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European Journal of Pharmacology 321 (1997) 157–162

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# Effects of monoamine receptor antagonists on nicotine-induced hypophagia in the rat

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Received 4 January 1996; revised 26 November 1996; accepted 29 November 1996

**Abstract**

(−)-Nicotine, in doses of 0.2–0.6 mg/kg intraperitoneally (i.p.), induced a dose-dependent anorexia 1 h, 2 h and 4 h after food presentation in 20-h food-restricted male rats. The anorectic response of nicotine (0.4 mg/kg, 30 min before the test) was prevented by pretreatment with the central nicotine receptor antagonist mecamylamine (0.5 and 1 mg/kg). The peripheral nicotine receptor antagonist hexamethonium (5 and 10 mg/kg), the muscarinic receptor antagonist atropine (5 and 10 mg/kg), the dopamine $D_2$ receptor antagonist pimozide (0.5 and 1 mg/kg), the dopamine $D_1$ receptor antagonist SCH23390 (*R*-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine-7ol maleate; 0.05 and 0.1 mg/kg), the α-adrenoceptor antagonist phenoxybenzamine (5 and 10 mg/kg), and the β-adrenoceptor antagonist propranolol (5 and 10 mg/kg) amplified the nicotine response while promoting anorexia by themselves. The dopamine $D_2$ receptor antagonist sulpiride (25, 50 and 100 mg/kg) increased food intake and amplified the anorectic effect of nicotine. The 5-HT receptor antagonists metergoline (0.5 and 1 mg/kg) and mianserin (1 and 2 mg/kg) increased the nicotine effect. When the antagonists were used alone, metergoline did not change food intake, while mianserin increased food intake. It can be concluded that part of nicotine-induced anorexia is mediated through central nicotinic receptors.

*Keywords:* Nicotine; Dopamine receptor agonist; Adrenoceptor antagonist; Acetylcholine receptor antagonist; 5-HT receptor antagonist; Anorexia; (Rat)

## 1. Introduction

Nicotine appears to be the prime reason why people are dependent on tobacco (Kumar and Lader, 1981; Stepeny, 1982) and is thus a drug of enormous social, economic and political importance. The drug may have some physiological effects, i.e., relaxing muscular tone, optimizing arousal levels, alleviating stress, reducing anxiety, suppressing appetite and reducing body weight, enhancing learning, memory and selective attention or sustaining mental concentration (Stepeny, 1982).

Body weight changes are inversely associated with cigarette smoking, as smokers weigh less than non-smokers (Grunberg, 1986) and gain weight on cessation (Perkins, 1993). Smoking may enhance satiety following meal consumption, thereby reducing eating (Perkins et al., 1995). In animals, nicotine is rapidly absorbed after parenteral administration, especially in alkaline solution. The peak brain concentration occurs within 15 min, and the half-life in brain is 60–90 min after systemic injection in rats (Schechter and Jellinek, 1975). Indeed, nicotine administration in animals decreases body weight gain and cessation of nicotine intake may be accompanied by excessive weight gain (Grunberg et al., 1986, 1987).

In both the central and peripheral nervous systems, nicotine mimics certain actions of the neurotransmitter acetylcholine, with most (if not all) actions of nicotine occurring at behaviorally relevant doses. These actions can be blocked by selective antagonists such as mecamylamine (Martin et al., 1989).

Nicotine has also been suggested to exert its action through catecholamine systems, especially dopamine systems (Goodman, 1974; Sandor et al., 1991). The drug also seems to increase the turnover of noradrenaline (Hall and Turner, 1972) and facilitates self-stimulation through the release of this catecholamine (Pradham and Bowling, 1971).

In this context it is noteworthy that central monoamines play a role in the control of feeding behaviour (Clineschmidt and Bunting, 1980). Numerous reports have pointed

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*PII* S0014-2999(96)00935-1

out the importance of central dopaminergic, noradrenergic and serotonergic systems for the control of food intake (Wise, 1982; Garattini et al., 1992). The contribution of each of these neurotransmitters to the changes in food consumption associated with nicotine administration could thus provide an insight into the mechanisms involved in the inverse relationship between nicotine administration and food consumption.

