, but within any one experiment the range was smaller. Rats were housed individually in rooms maintained at about 22°C, with a regular, light-dark cycle (light from 08 h 00 min–20 h 00 min).

Two weeks after rats arrived in the laboratory, their access to water was restricted to 1 h per day (10 h 00 min–11 h 00 min). Rats remained on this regimen for seven days before any flavoured solutions were presented, and on all days between flavour presentations throughout the rest of the experiment. The studies were carried out in the rats' living cages to which were attached two calibrated glass drinking tubes, one on each side of the food hopper. The cages had dimensions of 20 × 16 × 30 cm.

Conditioning procedure

The procedure was based on that used by Booth *et al.* (1977) but with several modifications. After the seven days of adaptation to the regimen of water presentation, one of two flavoured solutions (sodium saccharin 0.1% or sodium chloride 0.9%) was presented for 15 min on every second day (beginning at 10 h 00 min). The two flavoured solutions were presented alternately, and thus each flavour was presented to a given rat every fourth day. Immediately after the flavoured solutions were removed, the rats were injected with either nicotine or saline (flavour-injection 'pairing'). For half of the rats in which a given dose of nicotine was being tested, one flavour was repeatedly paired with that dose, whereas the other flavour was paired with saline. The flavour-injection pairings were reversed in the remaining rats, thus ensuring that effects of the inherent palatabilities of the flavours were balanced out in the averaged results. The order of nicotine and saline injections was also counterbalanced at each dose. An additional 10 ml of water was presented 15 min after removing the flavoured solutions, to ensure that the rats had sufficient fluids each day. To minimize position preferences, the rats were given an equal number of opportunities to drink both flavoured solutions, and water on each side of the cage.

The first experiment used a 'four-trial procedure'; injections were stopped after four flavour-nicotine and four flavour-saline pairings ('one-stimulus tests'), as in Booth *et al.* (1977). Two days later, nicotine- and saline-paired flavoured solutions were presented simultaneously for 15 min ('two-stimulus test'). On the next day, the test was repeated with the positions of the two stimuli (flavours) reversed to balance out side preferences. The mean scores for the two days of two-stimulus tests are presented. In later experiments, injections were stopped after either one or two sets of flavour-injection pairings ('one-trial' and 'two-trial' procedures), and the two-stimulus tests began two days later in each case. Two-stimulus tests provided the main measure of CTA since they were known from many previous studies to be more sensitive than one-stimulus tests.

Pretreatment experiments (acute)

The two-trial conditioning procedure was used throughout and the effects of administering putative blocking drugs before the one-stimulus tests (conditioning trials) were examined. Different groups of rats were pretreated with either a dose of a drug or its vehicle, and these groups were then compared with respect to the degree of CTA produced by nicotine (or apomorphine). This CTA was assessed during two-stimulus tests beginning two days after the final one-stimulus test, and no additional injections were given at that stage. The interval between pretreatment injections and access to flavoured solutions was 15 min for mecamylamine and hexamethonium, and for each group of rats, the same pretreatment injections were given before each of the four one-stimulus tests.

Pretreatment experiments (prolonged)

Experimental rats were presented with solutions of mecamylamine in place of their usual drinking water for 20 days. These solutions were freely available at all times and fresh solutions were normally supplied every other day. The concentration of mecamylamine was initially 0.025 mg/ml, and this was increased to 0.05 mg/ml and 0.1 mg/ml after one and two days respectively. On the eighth day, the concentration was increased to 0.15 mg/ml, which was then held constant for 12 days. Control rats received water throughout this period. The solutions of mecamylamine were removed on the 21st day and all rats were allowed access only to water for 1 h on the 22nd day (10 h 00 min–11 h 00 min). The first one-stimulus test began at 10 h 00 min on the 23rd

day and, thereafter, the standard two-trial conditioning procedure was followed. Subgroups of the control rats and of those previously exposed to mecamylamine for 20 days were conditioned with different doses of nicotine, so that any effects of the mecamylamine on the nicotine dose-response relationship could be examined.

