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The bronchodilator action of analeptics in the guinea-pig

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Picrotoxin, leptazol, nikethamide and bemegride were found to antagonize the bronchoconstrictor effects of acetyl-β-methylcholine in the guinea-pig anaesthetized with urethane. The analeptics were also active in pithed animals but not in animals that had been adrenalectomized or pretreated with propranolol. Catecholamine release from the adrenals can account for the effects observed.

A given total respiratory ventilation can be achieved by a wide variety of combinations of tidal volume and frequency. The optimal breathing frequency for a given ventilation may be defined as the one that leads to the least energy cost. That this frequency is the one chosen has been confirmed in man and various animals (Milic-Emili & Petit, 1959; Agnostoni, Thimm & Fenn, 1959; Crosfill & Widdicombe, 1961). The equations used in calculations of optimal frequency involve a number of factors including the flow-resistive properties of the system (Otis, Fenn & Rahn, 1950).

It might therefore be predicted that a change in the flow-resistive properties of the system would accompany changes in the ventilation pattern, namely alterations in tidal volume and frequency. That such alterations do occur after bronchodilator or bronchoconstrictor agents has often been reported (Stroud, Lambertsen & others 1955; Dautrebande, Philippot & others, 1942a, b). Conversely one might postulate that analeptic agents, which have a well-defined effect upon respiratory rate and frequency (Dautrebande & Stolport, 1948; Marshall, Walzl & Le Mesurier, 1937), might also have effects upon the diameter of the bronchioles; but the action of none of these drugs has ever been reported, except in the guinea-pig isolated perfused lung (Warnant, 1930).

In preliminary plethysmographic experiments using conscious rabbits we have consistently observed bronchodilator effects with picrotoxin. This agent, together with other analeptics, have consequently been examined to assess their direct bronchodilator effects uncomplicated by alterations of frequency and tidal volume, which always characterize the actions of these agents in the intact animal. For this purpose the Konzett-Rössler preparation of the guinea-pig was used.

EXPERIMENTAL

Method

The method was based on that of Konzett & Rössler (1940) and modified as suggested by Collier, Holgate & others (1960). Electrical recording was used and the piston recorder replaced by a pneumotachograph.

Animals of 300–350 g were anaesthetized with urethane (1·5–2·5 g/kg, i.p.), further doses being administered when necessary to abolish spontaneous respiratory movements.

The trachea was cannulated and inflated by means of a pump delivering about 5 ml stroke volume at 72 strokes/min. A side arm from the cannula allowed about 2 ml of air to escape through a water valve offering a resistance of 10 cm water, the flow being measured by means of the pneumotachograph connected to a sensitive differential pressure transducer. Increases of overflow volume are therefore represented as an increased excurison on the recorder. Bilateral vagotomy was carried out since this seemed to make the response of the preparation more consistent. In some experiments animals were also adrenalectomized or pithed.

Solutions of drugs in saline were injected into the external jugular vein at regular intervals. In all experiments acetyl-β-methylcholine (methacholine) (3–8 μg/kg, i.v.) was used to produce an increase in resistance to inflation. Isoprenaline and papaverine were also used as reference drugs. Doses are of the bases.

RESULTS

Picrotoxin (1·0–3·0 mg/kg, i.v.) consistently reduced the increased resistance to inflation produced by methacholine (Fig. 1). This effect of picrotoxin lasted up to 2 h when the larger doses were used. Isoprenaline (4 μg/kg) and papaverine (2 mg/kg) were also effective though their effects only lasted 10–15 min.

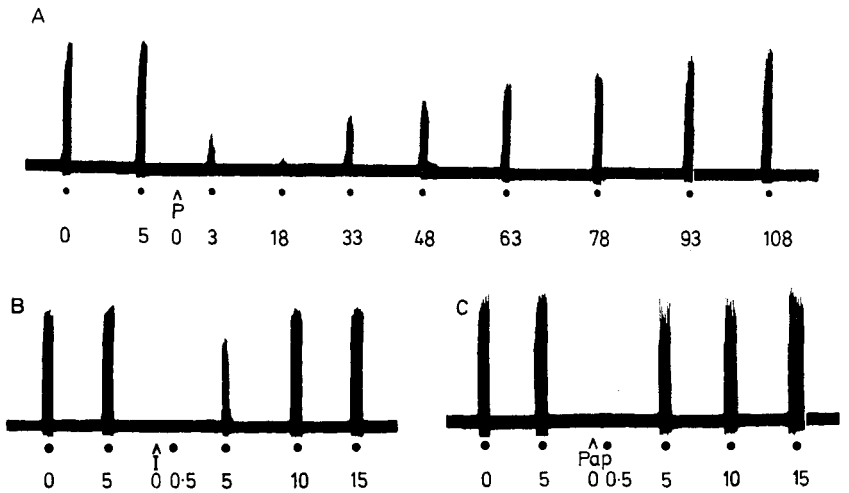

FIG. 1. Vagotomized guinea-pig. Increased resistance to inflation caused by methacholine and its reduction by picrotoxin (P), isoprenaline (I) and papaverine HCl (Pap). Doses were administered intravenously at the intervals shown (min).