In the present work, the effects of nicotine on food intake in rats and its relation with some brain neurotransmitters have been investigated.

## 2. Materials and methods

### 2.1. Animals

Male albino Wistar rats (bred in our laboratory) weighing 180–200 g at the start of experiments were used in these experiments.

### 2.2. Procedure

Animals were housed three per cage at $20 \pm 1$°C with a 12-h light/dark schedule (lights on at 06.00 h). The rats had free access to tap water and were maintained on a food-restricted schedule which allowed free access to the food for 4 h a day (10.00–14.00 h). They were trained at least 2 weeks before drug administration to reach a stable food intake. The amount of food consumed by each group of three rats, after 1, 2 and 4 h was recorded. Nicotine was always administered 30 min before the onset of the feeding period, and antagonist injections were given as indicated in Section 3. The drugs were prepared immediately before use and were injected intraperitoneally except for mecamylamine, which was injected subcutaneously. Food intake was recorded throughout the 1st, 2nd and 4th hour following presentation of the food. $ED_{50}$ values were defined as the doses required for 50% inhibition of food intake. The method we used in this study has been based on our previous works on the eating behaviour of food-restricted rats, that were used to eating their entire daily ration of food in 4 h (Zarrindast et al., 1987, 1989, 1991; Zarrindast and Hosseini-Nia, 1988).

### 2.3. Drugs

The following drugs were used: atropine sulfate (Merck, Germany), hexamethonium bromide (Sigma, UK), mecamylamine HCl (Merck, Germany), nicotine hydrogen (+)-tartrate (BDH Chemicals, UK), phenoxybenzamine HCl (SK&F, USA), propranolol (ICI, UK), SCH 23390 (Research Biochemical Int., USA), sulpiride (Sigma, UK), pimozide (Janssen, France), metergoline (Sandoz, Switzerland), mianserin (Research Biochemical Int., USA). Nicotine solutions were prepared in saline and the pH was adjusted to $7.2 \pm 0.1$ with sodium hydroxide. The drugs were dissolved in saline except for sulpiride, pimozide and metergoline, which were dissolved in a drop of acetic acid, and SCH 23390 (*R*-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine-7ol maleate), which was dissolved in a drop of lactic acid then diluted with saline. The vehicle control in respective cases was acetic acid or lactic acid in saline, at the same concentration used in the antagonist solutions. The drugs were given in a volume of 10 ml/kg and were prepared immediately before use.

### 2.4. Statistical analysis

Comparisons between groups were made with analysis of variance (ANOVA) and post-hoc tests (Tukey) were used to evaluate inter-group differences.

## 3. Results

### 3.1. The anorectic effect of nicotine in food-restricted rats

Fig. 1 shows the anorectic effects of nicotine in food-restricted rats. Intraperitoneal (i.p.) injection of different doses of nicotine (0.2–0.6 mg/kg) to animals produced anorexia 1 h, 2 h and 4 h after food presentation ($F(6,71) = 2.8$, $P < 0.05$) (two-way ANOVA with repeated measures). Further analysis with the Tukey test indicated that each dose of nicotine induced a significant decrease in food intake compared with saline. The anorectic effect of the drug was dose-dependent. The $ED_{50}$ value for nicotine-induced hypophagia in the rats was 0.4 mg/kg, and thus all antagonists were then challenged against this dose of nicotine.

