EFFECT OF DOPAMINE ON AIRWAYS CONDUCTANCE IN NORMALS AND EXTRINSIC ASTHMATICS

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- 1 Specific conductance was measured before and after infused and/or inhaled dopamine in nine normal subjects and twelve patients with extrinsic bronchial asthma.
- 2 There was no significant change in conductance in either group.
- 3 The α -adrenergic receptor antagonist thymoxamine infused in combination with dopamine had no significant effect on conductance in three asthmatics.
- 4 It is concluded that dopamine has no acute effect on airways resistance and that specific dopamine receptors are unlikely to exist in human airways.

Introduction

Dopamine is a naturally occurring catecholamine which is the immediate precursor of noradrenaline (Blaschko, 1957), and it has been suggested that it acts as an important neurotransmitter in the peripheral autonomic nervous system (Thorner, 1975). Dopamine stimulates adenosine 3':5' monophosphate (cyclic AMP) synthesis in postsynaptic ganglia causing hyperpolarization, which is associated with an increase in the threshold of excitability (Greengard, 1976). This modulating effect of dopamine on autonomic ganglia could thus indirectly affect bronchial smooth muscle tone. Furthermore, Newman Taylor, Soutar, Sneerson & Turner Warwick (1976) reported an improvement in pulmonary function in patients with chronic asthma who were treated with the specific dopamine receptor agonist bromocriptine.

Although specific dopamine receptors have been identified in renal, mesenteric, coronary and intracerebral arterial vascular beds (Goldberg, 1972; Von Essen, 1972), which when stimulated by dopamine cause vasodilation, it is unknown whether such receptors exist in the bronchial tree. Dopamine has, however, been found in significant amounts in the lung of ruminants (Von Euler & Lishayko, 1957), and in this lung dopamine has been located in the mast cells (Falck, Nystedt, Rosengren & Stenflo, 1964). Its release from isolated calf lung sensitized with horse serum by specific antigen and by compound 48/80 suggests that, at least in this species, it may be important in immediate type allergy (Eyre & Deline, 1971).

The present study was therefore undertaken to evaluate the effects of dopamine on airways resistance

in normal subjects and in patients with extrinsic asthma.

Methods

Twelve patients (ages 18–32 years) with extrinsic bronchial asthma and reversible airways obstruction were studied. All patients had positive skin tests to inhalant allergens, a blood eosinophilia and an IgE level above 200 u/ml. Disodium cromoglycate and bronchodilators were discontinued for 12–24 h before the test was carried out. Patients on oral or aerosol corticosteroids were excluded from the study. Nine normal subjects (aged 22–35 years) who were non-smokers and with no history of respiratory disease, were also studied. The nature and the purpose of the study were explained to both patients and normal subjects, although the patients were unaware that the study involved the use of a placebo infusion and/or inhalant as well as the active drug. The investigations were approved by the Ethical Committee of this hospital, and all patients and normal subjects gave informed consent. Airways resistance (R_{aw}) and thoracic gas volume were measured simultaneously in a constant-volume body plethysmograph (Dubois, Botelho & Comroe, 1956) and the results were expressed as specific conductance ($sGaw$), which is the reciprocal of airways resistance per litre of thoracic gas volume. The mean of four recordings was calculated to give $sGaw$. All plethysmographic measurements were carried out by one observer (N C T). In addition radial pulse rate and blood

pressure were measured 1 min before each measurement of sGaw. Statistical significance was tested in all instances by means of Student's paired *t*-test.

Dopamine by infusion

In six normal subjects following baseline measurements, an infusion of dopamine (200 mg/l) in dextrose (50 g/l) was commenced at a rate of $5 \mu\text{g kg}^{-1} \text{min}^{-1}$ for 10 minutes. The infusion was then stopped and measurements made at 1, 5, 10 and 20 minutes. In the asthmatic patients following initial measurements, a placebo infusion of dextrose (50 g/l) was commenced and after 10 min they were disconnected from the infusion and baseline measurements repeated. The patients were then reconnected to the infusion and without the subject's knowledge, dopamine (200 mg/l) in dextrose (50 g/l) was substituted and infused at a rate of $5 \mu\text{g kg}^{-1} \text{min}^{-1}$ for 10 minutes. The patients were again disconnected from the infusion and measurements made at 1, 5, 10 and 20 min, dextrose (50 g/l) being infused between these measurements.

Three of the asthmatic patients were given an additional infusion of thymoxamine (60 mg/l) in dextrose (50 g/l) for 10 min at a rate of 0.1 mg min^{-1} , which was then continued in combination with

dopamine (200 mg/l) in dextrose (50 g/l) at a rate of $5 \mu\text{g kg}^{-1} \text{min}^{-1}$ for a further 10 min. sGaw was measured prior to each infusion and at 1 and 5 min after the combined infusion.

