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Some effects of nicotine on food and water intake in undeprived rats

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1 Undeprived rats were tested in their home cages for intake of water and powdered food, starting 15 min after subcutaneous (s.c.) injection of (−)-nicotine bitartrate or 0.9% w/v NaCl solution (saline). In the first 2 h, nicotine (0–0.4 mg kg^{-1} base) markedly reduced water intake in a dose-related way, leaving food intake unchanged. Food and water intake up to 24 h after injection was unaffected.

2 Rats ($n = 6$ per group) were then injected daily with nicotine (0.4 mg kg^{-1} base, s.c.) or saline for one month. Intermittent tests with saline (in place of nicotine) during this period did not reveal any signs of abstinence. A dose-response study similar to the first was then carried out, and little or no tolerance was found to the hypodipsic action of nicotine. Nicotine also reduced food intake, irrespective of chronic treatment. Subsequently, daily injections were discontinued, and spontaneous intake did not differ in rats previously maintained on nicotine, relative to control animals.

3 Mecamylamine (0.3, 1.5 mg kg^{-1}, s.c.) prevented nicotine-induced hypodipsia, whereas chlorisondamine (0.02, 0.1 mg kg^{-1} s.c.) was ineffective. Both ganglion blockers reduced food intake.

4 Nicotine did not reduce drinking in rats preloaded with a hypertonic saline solution.

5 It is suggested that nicotine reduces water intake in undeprived rats, probably by acting centrally. Since this action changes little with repeated testing, it may provide a useful index of one or more central actions of the drug.

Introduction

Tobacco smoking is believed to suppress appetite, and weight gain is a common experience amongst abstinent smokers (Schiffman, 1979). The possible involvement of nicotine in such actions has received little attention, although Münster & Bättig (1975) observed a reduction of food and water intake in deprived rats following subcutaneous injection of nicotine. In other species, the drug has an emetic action (Laffan & Borison, 1957), which may be related to the nausea produced by nicotine in non-smokers. However, although smokers become tolerant to the nauseous effects of nicotine (Beckett *et al.*, 1971), tolerance to its hypophagic action has not been found in rats (Bättig *et al.*, 1980). The actions of nicotine on food and water intake in rats are prevented by mecamylamine, a secondary amine which is thought to enter the brain, whereas hexamethonium, a quaternary nicotine antagonist, is reportedly ineffective (Münster & Bättig, 1975). These findings suggest that nicotine may act at central cholinoceptors (Romano & Goldstein, 1980) to alter eating and drinking.

In the first experiment described below, the effects of nicotine on food and water intake were determined in rats which were initially drug-naive, before, during and after chronic administration of the drug. Rats were undeprived, so that measurements could be made at intervals up to 24 h after drug injection, in order to detect possible signs of nicotine-withdrawal. In the second experiment the role of central versus peripheral actions of nicotine was assessed by pretreating rats with subcutaneous mecamylamine or chlorisondamine. Both drugs act as nicotine-cholinergic antagonists at autonomic ganglia (van Rossum, 1962), but only mecamylamine is thought to enter the CNS in pharmacological amounts at the doses used (Mason, 1980). Chlorisondamine, a long-acting bisquaternary ganglion blocking drug (Plummer *et al.*, 1955), was used because its peripheral potency in rodents appears to be better established

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than that of hexamethonium (Stone *et al.*, 1958; Morrison *et al.*, 1969). Since nicotine was found to reduce water intake in undeprived rats, a third experiment was performed in rats preloaded with hypertonic saline, in order to assess the possible effects of nicotine on intracellular thirst.

Methods

General

Measurement of food and water intake Each rat was tested in its home cage (North Kent Plastic Cages Ltd), an opaque plastic box (17 cm × 22 cm × 35 cm) with a wire floor and top. Each cage was suspended above a plastic tray lined with absorbent paper which collected any spillage. A food hopper and water bottle were suspended from the top of the cage. The hopper (North Kent Plastic Cages Ltd) was a stainless steel box with a window (4.5 cm × 6 cm) through which the rat could obtain powdered food (diet 41B, Oxoid Ltd.). A wire mesh ledge inside the box reduced food spillage, which was weighed separately and taken into account when food intake was calculated. The water bottle (approx. 200 ml capacity) was held in a wire basket with its spout pointing vertically downwards. Loss of water due to evaporation and spillage was less than 0.2 g per test and was ignored. All measurements were made to the nearest 0.1 g.

