Methoxyphenamine inhibits basal and histamine-induced nasal congestion in anaesthetized rats

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1 Nasal resistance in anaesthetized rats was assessed by measuring air overflow during ventilation of the nasal passages at constant pressure. Nasal basal resistance was reduced in a dose-dependent manner by methoxyphenamine hydrochloride (0.01–30 mg kg⁻¹, i.v.), pseudoephedrine hydrochloride (0.03–3 mg kg⁻¹, i.v.) and adrenaline bitartrate (0.01–3 µg kg⁻¹, i.v.). Both methoxyphenamine and pseudoephedrine were less potent and less efficacious than adrenaline but caused longer-lasting responses.

2 Nasal congestion induced by histamine (0.2% nebulised solution passed into the nasal passages for 15 s) was inhibited by i.v. administration of methoxyphenamine, pseudoephedrine, adrenaline, methoxamine or tyramine: the ID₅₀s against 0.2% histamine-induced nasal congestion were 1.16 (95% confidence limits; 0.5, 1.8) mg kg⁻¹, 0.25 (0.19, 0.33) mg kg⁻¹, 0.037 (0.018, 0.06) µg kg⁻¹, 8.12 (6.74, 9.65) µg kg⁻¹ and 30.6 (26.1, 35.8) µg kg⁻¹ respectively.

3 The inhibitory effects of both methoxyphenamine and tyramine on histamine-induced nasal congestion were reduced after administration of desmethylinipramine (0.1 and 1 mg kg⁻¹, i.v.) or prazosin (0.1 and 0.3 mg kg⁻¹, i.v.). Similarly, the inhibitory effects of methoxamine were reduced after prazosin (0.1 and 0.3 mg kg⁻¹).

4 These results indicate that methoxyphenamine (1 mg kg⁻¹, i.v.) inhibits histamine-induced nasal congestion in the rat. This action, at least in part, is probably indirect being mediated by release of neuronal noradrenaline which then acts on α₁-adrenoceptors.

Introduction

Methoxyphenamine is a sympathomimetic agent which causes bronchodilatation (Curry *et al.*, 1949; Grater, 1960) and is used in commercial preparations as a nasal decongestant. It is thought to be an indirectly acting sympathomimetic agent (Bowman & Rand, 1980). Nevertheless there have been few studies of the nasal decongestant properties of methoxyphenamine: Brooks *et al.* (1984) compared its effects with those of phenylpropanolamine and placebo as nasal decongestants in patients suffering from ragweed hay fever, but could demonstrate no activity for methoxyphenamine at the doses used. In laboratory animals the drug has not been examined for nasal decongestant properties. In the present study we therefore looked for evidence that methoxyphenamine could have nasal decongestant effects in anaesthetized rats, comparing its activity with that of the known decongestants adrenaline and pseudoephedrine and examining the mechanisms underlying any effects observed.

Methods

Male Wistar rats, weighing 300–450 g, were anaesthetized with pentobarbitone sodium (65 mg kg⁻¹, i.p.), supplements (10 mg kg⁻¹, i.v.) being given as required during the course of each experiment. The caudal trachea was cannulated and each animal was allowed to breathe spontaneously. Systemic blood pressure and heart rate were monitored from a cannulated femoral artery using a Statham (P23) pressure transducer triggering a cardiometer, both parameters being displayed on a Grass polygraph (79D). The femoral vein was cannulated for intravenous administration of drugs, each dose in a volume of 0.5 ml kg⁻¹ body wt. All doses were flushed in with 0.2 ml saline (0.9% w/v NaCl).