Statistical analyses

The methods used for presenting dose-response data were those of Booth *et al.* (1977) and D'Mello *et al.* (1981). For the four-trial procedure only, the 'aversion index' was defined as the rate of change (linear regression coefficient) of flavoured solution intake over the four one-stimulus tests. This index was calculated separately for drug- and saline-paired flavoured solutions for each rat, and the data so obtained were analysed by *t* tests or analyses of variance. Modified ED_{50} values were calculated as described in detail by D'Mello *et al.* (1981). For all two-stimulus tests, the amount consumed of the flavoured solution previously paired with drug injections was calculated as a percentage of the total fluid intake for each rat. These percentage scores were subjected to arc-sine transformations to normalize their distributions (Winer, 1971), and then *t* tests were carried out to determine whether the means differed significantly from 50%. A mean score of 50% would indicate that a drug produced neither conditioned aversion nor conditioned preference. Scores significantly below 50% indicate CTA. A mean score of 25% was taken as a half-maximal degree of CTA when comparing different dose-response curves.

Drugs

(−)-Nicotine bitartrate (BDH) was dissolved in isotonic saline and the pH was adjusted to 7 with a dilute solution of sodium hydroxide. Optically pure (+)-nicotine bitartrate (supplied by Dr J.M. Littleton) was treated in the same way as (−)-nicotine. (+)-Amphetamine sulphate (SKF), mecamylamine hydrochloride (MSD), hexamethonium bromide (Sigma) were dissolved in saline. Apomorphine hydrochloride (Macfarlan Smith) was dissolved in a solution of ascorbic acid (0.2 mg/ml) in distilled water. All doses were expressed as those of the bases and all injections were given subcutaneously in the flank, in a volume of 1 ml/kg.

Results

Comparison of nicotine with reference drug (amphetamine)

The results at three doses of (−)-nicotine are shown in Figure 1. The mean intake of flavoured solutions paired with nicotine (0.08 mg/kg) fell steadily over successive presentations, whereas the intake of saline-paired flavoured solutions by the same rats remained relatively constant (Figure 1b, trials 1–4). The difference between the aversion indices for nicotine- and saline-paired flavours was highly sig-

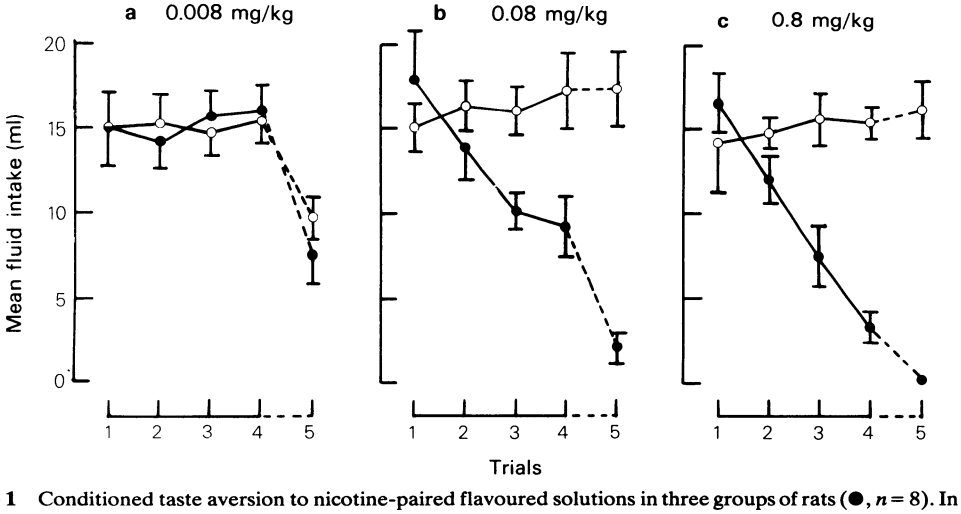

Figure 1 Conditioned taste aversion to nicotine-paired flavoured solutions in three groups of rats (●, $n = 8$). In the same rats, intakes of saline-paired flavoured solutions were not suppressed (○). Trials 1–4 were conditioning sessions (one-stimulus tests). Trial 5 was two-stimulus test with simultaneous presentation of both flavoured solutions, hence the fall apparent in consumption of each solution in (a). Vertical bars in this and subsequent figures show s.e.mean; overlapping bars and those shorter than diameters of symbols are omitted for clarity.

nificant ($t = 4.48$, d.f. 7, $P < 0.01$). The development of discriminative CTA was confirmed in the two-stimulus tests, where both the nicotine- and saline-paired flavoured solutions were presented simultaneously (trial 5).

