EFFECT OF β-ADRENOBLOCKERS ON SMOOTH MUSCLE OF THE TRACHEA AND BRONCHI

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Some β-adrenoblockers (propranolol, oxprenolol, etc.) under experimental and clinical conditions have a bronchoconstrictor action [2-4, 6-11]. The mechanism of this effect is not fully understood; all that is known is that the bronchoconstrictor action of propranolol is unconnected with blockade of bronchial β-adrenoreceptors or with potentiation of cholinergic effects on the bronchi [9-11].

The aim of this investigation was to study the effect of β-adrenoblockers belonging to different groups — unselective β-adrenoblockers (propranolol, oxprenolol, and trimepranol), the cardioselective β-adrenoblocker atenolol, and also labetalol, which has both β- and α-adrenoblocking action — on bronchial muscle tone in guinea pigs in the intact organism and on the musculature of the isolated trachea. Propranolol was used as the racemate (±), which has β-adrenoblocking action, and also in the dextrorotatory form (+), which has no β-adrenoblocking activity.

EXPERIMENTAL METHOD

The effect of β-adrenoblockers on bronchial tone and on the bronchoconstrictor action of histamine, acetylcholine, and serotonin was studied in experiments on guinea pigs anesthesized with urethane (1 g/kg intraperitoneally). The Konzett—Rossler method [1] was used to record bronchial tone. The drugs were injected intravenously: β-adrenoblockers in doses of 0.1, 1, and 5 mg/kg; histamine (2 μg/kg), serotonin (5 μg/kg), and acetylcholine (10 μg/kg) were injected 5-10 min after the β-adrenoblockers.

In experiments on the isolated guinea pig trachea the concentration of β-adrenoblockers in the Krebs' solution bathing the trachea was between 10^{-9} and 10^{-4} g/ml. In these experiments histamine (10^{-7} g/ml) also was injected 10-15 min after the β-adrenoblockers.

EXPERIMENTAL RESULTS

In experiments on guinea pigs only propranolol (± and +) caused an increase in bronchial tone which increased with the dose (Fig. 1). Oxprenolol, trimepranol, and atenolol had only a moderate, dose-independent bronchoconstrictor action in isolated experiments. Labetalol did not affect bronchial tone. Meanwhile all the β-adrenoblockers studied caused dose-dependent prolongation of the bronchoconstrictor action of histamine, serotonin, and acetylcholine, and labetalol and trimepranol in small doses also potentiated the effect of histamine.

In experiments on the isolated trachea none of the β-adrenoblockers affected muscle tone in concentrations below 10^{-7} g/ml. In concentrations of 10^{-6}-10^{-4} g/ml propranolol (± and +), oxprenolol, and trimerpranol caused contractions of the muscles (Fig. 2). Atenolol had no action in these concentrations, and labetalol (10^{-4} g/ml) caused moderate relaxation of the muscles. The spasmogenic action of propranolol (± and +), oxprenolol, and trimepranol developed slowly (in the course of 5-10 min) and was long-lasting.

On the isolated trachea labetalol was the only β-adrenoblocker to modify the spasmogenic effect of histamine. Labetalol reduced the action of histamine, and its antagonistic effect increased with an increase in dose.

The β-adrenoblockers studied thus differ from one another in their effect on the bronchial smooth muscles of the intact animal and on the isolated trachea. In the intact animal a definite bronchoconstrictor effect was induced only by propranolol (± and +), and an incon-

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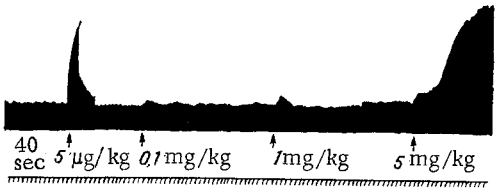

Fig. 1. Effect of propranolol on bronchial tone and bronchoconstrictor effect of histamine. Experiment on guinea pig anesthetized with urethane artificially ventilated. Propranolol (±) was injected intravenously in doses of 0.1, 1, and 5 mg/kg, histamine in a dose of 5 μg/kg.