Measurement of nasal airway resistance

The method used was a modification of that of Salem & Clemente (1972). A polyethylene cannula was inserted to a

depth of 2–3 cm into the cephalic end of the trachea (Figure 1). The oesophagus was ligated and the buccal cavity blocked with alginate impression material thus ensuring that air could only pass through the nose and nasal passages. A lack of passage of air via the mouth was confirmed by use of a detergent solution over the mouth which bubbled if air was coming out. A modified Konzett & Rössler (1940) apparatus was used to ventilate the nasal cavities at a constant pressure (7–12 cmH₂O) with a respirator (Ugo Basile 7025) delivering humidified air (bubbled through water at 37°C) with a stroke volume of approximately 8 ml kg⁻¹ (50 strokes min⁻¹). Changes in ventilation overflow (taken as a measure of changed intranasal resistance) were recorded with a bronchospasm transducer (Ugo Basile 7020) connected to a Ugo Basile unirecord (7050). Since the nasal cavities were ventilated at a constant pressure, decreased resistance of the nasal passages was reflected as a reduction in recorded air overflow.

Effects of drugs on nasal basal resistance

Measurements were made of the decreases in nasal ventilation overflow in response to 3–4 cumulative doses of methoxyphenamine (0.01–30 mg kg⁻¹, i.v.), adrenaline (0.01–3 µg kg⁻¹, i.v.) or pseudoephedrine (0.03–3 mg kg⁻¹). Doses were administered at intervals of approximately 15 min, each animal receiving in random order, either methoxyphenamine and adrenaline, or methoxyphenamine and pseudoephedrine.

Effects of drugs on histamine-induced nasal congestion

The method used was a modification of that of Misawa (1988). An ultrasonic nebuliser (DeVilbiss Pulmosonic; Middlesex, England) was placed in the respiratory circuit so that an aerosol passed into the nasal cavities with each stroke of the respirator (Figure 1). After an equilibration period of 15 min following surgical procedures, nebulised saline (0.9%) or histamine dihydrochloride (0.2% or 2%) was passed for 15 s into the nasal cavities, any change in ventilation overflow being measured. The ability of methoxyphenamine, adrenaline, pseudoephedrine, methoxamine or tyramine to inhibit histamine-induced congestion was determined by injecting intravenously a dose of drug 3 min after starting the 15 s

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Figure 1 Diagram to show both the method of application of nebulised saline or histamine to nasal cavities of the rat and the measurement of nasal resistance.

administration of nebulised histamine. After responses to the drug had stabilized (approximately 2 min) a response to a higher dose of the drug was determined in the same fashion. Responses to 2–4 cumulative doses of each drug were measured in any one animal in this way.

When prazosin or desmethylinipramine were used, dose-response curves to methoxyphenamine ($1\text{--}10\text{ mg kg}^{-1}$) were obtained initially, and then repeated 10–15 min after each of two i.v. cumulative doses of prazosin, desmethylinipramine or after the vehicle (time controls). In the same manner, decongestant effects of the selective α_1 -adrenoceptor agonist methoxamine ($1\text{--}30\text{ }\mu\text{g kg}^{-1}$) and the indirectly acting sympathomimetic amine tyramine ($10\text{--}100\text{ }\mu\text{g kg}^{-1}$) were tested and compared with the effect of methoxyphenamine in the anaesthetized rat.

Statistical analyses

Data represented graphically show means and standard errors. Significant differences between log dose-response curves were determined by linear regression analysis (Diem & Leutner, 1970). Values in parentheses are 95% confidence limits.

Drugs

The following drugs were used: methoxyphenamine hydrochloride (Upjohn), (–)-adrenaline bitartrate (Sigma), pseudoephedrine hydrochloride (Upjohn), histamine dihydrochloride (Sigma), prazosin hydrochloride (Sigma), desmethylinipramine hydrochloride (Sigma), methoxamine hydrochloride (Sigma) and tyramine monohydrochloride (Calbiochem). All, except the following, were dissolved in saline: prazosin was initially dissolved in glycerol and then diluted in 5% w/v glucose, and adrenaline in catecholamine diluent ($\text{NaCl } 9\text{ g l}^{-1}$; $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O } 0.156\text{ g l}^{-1}$ and

Figure 2 Tracings showing effects of methoxyphenamine, adrenaline and pseudoephedrine on nasal basal resistance in the anaesthetized rat.