Figure 1a shows that nicotine did not produce a detectable degree of CTA at a dose of 0.008 mg/kg; the mean intakes of the nicotine- and saline-paired flavoured solutions did not differ significantly even in the two-stimulus tests. The rather greater magnitude of the CTA when the dose of nicotine was increased to 0.8 mg/kg is shown in Figure 1c. In this example, the rats consumed an average of only 3.3 ml of the nicotine-paired flavoured solutions during the last of the one-stimulus tests (trial 4), despite having been deprived of all fluids for 23 h and not having received any nicotine for 4 days. The mean control score for the saline-paired flavoured solutions on their fourth presentations (to the same rats) was 15.4 ml.

The results at intermediate doses of nicotine are not presented in detail but are included in Figure 2, in comparison with data for amphetamine (0.06–0.60 mg/kg). The intakes of saline-paired flavoured solutions were not affected by the dose of nicotine or amphetamine which was paired with the alternate flavours, and the results for saline-paired flavoured solutions have therefore been pooled to yield the baseline data (0 mg/kg) for Figure 2. Clear dose-response relations for CTA to nicotine-paired and to amphetamine-paired flavoured solutions can be seen, with nicotine being clearly the more potent of the two drugs. The ED_{50} values (with 95% confidence limits) were 0.075 (0.037–0.144) mg/kg for nicotine and 0.22 (0.13–0.34) mg/kg for amphetamine. This difference was also reflected in the ED_{50} values calculated on a molar basis, which were 0.46 μmol/kg and 1.59 μmol/kg for nicotine and amphetamine respectively.

Nicotine-produced CTA related to number of conditioning trials

Figure 3 shows dose-response curves for the CTA effect of nicotine after previous exposure to either one, two or four conditioning trials. These data were all obtained from two-stimulus tests and in the case of the four-trial procedure, from the same set of rats used in the experiments shown in Figures 1 and 2. Figure 3 shows that the larger the number of previous conditioning trials, the smaller the dose of nicotine

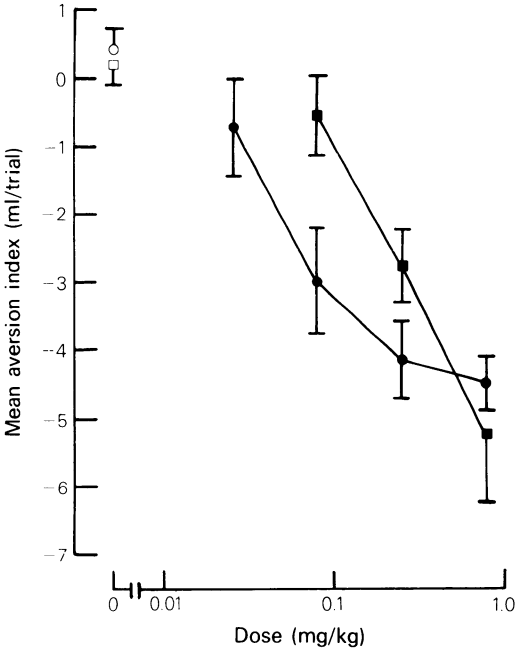

Figure 2 Dose-response curves (n =8) for conditioned taste aversions produced by nicotine (●) and amphetamine (■). Ordinate scale shows mean aversion index calculated from one-stimulus tests. A different group of rats was used to obtain each datum point. Pooled results for saline-paired flavoured solutions provided control data from same rats (○ and □).