### 3.2. The effects of nicotinic and acetylcholine receptor antagonists on nicotine-induced anorexia in rats (Table 1)

When animals were pretreated 15 min beforehand with the nicotinic receptor antagonists mecamylamine (0.5 and 1 mg/kg, s.c.) and hexamethonium (5 and 10 mg/kg, i.p.), and the muscarinic receptor antagonist atropine (5 and 10 mg/kg, i.p.), there was a significant effect of nicotine ($F(1,35) = 121.7$, $P < 0.001$), and mecamylamine ($F(2,35) = 28.4$, $P < 0.0001$), and a nicotine × mecamylamine interaction ($F(2,35) = 24.7$, $P < 0.0001$). In animals pretreated with hexamethonium, there was a significant effect of nicotine ($F(1,35) = 5.6$, $P < 0.05$), and hexamethonium ($F(2,35) = 4.3$, $P < 0.05$), but the nicotine × hexamethonium interaction ($F(2,35) = 2.3$, $P > 0.05$) was not significant. In the case of atropine pretreatment, there was a significant effect of nicotine ($F(1,35) = 169.5$, $P < 0.0001$), and atropine ($F(2,35) = 405.3$, $P < 0.0001$), and a significant nicotine × atropine interaction ($F(2,35) = 35.4$, $P < 0.0001$). Further analysis

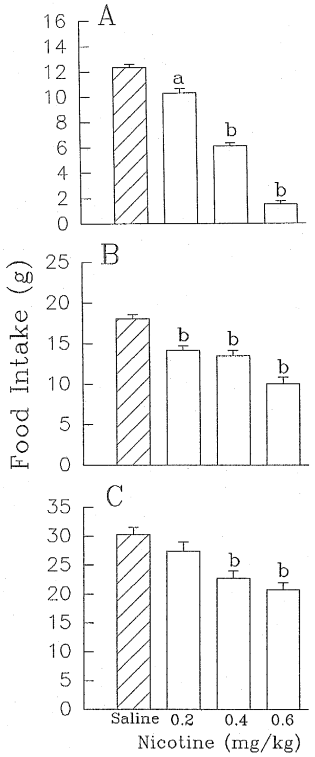


Fig. 1. Effect of nicotine on food intake in food-restricted rats. Animals were injected intraperitoneally (i.p.) with saline (10 ml/kg) or different doses of nicotine (0.2, 0.4 and 0.6 mg/kg), 30 min prior to food presentation. Food intake was recorded 1 h (A), 2 h (B) and 4 h (C) after food presentaion. Each point is the mean ± S.E.M. of 6 experiments. [a] $P < 0.05$, [b] $P < 0.01$, for the difference between saline- and nicotine-treated animals.

Table 1
Effects of nicotinic and muscarinic antagonists in the presence or absence of nicotine (0.4 mg/kg) on food intake in rats

| Pretreatment | Dose (mg/kg) | Food intake (g) (mean ± S.E.M.) | |
|---|---|---|---|
| | | Saline treatment | Nicotine treatment |
| Saline | | 11.8 ± 0.4 | 6.0 ± 0.5 |
| Mecamylamine | 0.5 | 12.4 ± 0.3 | 10.0 ± 0.3 [b] |
| Mecamylamine | 1 | 11.6 ± 0.2 | 10.6 ± 0.3 [b] |
| Saline | | 13.7 ± 0.6 | 6.7 ± 0.4 |
| Hexamethonium | 5 | 6.3 ± 0.4 [b] | 3.6 ± 0.4 [b] |
| Hexamethonium | 10 | 7.4 ± 0.5 [b] | 5.1 ± 0.6 [a] |
| Saline | | 12.0 ± 0.5 | 5.8 ± 0.4 |
| Atropine | 5 | 1.8 ± 0.1 [b] | 0.5 ± 0.2 [b] |
| Atropine | 10 | 2.7 ± 0.2 [b] | 0.4 ± 0.1 [b] |

Animals were pretreated intraperitoneally (i.p.) and with saline (10 ml/kg), and hexamethonium (5 and 10 mg/kg) 15 min, or with atropine (5 and 10 mg/kg) 15 min, or with subcutaneously (s.c.) injected mecamylamine (0.5 and 1 mg/kg) 15 min prior to saline (10 ml/kg) or nicotine (0.4 mg/kg, i.p.) administration. Nicotine or saline was administered 30 min before food presentation. Food intake was measured 1 h after food presentation. Each point is the mean ± S.E.M. of 6 experiments. [a] $P < 0.05$, [b] $P < 0.01$ for the difference between saline- and antagonist-treated animals.