Drugs (−)-Nicotine hydrogen-(+) tartrate (BDH) was dissolved in 0.9% w/v NaCl solution (saline) and neutralised to pH 7.2 ± 0.2 with NaOH. Mecamylamine HCl (MSD) and chlorisondamine Cl (CIBA-GEIGY) were dissolved in saline. Injections were subcutaneous, made into the flank in a volume of 1 ml kg^{-1}. All doses refer to the base. Control injections were of saline.

Analysis of data Multivariate analysis of variance was employed, each rat acting as its own control. A 'dose-dependent' effect refers to a significant linear trend across absolute values of dose. Specific comparisons between saline and other levels of dose refer to paired *t* tests, with no adjustment for multiple comparisons. All probability values are 2-tailed.

Experiment 1: Effects of nicotine before, during, and after chronic treatment Twelve male Lister hooded rats (OLAC 76 Ltd, Bicester) were used; they were housed singly with *ad libitum* access to powdered food and tap water. The room was maintained at 22 ± 2°C, and was illuminated from 08 h 00 min to 20 h 00 min. Rats weighed 300 to 390 g at the start of testing.

Dose response study before chronic treatment Subjects were maintained on powdered food, and after several days, when body weight had reattained the previous baseline, testing was started. Each rat was tested with each dose of nicotine (0, 0.1, 0.2, 0.4 mg kg^{-1}), administered in a Williams Square design (Cox, 1958). Tests were spaced three or four days apart.

Chronic treatment Rats were maintained on powdered food and water for eight weeks, and they were then randomly assigned to two chronic treatment groups, each comprising six animals. Each rat was tested once with nicotine (0.4 mg kg^{-1}) and once with saline (days 1 and 3). Drug treatments were counterbalanced within each group. From days 4 through 48, excluding test days, each rat received a daily injection at around mid-day; one group was given nicotine (0.4 mg kg^{-1}), whilst the other group received saline instead. After one week (days 9 and 11) and three weeks (days 23 and 25) of chronic medication, all subjects were tested with nicotine and saline as on days 1 and 3. After one month, a dose-response study was carried out (days 35, 38, 42, 45). The same procedure was used as in the earlier dose-response study, except that rats continued to receive daily injections of nicotine or saline in-between test days.

Tests in abstinence: After day 48, daily injections of nicotine or saline were discontinued, and food and water intake were measured during the three days following the final injection. In order to reassess the drug effect following withdrawal, subjects were each tested with nicotine (0.4 mg kg^{-1}) and with saline on days 72 and 74, and finally on days 93 and 95.

Procedure: Rats were tested in their home cages, starting between 10 h 00 min and 11 h 00 min. The food hopper and water bottle were removed for weighing, 40 min beforehand. Subjects were weighed 30 min before the start of the test, and replaced in their cages. Food and water were reintroduced 15 min after injection, to avoid the time of maximal motor impairment produced by nicotine (Clarke & Kumar, 1983a). In the first dose-response study, food and water intake was measured from 15 min to 2 h 15 min after injection, and again from 2 h 30 min to 24 h. Subsequently, intake was measured across three intervals after injection (15 min – 2 h 15 min, 2 h 30 min – 6 h 30 min, and 6 h 45 min – 24 h).

The same methods were used in experiments 2 and 3, except as noted below.

Experiment 2: Pretreatment with nicotine antagonists

Ten male Lister hooded rats (OLAC 76 Ltd., Bicester) were used, initially weighing 390 to 510 g. They had taken part in a study of locomotor activity ending eight weeks before, in which nicotine (0.4 mg kg^{-1}, s.c.) had been given daily for two weeks.