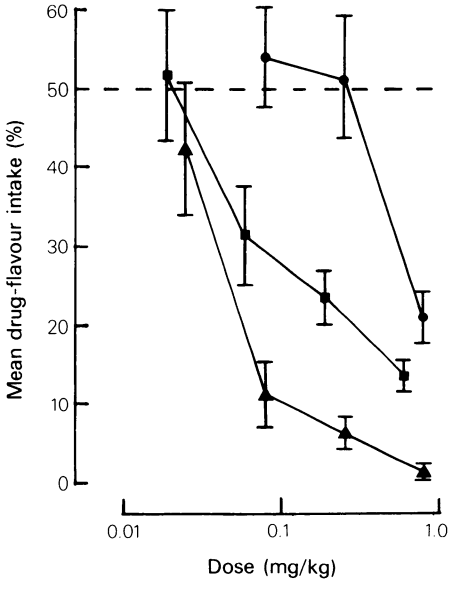

Figure 3 Dose-response curves for conditioned taste aversions produced by nicotine after different numbers of conditioning trials (n = 8). Ordinate scale shows mean intake of drug-paired flavoured solution in two-stimulus tests, expressed as a percentage of total fluid intake. CTA was weakest after one conditioning trial (●), and increased progressively after two trials (■) and four trials (▲). The horizontal dashed line shows expected mean score in absence of drug effects.

Table 1 Conditioned taste aversions produced by (+)-nicotine in rats

(+)-*Nicotine dose* (mg/kg)	n	*Drug-paired flavour intake* (% ± s.e.mean)
0.40	8	37.7 ± 8.6
0.71	8	24.7 ± 3.5***
1.26	8	13.6 ± 2.2***
4.00	8	16.9 ± 4.3***

Data are all derived from two-stimulus tests. Values for P relate to comparisons of mean scores with 50%, and thus test whether significant CTA was present. ***$P < 0.001$.

needed to produce a given degree of CTA. After a single conditioning trial, only a relatively large, 0.8 mg/kg dose of nicotine produced significant CTA ($t = 7.59$, d.f. 7, $P < 0.001$). In contrast, after two conditioning trials, nicotine (0.06 mg/kg) produced CTA ($t = 2.82$, d.f. 7, $P < 0.05$).

The change in sensitivity as a function of the number of conditioning trials was reflected in the doses of nicotine needed to produce half-maximal degrees of CTA. These doses fell from 0.66 (0.46–1.54) mg/kg after one conditioning trial to 0.15 (0.07–0.29) mg/kg after two trials, and to 0.046 (0.022–0.075) mg/kg after four trials. For further studies, the two-trial procedure was considered to maintain reasonable sensitivity without being as time-consuming as the previously used, four-trial technique.

CTA produced by (+)-nicotine

The stereoisomer (+)-nicotine was tested at several doses using the two-trial procedure described above. Table 1 shows that this compound produced CTA when given in doses of 0.71 mg/kg or more; the effect was dose-related although there was no significant difference between the CTA produced by the two largest doses tested. The rats conditioned with (+)-nicotine (1.26 mg/kg) may be considered as an example. The amounts consumed of the drug-paired flavoured solutions on their first and second presentations were 16.9 ± 2.4 ml and 12.9 ± 1.8 ml respectively, whereas the corresponding results for the saline-paired flavoured solutions were 16.1 ± 1.1 ml and 16.4 ± 1.3 ml; the possible weak CTA was not significant ($t = 2.15$, d.f. 7). However, in the subsequent two-stimulus tests, the intakes of the drug- and saline-paired flavoured solutions were 2.6 ± 0.6 ml and 12.8 ± 1.2 ml respectively, yielding the significant CTA represented by the percentage score in Table 1. The patterns of fluid intake at other doses of (+)-nicotine are not presented in detail since they resemble those for (−)-nicotine which are shown in Figure 3a.

The dose of (+)-nicotine needed to produce a half-maximal degree of aversion (i.e. mean score of 25%) was 0.67 (0.41–0.97) mg/kg, calculated from the sensibly linear portion of the dose-response curve (doses of 0.40–1.26 mg/kg). When compared with the previously determined value of 0.15 mg/kg for (−)-nicotine, a potency ratio of 4.5:1 was obtained.