In pithed animals the effects of picrotoxin were still apparent (Fig. 2), in fact there was a tendency for the effects of this agent to be more pronounced and of longer duration in these preparations. Also effective in the pithed animal were isoprenaline and papaverine.

However, in the adrenalectomized animal, picrotoxin was ineffective in reducing the increase in resistance produced by methacholine (Fig. 3) though isoprenaline and papaverine were still able to do so.

As may be seen in Fig. 4, pretreating the animals with a β-sympathetic blocker (propranolol, 1·5 mg/kg, i.v.) nullified the effects of both picrotoxin and isoprenaline. The effects of papaverine were perhaps slightly reduced.

Leptazol (10 mg/kg, i.v.), bemegride (10 mg/kg, i.v.) and nikethamide (100 mg/kg, i.v.) were examined in the guinea-pig preparation and found to abolish the responses to methacholine (Fig. 5) but, in the animals given propranolol (1·5 mg/kg, i.v.) these three analeptic agents agents were no longer effective (Fig. 6).

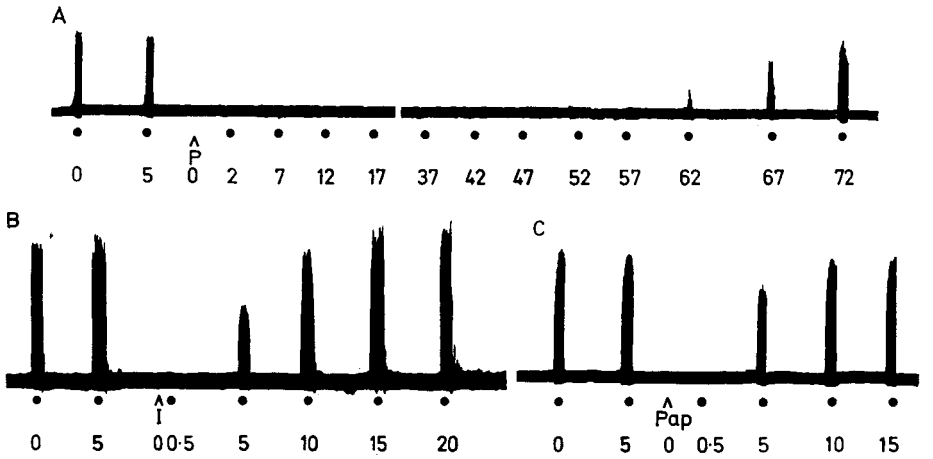

FIG. 2. Vagotomized, pithed guinea-pig. Increased resistance to inflation caused by methacholine and its reduction by picrotoxin (P), isoprenaline (I) and papaverine (Pap). Doses were administered intravenously at the intervals shown (min).

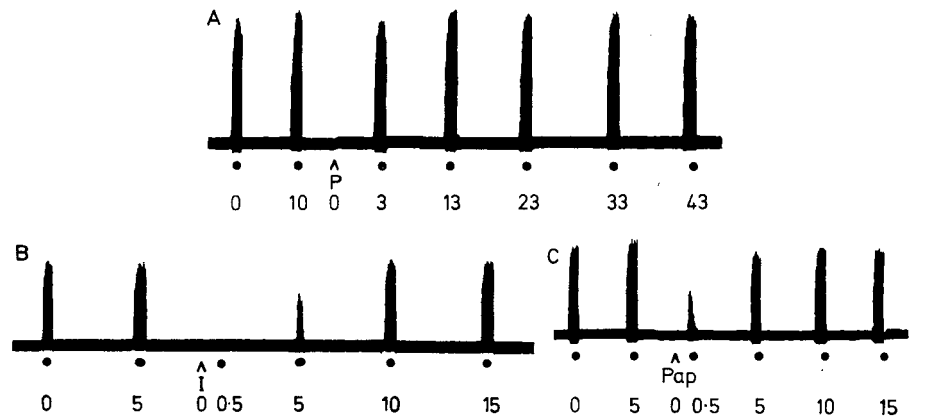

FIG. 3. Vagotomized and adrenalectomized guinea-pig. Increased resistance to inflation caused by methylcholine and to modification by picrotoxin (P), isoprenaline (I) and papaverine (Pap). Doses were administered intravenously at intervals shown (min).