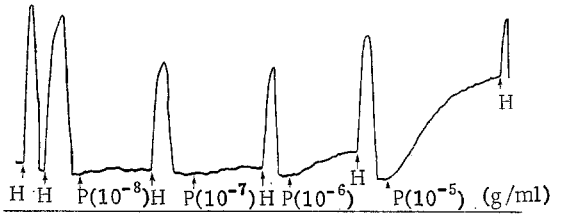

Fig. 2. Effect of propranolol on isolated trachea and on spasmogenic effect of histamine. Experiment on isolated guinea pig trachea. Changes in spontaneous tone of trachea in response to propranolol (P), 10^{-8}-10^{-5} g/ml, and its action on spasmogenic effect of histamine (H), 10^{-7} g/ml.

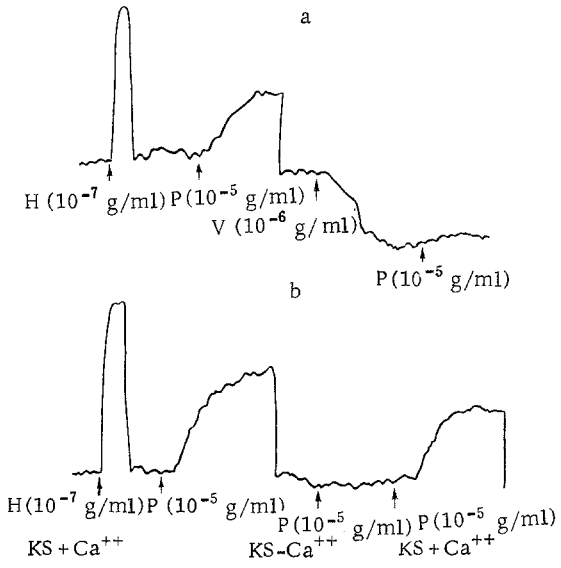

Fig. 3. Effect of verapamil and Ca^{++}-deprived Krebs' solution on spasmogenic effect of propranolol. Experiment on isolated guinea pig trachea. Effect of preliminary injection of verapamil (V) and also perfusion of preparation with Ca^{++}-deprived Krebs' solution (KS), on spasmogenic effect of propranolol (P)

stant and weak action was exhibited by oxprenolol, trimepranol, and atenolol, but not by labetalol. In experiments on the isolated trachea, however, propranolol (± and +), oxprenolol, and trimepranol had a spasmogenic effect, whereas atenolol was ineffective and labetalol caused relaxation of the muscles. Consequently, the bronchoconstrictor action observed in certain β-adrenoblockers is not directly connected with blockade of the bronchial β-adrenoreceptors. Further evidence in support of this view is given by the practically equal bronchoconstrictor action of the two forms of propranolol (± and +), of which only the former has β-adrenoblocking activity.

To elucidate the mechanism of the bronchoconstrictor action of propranolol experiments were carried out on the isolated trachea in which propranolol (10^{-5} g/ml) was preceded by the addition of atropine (10^{-7} g/ml), diphenhydramine (10^{-7} g/ml) and lysergic acid diethylamide (10^{-7} g/ml). None of these substances reduced the spasmogenic effect of propranolol, indicating that the action of propranolol is unconnected with stimulation of cholinergic, serotoninergic, or histamine receptors. At the same time, it was found that the bronchoconstrictor action of propranolol was reduced by verapamil, a blocker of Ca channels (Fig. 3), added in a concentration of 10^{-6} g/ml 5 min before propranolol. Propranolol likewise had no spasmogenic action in experiments in which the Krebs' solution was deprived of Ca^{++}. The possibility thus cannot be ruled out that the spasmogenic action of propranolol is connected somehow with Ca^{++} transport. This hypothesis is also supported by our data showing a reduction in the spasmogenic action of propranolol by indomethacin (10^{-6}-10^{-5} g/ml). The antagonistic action of indomethacin is unconnected with its effect on prostaglandin biosynthesis, for acetylsalicylic acid and diclofenac sodium (Voltaren) had no antagonistic action under similar conditions; meanwhile there is evidence that indomethacin has the properties of a blocker of Ca^{++} transport [12].

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