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The nature of the antagonism of bronchospasm in the guinea-pig by ascorbic acid

SIR,—In a Communication presented to the British Pharmacological Society in July 1964, we showed that ascorbic acid exerted a protective action on anaphylactic shock in the guinea-pig (Dawson & West, 1965). This result has recently been confirmed by Guirgis (1965). We have now found that this protective action seems to be a direct effect of ascorbic acid on the bronchial muscle.

Guinea-pigs were anaesthetised with chloralose (100 mg/kg) intraperitoneally, and artificially ventilated with a constant volume pump through a tracheal cannula. Bronchoconstriction was measured from changes in ventilation pressure in the trachea using a transducer system, and arterial blood pressure was recorded from the external carotid artery. Drugs were injected into the exposed jugular vein. Similar degrees of bronchoconstriction were produced by 5-hydroxytryptamine (5 μg), bradykinin (10 μg), and histamine (5 μg), and all these actions were prevented by previously injecting ascorbic acid (500 mg/kg) in neutral solution within 10 min of the injection of the spasmogens (see Fig. 1).

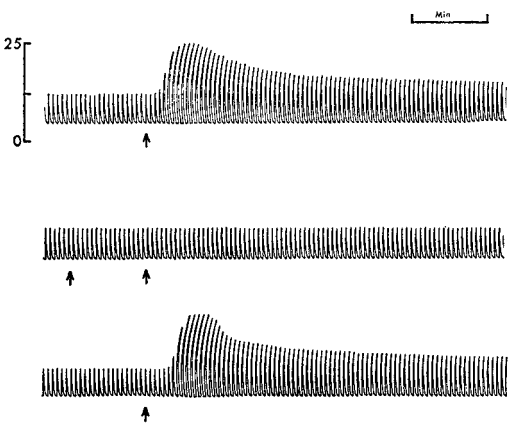

FIG. 1. Record of tracheal pressure of an anaesthetised guinea-pig. Upper tracing, response to histamine (5 μg); middle tracing, effect of ascorbic acid (500mg/kg) given at the first arrow one min before the next histamine dose; lower tracing, response to histamine 30 min later. Time in min. Pressure in mm Hg.

Smaller doses of ascorbic acid (100 and 200 mg/kg) proportionately reduced the actions. Doses of adrenaline (1–5 μg) also abolished the bronchoconstrictor action of the three spasmogens, but adrenaline raised the arterial blood pressure whereas ascorbic acid did not. Pretreatment of the animals with pronethalol

(10 mg/kg intravenously) abolished the inhibitory effect of adrenaline on the bronchial muscle but not that of ascorbic acid. Reserpinisation of the animals with four daily doses of reserpine, 2 mg/kg, intraperitoneally, did not modify the action of ascorbic acid on the spasmogen response. Dr. Collier & Mrs. Piper also tell us that adrenalectomy does not reduce the protective effect of ascorbic acid on bradykinin bronchospasm.

The present results show that the inhibition of bronchospasm by ascorbic acid is not mediated by catecholamines, does not involve β-adrenergic receptors since its action is not prevented by pronethalol, and is probably a direct effect.

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Anorexigenic drugs and lipid mobilisation

SIR,—As reported previously (Santi & Fassina, 1964), dexamphetamine, a typical anorexigenic substance, strongly elevated the plasma level of free fatty acids. Effectiveness of anorexigenic sympathomimetic drugs, may thus be considered to be based, not only on modification of psychic function, but mainly related to an interference with the central mechanisms of regulating food intake (Andersson & Larsson, 1961).

TABLE 1. EFFECT OF SOME ANOREXIGENIC DRUGS ON PLASMA FREE FATTY ACIDS (FFA) IN RATS

Treatment and dose	Time of death min	Plasma FFA μequiv./litre mean ± s.e.
Saline	30	424 ± 30 (11)† —
Chlorphentermine hydrochloride 12 mg/kg ..	30	710 ± 10 (4) < 0·001*
Methylphenidate hydrochloride 14 mg/kg ..	30	713 ± 28 (7) < 0·001
Pipradol hydrochloride 16·5 mg/kg	30	847 ± 10 (4) < 0·001
Saline	60	403 ± 33 (19) —
Dexamphetamine sulphate 2 mg/kg	60	672 ± 26 (17) < 0·001

* P versus saline treated controls.
† number of animals.
Adult non-fasted female rats (Wistar strain, 200–250 g) were given drugs or saline intraperitoneally and decapitated under ether anaesthesia. Time of death corresponded to the maximum activity for each drug. Free fatty acids were titrated by the method of Dole (1956). Doses of chlorphentermine, methylphenidate and pipradol are equimolar (54 μmoles/kg); dose of dexamphetamine (10·8 μmoles/kg).

We have now investigated the effects of additional anorexigenic drugs on plasma free fatty acids in rats. The three different classes investigated show a particular pharmacological and structural interest. Chlorphentermine is closely related chemically to dexamphetamine, but is almost completely devoid of the typical central nervous system (CNS) stimulant activity (Holm, Huus, Kopf, Möller Nielsen & Petersen, 1960; Gylys, Hart & Warren, 1962). Methylphenidate and pipradol (Karczmar & Howard, 1959; Spengler & Waser, 1959) are CNS stimulants and differ from amphetamine in structure (piperidine-like compounds) and in adrenergic properties (Krueger & McGrath, 1964).