

Bronchodilator actions of papaverine in the anaesthetized guinea-pig

SIR,—It has been observed that intravenous injection of papaverine reduced the temporary increase in bronchial resistance produced by histamine in the anaesthetized guinea-pig. This fact accords with the well-known spasmolytic action of the drug. However we found, as did Dr G. James, that the spasmolytic action of papaverine on bronchial smooth muscle *in vivo* is reduced by the prior administration of pronethalol, a β -adrenergic blocking agent. We now describe the elucidation of the mechanism of the bronchodilator action of papaverine in the anaesthetized guinea-pig. The methods employed have been described in detail elsewhere (Farmer & Lehrer, 1966).

Papaverine (0.5 μ g/ml) and isoprenaline (5ng/ml) produced relaxation in approximately equal magnitude of the tracheal chain preparation (Castillo & de Beer, 1940; Akçasu, 1959). When pronethalol and phentolamine were added to the bath, each at a concentration of 2.5 μ g/ml, the response of the tissue to isoprenaline was abolished whilst that to papaverine remained unchanged. This evidence eliminated the possibility of an action of papaverine on adrenoceptive receptors. For the assessment of the activity of papaverine hydrochloride against histamine-induced bronchospasm in the anaesthetized guinea-pig (Konzett & Rossler, 1940), at time zero, 10 mg/kg of papaverine hydrochloride was injected intravenously and the response of the animal at various time intervals to intravenous injection of histamine was assessed. This procedure was performed in further guinea-pigs after pronethalol (10 mg/kg *i.m.*), bilateral adrenalectomy, total destruction of the central nervous system, and bilateral denervation of carotid sinuses (sinuses removed). The results (means of at least 4 guinea-pigs) showed that each procedure much reduced the duration of action of papaverine against histamine bronchospasm. The time for 50% recovery of the response to histamine, after injection of papaverine, was reduced from approximately 55 min to 14.22 min (depending on procedure). There was also some reduction in the absolute potency but the design of the experiment does not allow interpretation of this latter effect. Intravenous injection of papaverine, 10 mg/kg, in the anaesthetized guinea-pig produced a fall in arterial blood pressure of 58 ± 4.6 (5) mm Hg (maximum) and the time taken for 50% recovery was 16 ± 6.9 (5) min.

These experiments show that the antagonism by papaverine of histamine bronchospasm in the anaesthetized guinea-pig is mediated by at least two mechanisms. Firstly there is a direct action of papaverine on bronchial smooth muscle and secondly an action due to a release of catecholamines. The catecholamines originate mainly from the adrenal medulla and the effective stimulus for such a secretion is a fall in mean arterial blood pressure which results in a reflexly mediated increase in sympathetic outflow.

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