Table 2
Effects of adrenoceptor and serotonergic receptor antagonists in the presence or absence of nicotine (0.4 mg/kg) on food intake in rats

| Pretreatment | Dose (mg/kg) | Food intake (g) (mean ± S.E.M.) | |
|---|---|---|---|
| | | Saline treatment | Nicotine treatment |
| Saline | | 12.4 ± 0.6 | 6.2 ± 0.2 |
| Phenoxybenzamine | 5 | 7.0 ± 0.8 [b] | 3.7 ± 0.3 [b] |
| Phenoxybenzamine | 10 | 3.6 ± 0.5 [b] | 0.1 ± 0.1 [b] |
| Saline | | 11.5 ± 0.9 | 5.6 ± 0.5 |
| Propranolol | 5 | 8.4 ± 0.2 [b] | 1.1 ± 0.4 [b] |
| Propranolol | 10 | 8.6 ± 0.6 [b] | 1.6 ± 0.6 [b] |
| Vehicle | | 12.3 ± 0.4 | 6.0 ± 0.4 |
| Metergoline | 0.5 | 12.5 ± 0.4 | 2.9 ± 0.4 [b] |
| Metergoline | 1 | 12.4 ± 0.4 | 3.0 ± 0.5 [b] |
| Saline | | 11.9 ± 0.4 | 5.8 ± 0.2 |
| Mianserin | 1 | 16.9 ± 0.2 [b] | 2.9 ± 0.6 [b] |
| Mianserin | 2 | 15.8 ± 0.4 [b] | 1.4 ± 0.3 [b] |

Animals were pretreated (i.p.) with saline (10 ml/kg), vehicle (10 ml/kg), phenoxybenzamine (5 and 10 mg/kg) 60 min, propranolol (5 and 10 mg/kg) 60 min, metergoline (0.5 and 1 mg/kg) 90 min, or mianserin (1 and 2 mg/kg) 30 min prior to saline (10 ml/kg) or nicotine (0.4 mg/kg) administration. Nicotine was administered 30 min before food presentation. Food intake was measured 1 h after food presentation. Each point is the mean ± S.E.M. of 6 experiments. [b] $P < 0.01$ for the difference between saline- and antagonist-treated animals.

indicated that mecamylamine significantly prevented the nicotine anorectic response, whereas pretreatment of animals with atropine or hexamethonium did not prevent but even enhanced the nicotine-induced supression of food intake. Two-way ANOVA and post-hoc analysis also indicated that treatment of animals with hexamethonium and atropine by themselves but not mecamylamine decreased food intake in the animals.

### *3.3. The effects of adrenoceptor and serotonergic receptor antagonists on nicotine-induced anorexia (Table 2)*

Two-way ANOVA indicated a non-significant difference between animals pretreated with the α-adrenoceptor antagonist phenoxybenzamine ($F(2,35) = 0.05$, $P > 0.05$) (5 and 10 mg/kg, i.p.) 60 min beforehand and the β-adrenoceptor antagonist propranolol ($F(2,35) = 2.8$, $P > 0.05$) (5 and 10 mg/kg, i.p.) 60 min beforehand. The 5-HT receptor antagonists metergoline ($F(2,35) = 10.7$, $P < 0.001$) (0.5 and 1 mg/kg, i.p.) 90 min and mianserin ($F(2,35) = 87.4$, $P < 0.001$) (1 and 2 mg/kg, i.p.) 30 min beforehand enhanced the suppression of food intake induced by nicotine.

When animals were treated with phenoxybenzamine ($F(2,35) = 24.6$, $P < 0.001$) or propranolol ($F(2,35) = 7.2$, $P < 0.01$) alone, a reduction in food intake was observed. Although two-way ANOVA indicated a significant effect for metergoline ($F(2,35) = 8.5$, $P < 0.001$), further analysis with the Tukey test did not present any response for the drug. Mianserin administration increased the food intake significantly ($F(2,35) = 7.6$, $P < 0.01$).