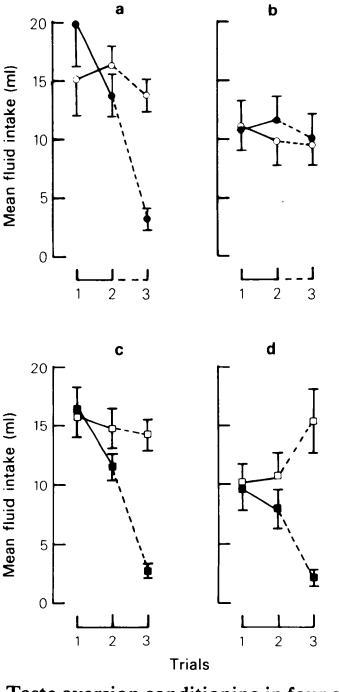

Figure 4 Taste aversion conditioning in four groups of rats with $n = 8$ except in (a) where $n = 6$. In (a) nicotine produced CTA which in (b) was blocked by mecamylamine. In (c) apomorphine produced CTA which in (d) was *not* blocked by same dose of mecamylamine. Doses of nicotine (●) and apomorphine (■) were 0.4 mg/kg. Intakes of control flavoured solutions for each group of rats provided baselines for assessing degree of CTA (○ and □).

Table 2 Effects of pretreatments with drugs on development of conditioned taste aversions (CTA) in rats

Pretreatment	n	*Drug-paired flavour intake* (% ±s.e.mean)
Nicotine (0.4 mg/kg) CTA		
Saline	14	17.6±2.6***
Mecamylamine 0.10 mg/kg	8	19.1±2.3**
Mecamylamine 0.32 mg/kg	8	33.1±5.9*
Mecamylamine 1.0 mg/kg	8	32.2±6.7*
Mecamylamine 2.0 mg/kg	8	48.7±9.8
Hexamethonium 1.0 mg/kg	4	15.4±4.4**
Hexamethonium 3.2 mg/kg	8	14.9±4.2***
Hexamethonium 10.0 mg/kg	8	21.9±7.0**
Apomorphine (0.4 mg/kg) CTA		
Saline	8	16.4±4.0***
Mecamylamine 2.0 mg/kg	8	15.9±4.8***

Data are all from two-stimulus tests (trial 3).
Mecamylamine and hexamethonium were given 15 min before access to flavoured solutions on previous conditioning trials 1 and 2 (data not shown; see Figure 3). Values for P relate to comparison of mean scores with 50%, thus testing whether significant CTA was present. *$P<0.05$; **$P<0.01$; ***$P<0.001$.

Acute effects of ganglion-blocking drugs

Initially, the effect of pretreatment with mecamylamine was tested on the development of CTA produced by nicotine. In rats receiving mecamylamine (2.0 mg/kg) before each conditioning trial, nicotine (0.4 mg/kg) did not produce a detectable degree of CTA (Figure 4b). Control rats from that experiment received saline injections whenever the experimental animals received mecamylamine, and in the controls the nicotine CTA was well established by trial 3 (Figure 4a). Mecamylamine (2.0 mg/kg) also reduced the mean amounts consumed of the flavoured solutions at trial 1, the baseline from which the development of CTA was assessed. Thus, Figure 4 shows that the control rats consumed 15–20 ml of the flavoured solutions, whereas the rats receiving mecamylamine consumed an average of only 11 ml. It is not known whether mecamylamine (2.0 mg/kg) would also reduce the intake of plain water.

The results for all doses tested of mecamylamine are summarized in Table 2. The scores for the controls ($n=14$) were obtained by pooling the very similar results from all the control rats used in these experiments. It can be seen that the CTA produced by nicotine (0.4 mg/kg) was completely blocked by mecamylamine (2.0 mg/kg) and that the block seemed to be dose-related. Doses of mecamylamine less than 2.0 mg/kg had no significant effects on the baseline consumption of flavoured solutions. Table 2 also shows that none of the doses tested of hexamethonium influenced the CTA produced by nicotine.

The effect of mecamylamine (2.0 mg/kg) was then tested on the CTA produced by apomorphine (0.4 mg/kg). The results of these experiments are also shown in Figure 4 and Table 2. In control rats pretreated with saline, the apomorphine CTA was well developed at trial 3 (Figure 4c). The magnitude of the CTA was similar to that of the CTA produced by nicotine (0.4 mg/kg). At trial 1, mecamylamine reduced the mean amounts consumed of the flavoured solutions from 16.1 ml to 9.9 ml. However, mecamylamine did not prevent the development of the apomorphine CTA, as can be seen most clearly from the results for trial 3. The percentage scores in Table 2 confirm that mecamylamine (2.0 mg/kg) did not influence the development of the apomorphine CTA, despite the reduced intake of the flavoured solutions during the conditioning trials.