Plan of experiment: Each rat received each combination of pretreatment and treatment in a Williams Square design (Cox, 1958). The five pretreatments were saline, chlorisondamine (0.02, 0.1 mg kg^{-1}), and mecamylamine (0.3, 1.5 mg kg^{-1}). The treatments were saline and nicotine (0.4 mg kg^{-1}). Tests were on alternate days. Starting three days later, tests with mecamylamine (0, 1.5 mg kg^{-1}) and nicotine (0, 0.4 mg kg^{-1}) were repeated.

Procedure: Food and water containers were removed, and the rats were then given the pretreatment injection, followed 20 min later by the treatment injection. Food and water intake was measured from 15 min to 2 h 15 min after treatment injection.

Experiment 3: Effects of nicotine in saline-preloaded rats

Sixteen male Wistar rats (A. Tuck & Son, Ltd, Southend) were used, weighing 360–475 g.

Plan of experiment Rats were handled and injected with 0.9% saline (1 ml kg^{-1}) each day for one week.

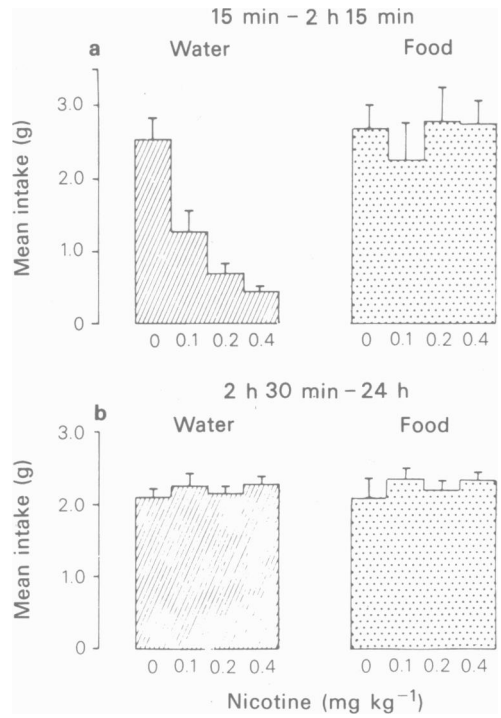

Figure 1 Effects of nicotine on water and food intake in rats before chronic treatment. Nicotine (0–0.4 mg kg^{-1}, s.c.) reduced water intake in the first two hours in a significant dose-related way (a), leaving food intake unaltered. In the second period, no effects were seen (b). Bars represent one s.e.mean either side of the mean ($n = 12$).

Five daily tests were then given, to check that baseline drinking in response to hypertonic saline was stable. Two days later, a dose-response study was begun. Rats were tested once with each dose of nicotine (0, 0.1, 0.2, 0.4 mg kg^{-1}) in a William Square (Cox, 1958), and tests were on alternate days.

Procedure Food and water containers were removed, and rats were then pretreated with hypertonic saline (0.29 g kg^{-1}, i.e. 5 mmol kg^{-1}, s.c.) given in a volume of 1 ml kg^{-1}, followed 15 min later by injection of nicotine or 0.9% saline. After a further delay of 15 min, water intake was measured for 1 h. Powdered food was available also, but food intake was not recorded.

Results

Experiment 1: Effects of nicotine before, during, and after chronic treatment

Dose-response study before chronic treatment In the first test interval (15 min – 2 h 15 min), nicotine reduced water intake in a dose-related manner ($F = 50.1$, d.f. 1, 11, $P < 0.0001$; Figure 1); this was significant even at the lowest dose ($t = 5.80$, d.f. 11, $P < 0.0005$), and the highest dose appeared to abolish drinking in many rats. Food intake during this period was unaffected. In the remainder of the 24 h period, nicotine altered neither water intake nor food intake significantly (Figure 1).

Effects of nicotine during chronic treatment In the three pairs of nicotine and saline tests leading up to the second dose-response study, nicotine once again reduced water intake in the first test interval after injection; concomitantly, there was a slight but significant reduction in food intake ($F = 6.99$, d.f. 1, 10, $P < 0.05$; data not shown). These drug effects were stable across successive tests and did not differ significantly between rats receiving daily nicotine and controls receiving saline instead.