Dopamine by inhalation

In six normal subjects following baseline measurements, a saline solution (9 g/l) was inhaled through a Wrights' nebulizer using compressed air at a flow rate of 8 l/min for 2 min, and sGaw recorded 1 min after the inhalation. After a further 4 min dopamine (0.5 g/l) was inhaled for 2 min and sGaw recorded 1 min later. If no change in airways calibre was observed, the dose of dopamine inhaled was increased to 1 g/l and then to 2 g/l, and sGaw measurements repeated at similar time intervals. A similar protocol was used in six extrinsic asthmatics.

Results

Table 1 shows the response of sGaw to dopamine infusion in six normal subjects and in eight patients with extrinsic asthma. No significant difference was produced by the infusion in normal subjects or patients with extrinsic asthma. In addition, the three asthmatic patients who received the combined infusion

Table 1 Effect of infused dopamine on sGaw in normals and extrinsic asthmatics

Groups (n)	Pre-infusion baseline	Infusion baseline	sGaw ($\text{s}^{-1} \text{k Pa}^{-1}$)				
			Time after dopamine infusion (min)				
			1	3	5	10	20
Normal (6)	1.46 ± 0.24		1.60 ± 0.21 NS	1.58 ± 0.24 NS	1.52 ± 0.28 NS	1.39 ± 0.22 NS	1.46 ± 0.21 NS
Extrinsic asthma (8)	0.71 ± 0.06	0.65 ± 0.07	0.61 ± 0.05 NS		0.59 ± 0.05 NS	0.60 ± 0.06 NS	0.59 ± 0.06 NS

Infusion baseline refers to value after dextrose (50 g/l) infusion without dopamine.

Table 2 Effect of inhaled dopamine on sGaw in normals and extrinsic asthmatics

Groups (n)	Baseline	Post-saline	sGaw ($\text{s}^{-1} \text{k Pa}^{-1}$)		
			Dose of dopamine (g/l)		
			0.5	1.0	2.0
Normal (6)	2.30 ± 0.37	2.28 ± 0.40	2.19 ± 0.39 NS	2.17 ± 0.34 NS	2.22 ± 0.36 NS
Extrinsic asthma (6)	0.97 ± 0.12	0.71 ± 0.18	0.67 ± 0.15 NS	0.81 ± 0.25 NS	0.67 ± 0.15 NS

of thymoxamine and dopamine showed no significant change in sGaw compared to thymoxamine alone.

Table 2 shows the response of sGaw to inhaled dopamine in six normal subjects and six patients with extrinsic asthma. No significant difference was produced by the inhalations in either group.

In all groups, pulse and blood pressure remained unchanged during the study period.

Discussion

Our studies indicated that dopamine infusion at a dose that has been reported to increase cardiac contractility (Whitsett & Goldberg, 1972), cardiac output and renal blood flow (McDonald, Goldberg, McNay & Tuttle, 1964), does not significantly alter airways resistance in normal subjects or in patients with extrinsic asthma. In addition, inhaled dopamine failed to effect airways resistance in a similar group of subjects. This lack of response in airways resistance suggests that specific dopamine receptors are unlikely to exist in human airways, and is in keeping with the extremely weak peripheral β -adrenergic agonist action of dopamine found in experimental animals (McNay & Goldberg, 1966). It is possible, however, that specific dopamine receptors remained unstimulated by the dose of dopamine infused. It was felt unethical to give higher doses of infused dopamine, and this may therefore have limited the access of the drug to receptor sites in the lung. Although it is not possible to accurately estimate the dose of dopamine inhaled it is less likely, by this means of administration that any lack of response was due to poor access to receptor sites on

the airways. If dopamine is released from human mast cells, as has been suggested to occur in bovine lung (Eyre & Deline, 1971), it is unlikely to be a clinically significant factor in the production of airways obstruction.

In doses above $30 \mu\text{g kg}^{-1} \text{min}^{-1}$ the predominant effect of infused dopamine in all vascular beds examined is vasoconstriction due to its action on α -adrenergic receptors (Goldberg, 1972). α -adrenergic receptors have also been reported in the airways of both normal subjects (Prime, Bianco, Griffin & Kamburoff, 1972) and asthmatic patients (Patel & Kerr, 1973).

The dose of dopamine infused in this study was low and therefore unlikely to stimulate α -adrenergic receptors. This was confirmed in three asthmatic patients, by the lack of airways response to dopamine when it was infused in combination with the α -adrenergic antagonist thymoxamine.

Although dopamine has no acute effect on airways resistance, a long-acting dopamine agonist such as bromocriptine may still influence airways calibre. Unlike dopamine (Oldendorf, 1971) bromocriptine crosses the blood brain barrier and may thus alter airways calibre by stimulating intracerebral dopamine receptors (Dray & Oakley, 1976). This may explain the improvement in lung function in asthma reported by Newman Taylor *et al.* (1976).

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