Prolonged treatment with mecamylamine

Rats readily consumed solutions of mecamylamine when these were substituted for their usual drinking water at concentrations increasing progressively from 0.025 mg/ml. Twenty-four of the 28 rats receiving mecamylamine in this way went on to consume the drug solution consistently and were used in the CTA experiments. For these animals, the dose of mecamylamine on the first day was 1.77±0.18 mg/kg (mean±s.e.mean), and this increased progressively as the concentration of mecamylamine was raised to 0.15 mg/ml. The mean dose for the last five days of access to solutions of mecamylamine was 10.4±0.2 mg/kg daily. During these five days, the mean amounts consumed by

Table 3 Conditioned taste aversions produced by nicotine after prolonged administration of mecamylamine in rats

Nicotine dose (mg/kg)	*Drug-paired flavour intake* (% ± s.e.mean) *Controls*	*Mecamylamine*
0.04	32.4 ± 5.2*	47.5 ± 8.1
0.126	22.7 ± 4.4***	25.0 ± 4.9**
0.40	18.3 ± 4.5***	10.2 ± 4.2***

Data are all derived from two-stimulus tests. Mecamylamine was administered continuously in drinking water for 20 days, and was then withdrawn for 2 days before conditioning began. Final dose of mecamylamine was 10.4 ± 0.2 mg/kg daily. *P* values relate to comparisons of mean scores with 50%, and thus test whether significant CTA was present. $*P<0.05$; $**P<0.01$; $***P<0.001$.

individual rats ranged from 8.1–12.2 mg/kg daily. Four additional rats were excluded from the CTA experiments because their intakes of the mecamylamine solution were somewhat variable from day to day.

The experiments failed to reveal any substantial change in the dose-related CTA produced by nicotine as a function of the previous, prolonged exposure to mecamylamine (Table 3). Analysis of the dose-response curves yielded no differences between the amounts of nicotine needed to produce half-maximal degrees of CTA, which were 0.093 mg/kg and 0.120 mg/kg for the control and experimental animals respectively. Mecamylamine did not significantly alter the magnitude of the CTA produced by any of the doses of nicotine that were tested.

Discussion

Nicotine is one of the most potent of the central nervous system stimulants in producing conditioned taste aversion. With an ED_{50} value as low as 0.46 μmol/kg, nicotine was about three times as potent as amphetamine; even apomorphine, the most potent agent identified previously, had an ED_{50} of 0.96 μmol/kg (D'Mello *et al.*, 1981). It may be noted that the present value of 1.59 μmol/kg for amphetamine agrees reasonably well with the value of 2.55 μmol/kg determined with the original version of the present technique (Booth *et al.*, 1977). There is some doubt as to whether the efficacy of even large doses of nicotine is equal to that of amphetamine, which in doses of 3.2 mg/kg (17 μmol/kg) can almost completely suppress intake in one-stimulus tests after only a single conditioning trial (Booth *et al.*, 1977). Such powerful effects have not been obtained with even the largest dose of nicotine tested to date.

Does the relatively high potency of nicotine in CTA suggest that the effect may have implications for the human use of tobacco? A partial answer to this question can be obtained by comparing the plasma concentrations of nicotine in the rats with those in users of tobacco. Relations between subcutaneously injected dose of nicotine and plasma concentrations 15 min later have been reported for rats of the same sex, strain and age as those used in the present experiments (Garcha, Kumar, Pratt & Stolerman, 1982). Half-maximal CTA in the four-trial procedure (at 0.046 mg/kg) is associated with a mean plasma nicotine concentration of 13.4 ng/ml. The corresponding plasma concentration rises to 51.9 and 241 ng/ml in the two-trial and one-trial procedures. In cigarette smokers who inhale, plasma concentrations of nicotine, although quite variable, are frequently in the range 15–40 ng/ml (Russell, Wilson, Patel, Feyerabend & Cole, 1975; Russell & Feyerabend, 1978). It follows that nicotine can produce CTA in rats at doses that probably are relevant to the nicotine exposure of many smokers, and which are similar to the doses that produce the nicotine discriminative stimulus in rats (Garcha *et al.*, 1982).