Figure 3 Effects of methoxyphenamine (○), adrenaline (□) and pseudoephedrine (△) on nasal basal resistance ($n = 3\text{--}9$). Values are given as the mean and the vertical bars show 1 s.e.mean or $\pm$ s.e.mean.

ascorbic acid 0.04 g l^{-1}). All drug doses are expressed in terms of the salt.

Results

Effects of methoxyphenamine, adrenaline or pseudoephedrine on nasal basal resistance

Administration of saline or catecholamine diluent (i.v.) did not alter nasal basal resistance in the anaesthetized rat. Figures 2 and 3 show the decongestant effects (indicated by decreases in ventilation overflow) caused after methoxyphenamine ($0.01\text{--}30\text{ mg kg}^{-1}$, i.v.), adrenaline ($0.01\text{--}3\text{ }\mu\text{g kg}^{-1}$, i.v.) or pseudoephedrine ($0.03\text{--}3\text{ mg kg}^{-1}$, i.v.). Adrenaline produced a dose-dependent decongestant effect which was relatively short-lasting (2–3 min). Both methoxyphenamine and pseudoephedrine were less potent and less efficacious than adrenaline, but produced longer-lasting responses ($> 15\text{ min}$) (Figure 2).

Effects of methoxyphenamine, adrenaline, pseudoephedrine, tyramine or methoxamine on histamine-induced nasal congestion

Nebulised saline passed for 15 s into the nasal cavities sometimes resulted in a slight increase in ventilation overflow

Figure 4 Tracings showing effects of saline, methoxyphenamine, adrenaline and pseudoephedrine on histamine-induced nasal congestion.

Figure 5 Effects of methoxyphenamine ($\circ$, $\bullet$), adrenaline ($\square$) and pseudoephedrine ($\triangle$) on histamine-induced nasal congestion ($n = 3-7$). Open symbols are with 0.2% histamine, closed symbols with 2% histamine. The points show the mean and the bars indicate 1 s.e.mean or $\pm$ s.e.mean.

which returned to the baseline level after ceasing administration. However, in contrast to this, an increase in ventilation overflow was observed 1–2 min after the start of a 15 s inhalation of histamine (0.2% or 2%) which persisted for 5–10 min thereafter (Figure 4). As shown in Figure 5, methoxyphenamine ($1-10 \text{ mg kg}^{-1}$, i.v.), adrenaline ($0.03-0.3 \mu\text{g kg}^{-1}$, i.v.) or pseudoephedrine ($0.1-1 \text{ mg kg}^{-1}$, i.v.) caused dose-dependent decreases in histamine-induced nasal resistance. The effects of methoxyphenamine and pseudoephedrine were again longer-lasting than adrenaline (Figure 4). Analysis of these data by linear regression showed that methoxy-

Figure 6 (a) Effects of prazosin ($\circ$, 0 mg kg^{-1} ; $\blacktriangle$, 0.1 mg kg^{-1} and $\blacksquare$, 0.3 mg kg^{-1}) on inhibition by methoxamine of histamine-induced nasal congestion ($n = 4$). (b) Effects of desmethylinipramine ($\circ$, 0 mg kg^{-1} ; $\blacktriangle$, 0.1 mg kg^{-1} and $\blacksquare$, 1 mg kg^{-1}) on inhibition by methoxamine of histamine-induced nasal congestion ($n = 4$). The points show the mean with the error bars indicating 1 s.e.mean or $\pm$ s.e.mean.

Figure 7 (a) Effects of prazosin ($\circ$, 0 mg kg^{-1} ; $\blacktriangle$, 0.1 mg kg^{-1} and $\blacksquare$, 0.3 mg kg^{-1}) on inhibition by tyramine of histamine-induced nasal congestion ($n = 6$). (b) Effects of desmethylinipramine ($\circ$, 0 mg kg^{-1} ; $\blacktriangle$, 0.1 mg kg^{-1} and $\blacksquare$, 1 mg kg^{-1}) on inhibition by tyramine of histamine-induced nasal congestion ($n = 4$). The points show the mean with the error bars indicating 1 s.e.mean or $\pm$ s.e.mean.