The second dose-response study, initiated after one month of daily injections, confirmed these observations (see Figure 2). Nicotine (0.1–0.4 mg kg^{-1}) continued to depress water intake (15 min – 2 h 15 min). Although some degree of tolerance seemed to have developed among rats treated chronically with nicotine, there was no significant difference between groups with respect to the main effect of dose ($F = 1.27$, d.f. 3, 8) or to its linear component ($F = 2.28$, d.f. 1, 10). There was also no group difference in the effect of nicotine on food intake; the pooled data revealed a modest but dose-dependent hypophagic action ($F = 7.43$, d.f. 1, 10, $P < 0.05$). Intake of food and water was unaffected by nicotine in the two remaining time intervals after injection,

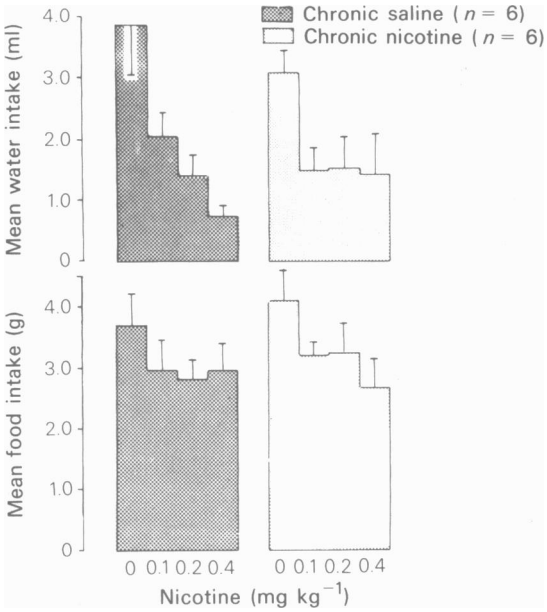

Figure 2 Effects of nicotine on water and food intake (15 min – 2 h 15 min): chronic treatment phase. Nicotine reduced water intake, and this effect did not differ significantly between rats receiving daily injections of nicotine (0.4 mg kg^{-1}) and control rats receiving daily saline. Food intake was also slightly reduced by the drug. Bars represent one s.e.mean from the mean.

irrespective of chronic treatment group. Total daily intakes of food and water were also unaffected by the drug.

Tests in abstinence Signs of acute abstinence were assessed by the intake of food and water in the 24 h period following a test injection of saline, during the period of daily injections. Comparisons between the rats which normally received a daily injection of nicotine and controls which received chronic saline did not reveal any difference (Figure 3). When the chronic nicotine treatment was stopped on day 48, the possibility of longer-term changes was assessed by similar between-group comparisons of food and water intake during 24 h periods following the saline injections given intermittently from day 49 up to day 95. Such comparisons failed to reveal any signs of chronic abstinence (see Figure 3).

Body weights: During the period of daily injections (days 4 to 48), rats injected with nicotine gained weight at the same rate as controls (group difference of linear trend over days, $F = 0.51$, d.f. 1,10, NS). Body weights were stable over the first three days of abstinence, irrespective of previous chronic treatment.

Experiment 2: Pretreatment with nicotinic antagonists

When given alone, nicotine (0.4 mg kg^{-1}) reduced water intake ($t = 3.21$, d.f. 9, $P < 0.02$), but this