Table 3
Effects of dopamine antagonists in the presence or absence of nicotine (0.4 mg/kg) on food intake in rats

| Pretreatment | Dose (mg/kg) | Food intake (g) (mean ± S.E.M.) | |
|---|---|---|---|
| | | Saline treatment | Nicotine treatment |
| Vehicle | | 13.3 ± 0.6 | 6.7 ± 0.4 |
| Pimozide | 0.5 | 11.1 ± 0.3 [a] | 3.6 ± 0.4 [b] |
| Pimozide | 1 | 8.0 ± 0.6 [b] | 2.4 ± 0.5 [b] |
| Vehicle | | 11.5 ± 0.9 | 5.9 ± 0.5 |
| SCH 23390 | 0.5 | 8.5 ± 0.2 [a] | 1.6 ± 0.4 [b] |
| SCH 23390 | 1 | 7.2 ± 0.6 [b] | 3.7 ± 0.5 [b] |
| Vehicle | | 11.8 ± 0.8 | 6.1 ± 0.4 |
| Sulpiride | 25 | 11.6 ± 0.7 | 3.0 ± 0.4 [b] |
| Sulpiride | 50 | 12.7 ± 0.6 | 3.3 ± 0.5 [b] |
| Sulpiride | 100 | 15.6 ± 0.4 [b] | 0.4 ± 0.3 [b] |

Animals were pretreated (i.p.) with respective vehicle (10 ml/kg), pimozide (0.5 and 1 mg/kg) 30 min, SCH 23390 (0.05 and 0.1 mg/kg) 30 min, or sulpiride (25, 50 and 100 mg/kg) 30 min prior to saline (10 ml/kg) or nicotine (0.4 mg/kg) administration. Nicotine or saline was administered 30 min before food presentation. Food intake was measured 1 h after food presentation. Each point is the mean ± S.E.M. of 6 experiments. [a] $P < 0.05$, [b] $P < 0.01$ for the difference between saline- and antagonist-treated animals.

### *3.4. The effects of dopamine receptor antagonists on nicotine-induced anorexia*

Table 3 shows the effects of dopamine receptor antagonists on nicotine-induced anorexia. Two-way ANOVA indicated a non-significant difference between the animals pretreated with either the dopamine receptor antagonists pimozide ($F(2,35) = 1.4$, $P > 0.05$) (0.5 and 1 mg/kg, i.p.) 30 min or SCH 23390 ($F(2,35) = 3.2$, $P > 0.05$) (0.05 and 0.1 mg/kg, i.p.) 30 min beforehand. However, a significant effect was observed when the animals were pretreated with the dopamine receptor antagonist sulpiride ($F(2,47) = 23.5$, $P < 0.001$) (25, 50 and 100 mg/kg, i.p.) 30 min beforehand. Further analysis (Tukey test) indicated that the dopamine antagonists amplified the suppression of food intake induced by nicotine.

When animals were treated with the dopamine antagonists alone, pimozide and SCH 23390 decreased, whereas the high dose of sulpiride increased food intake.

## 4. Discussion

Nicotine is the most pharmacologically active component of tobacco products (Benowitz, 1988; Henningfield and Goldberg, 1988). It exhibits widespread pharmacological effects in the central and peripheral nervous systems. Many of these effects are due to the ability of nicotine to release various neurotransmitters (Balfour, 1982), including acetylcholine from the cortex (Nordberg et al., 1989), noradrenaline from the hippocampus (Hall and Turner, 1972; Goodman, 1974) and dopamine from the limbic system (Imperato et al., 1986) and from striatal slices (Giorguieff et al., 1979).

In the present work, nicotine administration decreased food intake in food-restricted male rats. Since sex differences have been shown regarding nicotine's effect on consummatory behaviour and body weight in rats (Grunberg et al., 1986; Grunberg et al., 1987), we used male rats in our experiments.