phenamine gave ID_{50} s of 1.16 (0.5, 1.8) and 1.9 (1.1, 2.7) mg kg^{-1} for inhibition of 0.2% and 2% histamine-induced nasal resistance respectively (Figure 5). This compares with ID_{50} s for adrenaline and pseudoephedrine of 0.037 (0.018, 0.06) $\mu\text{g kg}^{-1}$ and 0.25 (0.19, 0.33) mg kg^{-1} (Figure 5) respectively (both for inhibition of 0.2% histamine-induced nasal congestion). As shown in Figures 6 and 7, both methoxamine ($1-30 \mu\text{g kg}^{-1}$) and tyramine ($10-100 \mu\text{g kg}^{-1}$) also inhibited 0.2% histamine-induced nasal congestion. The ID_{50} s were 8.12 (6.74, 9.65; $n = 5$) $\mu\text{g kg}^{-1}$ and 30.6 (26.1, 35.8; $n = 6$) $\mu\text{g kg}^{-1}$ respectively.

Effects of prazosin and desmethylinipramine on methoxyphenamine, methoxamine or tyramine-induced decrease of nasal resistance

Repeated dose-response curves obtained for agonist inhibition of histamine-induced nasal resistance did not vary significantly with time or with injection of vehicle at the same time intervals as antagonists. The test was performed over 2–3 h with 20 min intervals between dose-response curves for methoxyphenamine or methoxamine and a period of 30 min for tyramine. As shown in Figure 8a, prazosin (0.1 and 0.3 mg kg^{-1} i.v.) antagonized the inhibitory effects of methoxyphenamine on histamine-induced nasal resistance. For both doses of prazosin, there was a significant parallel shift of the log dose-response curve to methoxyphenamine, as assessed by linear regression analysis (Table 1). Similarly, as shown in Figure 8b, desmethylinipramine (0.1 and 1 mg kg^{-1} , i.v.) reduced the effects of methoxyphenamine on histamine-induced nasal resistance. Both doses of desmethylinipramine

Figure 8 (a) Effects of prazosin (○, 0 mg kg⁻¹; ▲, 0.1 mg kg⁻¹ and ■, 0.3 mg kg⁻¹) on inhibition by methoxyphenamine of histamine-induced nasal congestion ($n = 5$). (b) Effects of desmethylimipramine (○, 0 mg kg⁻¹; ▲, 0.1 mg kg⁻¹ and ■, 1 mg kg⁻¹) on inhibition by methoxyphenamine of histamine-induced nasal congestion ($n = 5$). The points show the mean with the error bars indicating 1 s.e.mean or $\pm$ s.e.mean.

caused a significant parallel shift to the right of the log dose-response curve to methoxyphenamine (Table 1). Methoxamine (1–30 μ g kg⁻¹) and tyramine (10–100 μ g kg⁻¹) produced dose-dependent decreases of histamine-induced nasal congestion (Figures 6 and 7). As shown in Figure 6, prazosin (0.1 and 0.3 mg kg⁻¹), but not desmethylimipramine (0.1 and 1 mg kg⁻¹) significantly inhibited the effects of methoxamine. Figure 7 shows that the same doses of prazosin and desmethylimipramine significantly inhibited the effect of tyramine. Rightward parallel shifts in the linear portion of the log dose-response curves are summarised in Table 1. For either dose of prazosin, there was no significant difference in the degree of shift of the log dose-response curve to methoxamine compared with that to methoxyphenamine. Similarly, for either dose of desmethylimipramine, there was no significant difference in the degree of shift of the log dose-response curve to tyramine compared to that of methoxyphenamine.

Discussion

In the present study, methoxyphenamine (0.01–30 mg kg⁻¹, i.v.), adrenaline (0.01–3 μ g kg⁻¹, i.v.) and pseudoephedrine (0.03–3 mg kg⁻¹, i.v.) reduced the nasal basal resistance in anaesthetized rats. Neither methoxyphenamine nor pseudoephedrine were as potent or as efficacious as adrenaline in this test, but they produced longer-lasting decongestant effects. Adrenaline at a dose as low as 0.01 μ g kg⁻¹ reduced nasal basal resistance, as has been previously shown by Bentley & Jackson (1970).