The stereoisomer (+)-nicotine was able to produce clear CTA with a maximum of about the same intensity as that found for (−)-nicotine. The present findings confirm preliminary data obtained with smaller numbers of rats (Pratt & Stolerman, 1982). The naturally occurring isomer was about four to five times as potent as (+)-nicotine, as assessed by the amounts of the two drugs needed to produce equal degrees of CTA. Rats trained with (−)-nicotine as a discriminative stimulus identify (+)-nicotine as producing nicotine-like effects, and in this very specific procedure the potency ratio is about 9:1 (Meltzer, Rosecrans, Aceto & Harris, 1980; Romano, Goldstein & Jewell, 1981). There is probably no meaningful difference between the potency ratios in the CTA procedure and in the discriminative stimulus paradigm, and our findings should not be taken as evidence for different central mechanisms mediating these two aspects of nicotine's stimulus properties. Connelly & Littleton (1982) have suggested that the stereoisomers are equipotent in producing some neurochemical effects in the central nervous system of the rat, whereas Aceto, Martin, Uwaydah, May, Harris, Izazola-Conde, Dewey, Bradshaw & Vincek

(1979) reported relatively high potency ratios of about 17:1 on rat blood pressure and heart rate.

Mecamylamine, a ganglion-blocking drug thought to penetrate readily to the CNS, blocks most behavioural effects of nicotine (Morrison, Goodyear & Sellers, 1969; Schechter & Rosecrans, 1971; Goldberg *et al.*, 1981; Spealman, Goldberg & Gardner, 1981). The same studies show that hexamethonium generally does not block behavioural effects of nicotine, presumably because this quaternary compound penetrates the blood-brain barrier poorly. CTA is no exception to this pattern and the present results indicate that this effect is also of central origin.

Pretreatment with one drug has often been found to attenuate the CTA effects of the same or a quite different agent, even when there were no grounds for expecting a pharmacological interaction (Cappell & Le Blanc, 1975; Domjan, 1980). Such results are often interpreted in terms of learning processes. The finding that mecamylamine did not block the apomorphine CTA shows that the block of the nicotine CTA has some pharmacological specificity that cannot easily be explained by learning processes.

The *area postrema* lacks a blood-brain barrier and is accessible to drugs (such as hexamethonium) which do not penetrate to many other regions of the brain. In several species, either hexamethonium or lesions of the *area postrema* can at least partly block the emetic effect of nicotine (Laffan & Borison, 1957; Spealman *et al.*, 1981), whereas the present experiments show that hexamethonium does not block the CTA effect of nicotine. Despite the fact that rats do not vomit, lesions of the *area postrema* can attenuate some taste aversions and attempts have often been made to explain CTA by reference to nausea and emetic mechanisms (Berger, Wise & Stein, 1973; Ritter, McGlone & Kelly, 1980). Such explanations seem unlikely to account for the CTA produced by even the known emetic drug nicotine since its CTA effect may be pharmacologically dissociated from its emetic effect. Experiments in a species (e.g. cat) that can both exhibit CTA and vomit would provide a more conclusive test of this hypothesis.

The study of nicotine CTA carried out after 20 days exposure to mecamylamine suggested that central nicotinic receptors do not develop supersensitivity easily. This contrasts with comparable experiments involving chronic treatment with neuroleptics, which readily induce supersensitivity to dopamine agonists (Tarsy & Baldessarini, 1974). However, our findings have to be considered preliminary since other doses or durations of mecamylamine administration might have different effects. Nevertheless, the final daily dose of mecamylamine was five times larger than the amount needed acutely to block the nicotine CTA, and mecamylamine is well absorbed orally (Mason, 1980).

In conclusion, nicotine is potent in producing CTA in rats, an effect which is clearly related to the dose of the drug and the number of conditioning trials. Firstly, therefore, the procedure provides another behavioural assay which may have some contribution to make in studies of nicotine's mode of action. Secondly, the CTA effect of nicotine is associated with plasma nicotine concentrations similar to those in cigarette smokers who inhale. Thirdly, the effect may be mediated through receptor mechanisms since it is stereospecific and it is blocked by the nicotinic-cholinoceptor antagonist, mecamylamine. Finally, experiments with hexamethonium suggest that the CTA effect of nicotine is largely central and may be dissociable from its emetic effect.

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