The present data indicate that the hypophagic response to nicotine was dose-dependent, with a maximum effect obtained 1 h after food presentation with 0.6 mg/kg of the drug. This is in agreement with Münster and Bättig (1975), who reported anorexia, nicotine-induced hypophagia, in food-restricted rats. In contrast, other reports have indicated that nicotine induces weight loss without an effect on appetite (Schechter and Cook, 1976), this effect being observed, however, after chronic nicotine administration. There are also reports indicating that nicotine (0.1–0.4 mg/kg) does not alter food intake in undeprived rats (Clarke and Kumar, 1984), and that nicotine injection in the substantia nigra elicits hyperphagia in the rat (Parker and Winn, 1992). A possible reason for the discrepancies may lie in the use of fed animals or different routes of drug administration. The present data showed that the centrally active nicotinic receptor antagonist mecamylamine (Martin et al., 1989) but not the nicotinic receptor antagonist hexamethonium, which does not enter the brain except after administration of very high doses (Asghar and Roth, 1971), decreased nicotine-induced anorexia. The antimuscarinic agent atropine also did not reduce the nicotine response. Other responses induced by nicotine such as hypothermia (Zarrindast et al., 1995) and purposeless chewing (Samini et al., 1995) have been shown to be reduced by mecamylamine. Thus, it is likely that central nicotinic receptors mediate the anorectic effect of nicotine.

Because nicotine increases the release of dopamine from the limbic system (Imperato et al., 1986) and from striatal slices (Giorguieff et al., 1979), and dopamine plays a role in feeding behaviour (Wise, 1982; Zarrindast et al., 1991), we then examined whether dopaminergic systems mediate nicotine-induced anorexia. Dopamine exerts its effects via different receptor sites, including dopamine $D_1$ and $D_2$ receptor subtypes (Kebabian and Calne, 1979). It has been shown that the anorectic response to dopaminergic drugs can be reduced by the dopamine receptor antagonists sulpiride or SCH 23390 (Zarrindast et al., 1991). In the present study, the dopamine $D_2$ receptor antagonists pimozide (Hyttel, 1983) and sulpiride (Di Chiara et al., 1976; Stoof and Kebabian, 1984) and the $D_1$ antagonist SCH 23390 (Hyttel, 1983) actually amplified the nicotine response (an effect due to the intrinsic effect of the pretreatment in the case of SCH 23390 and pimozide). The data may indicate that dopaminergic mechanisms (at least those examined herein) are not involved in the effects of nicotine. Moreover, the respective effects of the two dopamine $D_2$ receptor antagonists analysed herein may be due to different effects of the drugs regarding pre- and post-synaptic dopamine $D_2$ receptors. That SCH 23390

induced anorexia by itself is in agreement with our previous work (Zarrindast et al., 1991). Because this dopamine receptor antagonist has been proposed to release dopamine from the dorsal caudate (Imperato et al., 1987), it would be interesting to analyse whether this mechanism is involved in our paradigm. The α- and β-adrenoceptor antagonists phenoxybenzamine and propranolol did not reduce but increased the nicotine effect. Therefore, the involvement of adrenergic mechanism(s) in the nicotine response is unlikely. Since the adrenoceptor antagonists induced anorexia by themselves, the increase in the nicotine response may be a summation of the effects elicited by both drugs.

Nicotine also has been shown to enhance the release of serotonin (Balfour, 1982) from the hippocampus. Considering the involvement of 5-HT mechanisms in feeding suppression (Garattini et al., 1992), we used the 5-HT receptor antagonists metergoline (Dourish et al., 1987) and mianserin (Neal and Sparber, 1986) to see whether a 5-HT receptor mechanism is involved in the nicotine effect. These 5-HT receptor antagonists did not reduce the nicotine response, suggesting that the 5-HT mechanisms are not involved.

## Acknowledgements

The authors wish to thank Dr. Shirin Parvini for her helpful comments on the research project and Dr. Mahmoud Ghazi-Khansari for his help in the statistical evaluation of data.

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