The present results also showed that nasal congestion induced by 0.2% histamine solution, passed for 15 s into the ventilated nasal passages of the rat, was reduced by methoxyphenamine, adrenaline, pseudoephedrine, methoxamine or tyramine. Pseudoephedrine was approximately 4–5 times more potent than methoxyphenamine in this test. Pseudoephedrine is a stereoisomer of ephedrine possessing both direct and indirect sympathomimetic activity. Empey *et al.* (1980) showed that an oral dose of 60 mg could inhibit histamine-induced nasal congestion in normal human subjects. Histamine is an important mediator in the symptoms of allergic rhinitis; exposure of the nasal mucosa to histamine can cause irritation, sneezing, vascular engorgement and congestion, oedema of the mucosa and production of excessive nasal secretions (Bentley & Jackson, 1970; Misawa, 1988). Although Brooks *et al.* (1984) found that methoxyphenamine was not effective in patients suffering from ragweed hay fever, combinations of methylprednisolone and methoxyphenamine have been shown to have decongestant effects in patients with allergic rhinitis (Grater, 1960); the effects of the steroid were enhanced in the presence of methoxyphenamine.

The effects of methoxyphenamine on histamine-induced nasal congestion were reduced by desmethylimipramine and prazosin, suggesting an indirect action of methoxyphenamine by its release of neuronal noradrenaline which then acts on α_1 -adrenoceptors. The decongestant effect of methoxamine was sensitive to blockade by prazosin but unaffected in the presence of desmethylimipramine. In contrast, the response to tyramine was inhibited by prazosin and desmethylimipramine. The inhibitory effect of prazosin suggests that methoxyphenamine, tyramine and methoxamine all act at least in part via activation of α_1 -adrenoceptors in the nasal vasculature of the rat.

The nasal decongestant activity of sympathomimetic agents is thought to be mediated through an action, either directly or indirectly, on α -adrenoceptors on local blood vessels in the nasal mucosa with consequent reduction in oedema. Vessels controlling blood flow to and vascular volume of the nasal mucosa are richly innervated by adrenergic nerve fibres (Dahlström & Fuxe, 1965). Adrenaline or noradrenaline either administered into the circulation or applied directly to the nasal mucosa cause pronounced nasal vasoconstriction (Malcomson, 1959; Jackson, 1970). These vasoconstrictor responses are mediated by α -adrenoceptors and are reduced after administration of α -adrenoceptor antagonists such as phentolamine (Eccles & MacLean, 1977). Drugs such as cocaine and desmethylimipramine which interfere with the neuronal uptake of noradrenaline into nerve endings therefore potentiate the nasal vasoconstriction induced by sympathetic

Table 1 Degree of shift of the linear portion of the log dose-decongestant response curves to agonists in the presence of antagonists

Antagonist	Dose (mg kg ⁻¹)	Degree of shift (and 95% confidence limits)		
		Methoxyphenamine (n = 5)	Methoxamine (n = 4)	Tyramine (n = 4–6)
Prazosin	0.1	2.3 (1.8; 2.98)	2.7 (1.85; 4.03)	1.98 (1.58; 2.52)
	0.3	7.48 (5.39; 11.15)	6.5 (4.25; 10.08)	5.33 (3.77; 8.33)
Desmethylimipramine	0.1	1.75 (5.39; 2.66)	1.01 (0.84; 1.22)	2.42 (1.91; 3.07)
	1	2.96 (1.46; 8.41)	1.17 (0.96; 1.42)	5.72 (4.41; 7.51)

Values are given as the mean with the 95% confidence limits shown in parentheses. The number of animals in the group is given by n .

nerve stimulation (Eccles & MacLean, 1977) but reduce the effects of indirectly acting sympathomimetic amines.

In summary, the present study provides evidence that methoxyphenamine has nasal decongestant properties in the rat. Its sympathomimetic action in reducing histamine-

induced nasal congestion is probably mediated, at least in part indirectly, with involvement of α_1 -adrenoceptors.

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