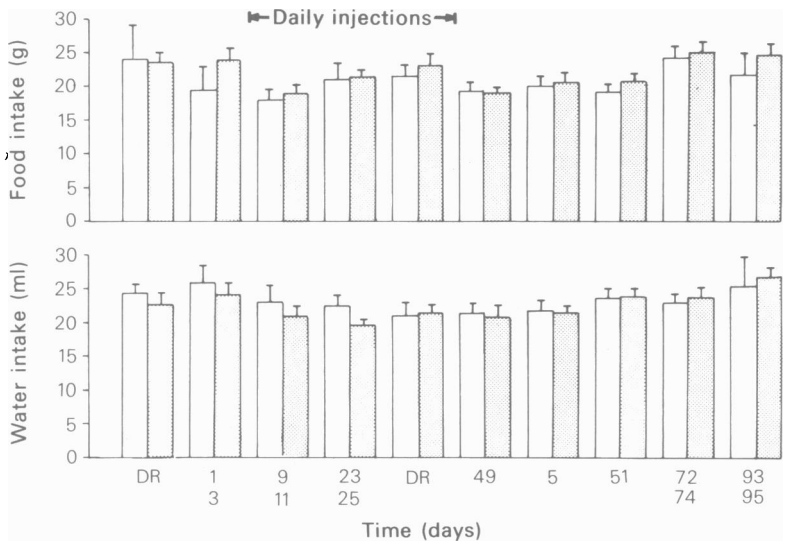

Figure 3 Food and water intakes 0–24 h after saline injection before, during, and after chronic treatment with nicotine or saline. During the period of chronic maintenance, six rats (stippled columns) were injected daily with nicotine except on saline test days: six control rats (open columns) were injected chronically with saline instead of nicotine. These measures of food and water intake did not reveal any signs of nicotine abstinence, either acutely during chronic maintenance, or in the longer term after chronic treatment was stopped. Bars show one s.e.mean from the mean.

Table 1 Food and water intake: pretreatment with antagonists (experiment 2)

Pretreatment		*Saline treatment*	*Nicotine treatment* ($0.4\ mg\ kg^{-1}$)	*Effect of nicotine* (*P* value, 2-tailed)
Water intake (g) Group mean ± s.e.mean				
Saline		2.3 ± 0.5 (2.4 ± 0.3)	1.2 ± 0.4 (1.2 ± 0.3)	< 0.02 (< 0.01)
Chlorisondamine	$0.02\ mg\ kg^{-1}$	2.9 ± 0.2	1.2 ± 0.3	< 0.001
	$0.1\ mg\ kg^{-1}$	2.1 ± 0.4	0.6 ± 0.2	< 0.01
Mecamylamine	$0.3\ mg\ kg^{-1}$	2.3 ± 0.3	2.3 ± 0.4	NS
	$1.5\ mg\ kg^{-1}$	2.3 ± 0.5 (2.8 ± 0.3)	1.0 ± 0.2 (2.2 ± 0.4)	< 0.05 (NS)
Food intake (g) Group mean ± s.e.mean				
Saline		3.7 ± 0.5 (3.5 ± 0.4)	3.9 ± 0.4 (3.3 ± 0.6)	NS (NS)
Chlorisondamine	$0.02\ mg\ kg^{-1}$	2.7 ± 0.3	3.2 ± 0.4	NS
	$0.1\ mg\ kg^{-1}$	2.1 ± 0.3	2.8 ± 0.4	NS
Mecamylamine	$0.3\ mg\ kg^{-1}$	2.9 ± 0.3	3.3 ± 0.5	NS
	$1.5\ mg\ kg^{-1}$	2.0 ± 0.3 (2.1 ± 0.4)	2.6 ± 0.4 (2.0 ± 0.4)	NS (NS)

Each rat ($n = 10$) was tested with each combination of pretreatment and treatment. The results of repeated tests are shown in parentheses. Statistical *P* values are 2-tailed and refer to paired *t* tests.

action appeared to be less marked than in the acute dose-response study (Table 1). Neither pretreatment drug when given alone significantly altered water intake at any dose. Nicotine reduced water intake significantly after pretreatment with either dose of chlorisondamine (Table 1). The lower dose of mecamylamine prevented the hypodipsic action of nicotine. Surprisingly, the higher dose did not prevent the hypodipsic action upon first testing; however, when tests were repeated, a blocking action was found.

Nicotine did not significantly affect food intake, either alone or in combination with either ganglion blocking drug (Table 1). In contrast, food intake was reduced by chlorisondamine (0.02, $0.1\ mg\ kg^{-1}$, respectively: $P < 0.05$, $P < 0.01$) and by mecamylamine ($1.5\ mg\ kg^{-1}$, $P < 0.01$) when given alone.

Experiment 3: Effects of nicotine in saline-preloaded rats

Intake of water in response to injection of hypertonic saline solution, was stable across successive daily baseline tests (linear trend over days, $F = 4.39$, 1, 15); the group mean (± s.e.mean) intake in 1 h was 5.67 ± 0.41 g. Nicotine did not alter water intake at any dose, and the linear trend over dose was not significant ($F = 1.07$, d.f. 1,15).