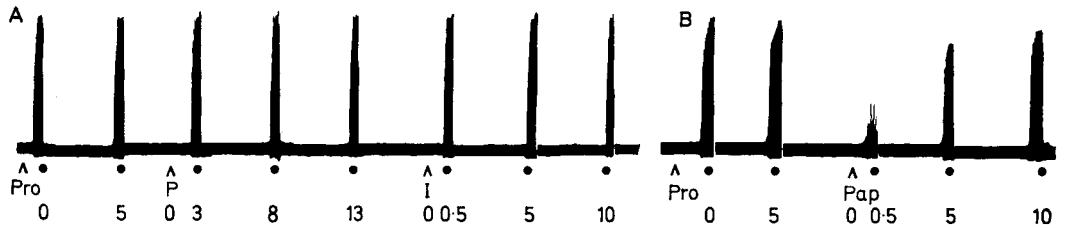

FIG. 4. Vagotomized guinea-pigs. Increased resistance to inflation caused by methylcholine and its modification by picrotoxin (P), isoprenaline (I) and papaverine (Pap) in animals given propranolol (Pro). Doses were administered intravenously at the intervals shown (min).

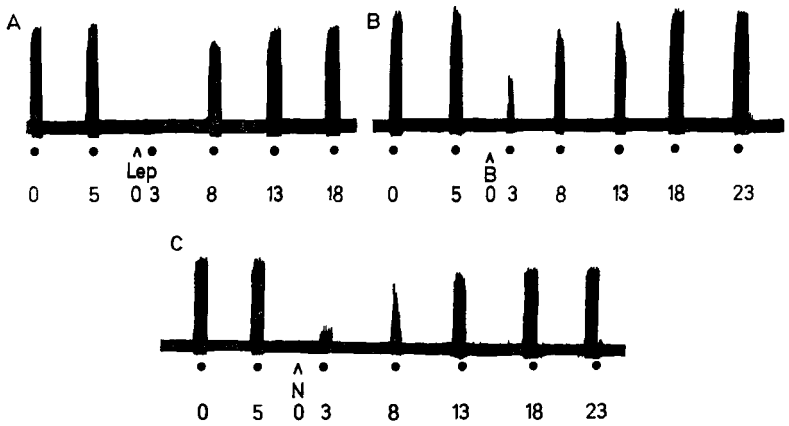

FIG. 5. Vagotomized guinea-pig. Increased resistance to inflation caused by methylcholine and its reduction by leptazol (Lep), bemegride (B) and nikethamide (N). Doses were administered intravenously at the intervals shown (min).

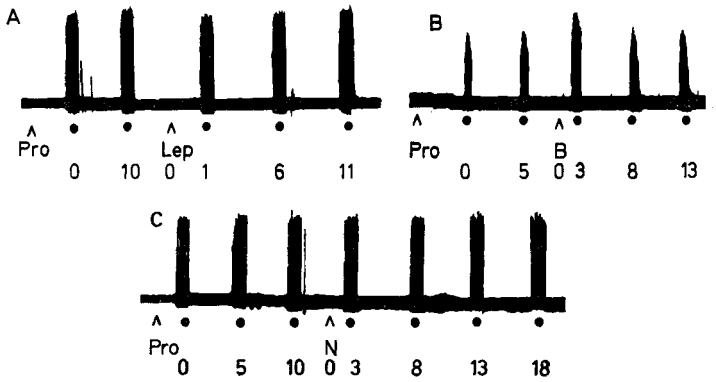

FIG. 6. Vagotomized guinea-pigs. Increased resistance to inflation caused by methylcholine and its persistence after leptazol (Lep), bemegride (B) and nikethamide (N) in animals given propranolol (Pro). Doses were administered intravenously at the intervals shown (min).

DISCUSSION

The experiments indicate that picrotoxin, leptazol, bemegride and nikethamide can exert a "bronchodilator" effect, as measured in the Konzett-Rössler preparation, and that, moreover, their potency ratios in this test situation are similar to their activities as convulsive agents (Hahn, 1941) which might suggest that they are exerting a central action. However, since these agents are still active in the pithed animal, central properties cannot be invoked to explain these results, and some peripheral mechanism must therefore be sought.

The absence of activity when using these analeptics in adrenalectomized or propranolol-pretreated animals suggests that the analeptic drugs tested exert their effects on the lungs by releasing catecholamines from the adrenals. Such a concept is in accord with the findings of Vogt (1954) who has already shown that picrotoxin in convulsive doses depletes the adrenal medulla of its adrenaline, though she did not observe the same depleting effect using leptazol. Nevertheless, the failure of leptazol to deplete does not necessarily imply that this drug does not release adrenaline, since depletion might only occur after large repeated doses which might not have been

realized in her experiments. Certainly the pressor effects of leptazol in dogs can be reduced by adrenalectomy and Cicardo (1954) concluded that release of catecholamines was involved.

As far as the experiments on guinea-pigs are concerned, we may conclude that, picrotoxin, leptazol, bemegride and nikethamide all have one property in common, in that they exert an apparent bronchodilator effect by the release of catecholamines from the adrenals.

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