Discussion

Nicotine reliably reduced water intake in undeprived rats within a 2 h period starting shortly after subcutaneous injection. Little if any tolerance developed with chronic administration. Tests with antagonists were not entirely clear-cut, but suggested a direct central action of the drug. In contrast, nicotine had little or no effect on food intake in undeprived rats, and the drug also failed to affect drinking in response to an injection of hypertonic saline.

It is difficult to compare these results with those of previous studies, because of procedural differences. In non-tolerant rats deprived of food and water, nicotine reduced food intake more than water intake, and the drug effects were largely confined to two hours after systemic injection (Münster & Bättig, 1975). In a subsequent study incorporating several procedural changes, nicotine reduced food intake only to a modest extent (Bättig *et al.*, 1980). Chronic administration of higher doses of nicotine to rats may lead to reduced body weight with or without persistent hypophagia (Schecter & Cook, 1976; Bättig *et al.*, 1980). However, we found no weight loss with daily drug injections, nor did measurements of food and water intake reveal any signs of abstinence. In contrast, Hall & Morrison (1973) were able to detect behavioural deficits in rats trained to perform a Sidman avoidance task when the animals were deprived of their daily injection of nicotine ($0.4\ mg\ kg^{-1}$, s.c.).

Certain observations suggest that the undeprived rats did not generally drink within the first 2 h of injection merely to protect their fluid balance. When food and water was reintroduced after weighing, the rats began to eat immediately, and drinking followed. Such behaviour may be adjunctive. Sanger (1978) reported that nicotine reduced schedule-induced polydipsia; however, the drug also produced signs of

sedation. Nicotine, especially in chronically-treated rats, stimulates both unconditioned locomotor activity and conditioned behaviour (Clarke & Kumar, 1983a, b), but the reduced drinking cannot be readily attributed to competition with other behaviours, because food intake was barely affected. Similarly, although nicotine produces ataxia for some minutes after injection (Clarke & Kumar, 1983a), subtle motor impairments are unlikely to account for reduced water intake in undeprived rats, since no such change was seen in subjects challenged with hypertonic saline.

Possibly, nicotine suppressed water intake by promoting water retention. Rats pretreated with salt drank less than the amount necessary to compensate for the extra electrolyte load; water retention may thus have been maximal in the absence of nicotine. In moderate to large doses, nicotine induces antidiuresis in rats (De Wied & Jinks, 1958; Bisset & Chowdrey, 1981), an action that is blocked by mecamylamine but not by the systemic administration of the quaternary nicotinic antagonist, hexamethonium (Mansner & Mattila, 1975). Nicotine also has been found to release vasopressin (Bisset & Feldberg, 1977; Sladek & Joynt, 1979).

The failure to show really convincing antagonism with mecamylamine in the second experiment is surprising since it reliably blocks other behavioural actions of nicotine which are thought to be central (Stitzer *et al.*, 1970; Rosecrans & Chance, 1977; Clarke & Kumar, 1983a). The reduction of food intake occurring after administration of either mecamylamine or chlorisondamine confirms that behaviourally-active doses were given and the doses used should have been sufficient to protect against peripheral actions of nicotine (Morrison *et al.*, 1969). We were unable to confirm a previous report (Glick & Greenstein, 1973) that mecamylamine selectively reduces prandial drinking.

Little if any tolerance developed to the hypodipsic action of nicotine in rats injected daily with the drug for one month. A similar chronic regime also failed to produce tolerence to the stimulant effects of nicotine on locomotor activity and on responding for electrical brain stimulation (Clarke & Kumar, 1983a, b). However, these stimulant actions, which at least in the case of locomotor activity, are of central origin (Clarke & Kumar, 1983a, c), become more pronounced with the first few injections of nicotine. The hypodipsic action, in contrast, seems to change little if at all with chronic administration, and may thus commend itself as a particularly convenient 'behavioural assay' reflecting one or more central actions of nicotine.

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