Evidence for Stimulation of 5-HT Receptors in Canine Saphenous Arteries by Ergotamine

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Summary. Changes in tension of spiral strips from dog saphenous arteries were monitored isometrically. Dose-response curves for noradrenaline, 5-HT and ergotamine were established without and after a 30 min incubation with phentolamine or pizotifen. Phentolamine was about 15 times more potent in antagonizing responses to noradrenaline (pA2 value = 7.4) than those to 5-HT (pA2 value = 6.2) but it was nearly equipotent in antagonizing responses to ergotamine (pA2 value = 6.5) and those to 5-HT. Pizotifen was about 500 times less potent in antagonizing noradrenaline effects than 5-HT but again nearly equipotent when tested against ergotamine and 5-HT.

It is suggested that in canine saphenous arteries the stimulant activity of ergotamine is mediated mainly through 5-HT receptor sites.

Key words: Arteries – Ergotamine – 5-HT Receptors – Pizotifen – Phentolamine.

INTRODUCTION

Investigations on the mode of action of ergotamine in isolated canine veins provided evidence that the vasoconstrictor activity of ergotamine is mediated largely through alpha-adrenergic receptors (Müller-Schweinitzer and Stürmer, 1974a, b) and that enhanced formation of prostaglandin E-like substance(s) may also contribute to it (Müller-Schweinitzer, 1974; Müller-Schweinitzer and Brundell, 1975). In canine arteries from different vascular beds ergotamine proved to antagonize responses to 5-HT in a non-competitive way (Müller-Schweinitzer and Stürmer, 1975) and investigations of the stimulating activity suggested that in canine arterial smooth muscle the stimulant activity of ergotamine is mediated mainly through 5-HT receptor sites (Müller-Schweinitzer, 1976).

The present investigations were undertaken to study in more detail the receptor sites involved in the stimulant activity of ergotamine in canine arteries.

MATERIALS AND METHODS

Mongrel dogs of either sex weighing between 20 and 30 kg were anaesthetized by rapid i.v. injection of pentobarbitone (50 mg/kg) and killed by injecting 100 ml air i.v. The saphenous arteries were removed and placed in a modified Krebs-Henseleit solution (mM): NaCl 118, KCl 4.7, MgSO4·7 H2O 1.2, CaCl2·2 H2O 2.5, KH2PO4 1.2, NaHCO3 25, glucose 11 at 37 °C, gassed with 95 % O2 – 5 % CO2. The vessels were cut into spiral strips, approximately 25 mm long and suspended in 10 ml organ baths containing Krebs-Henseleit solution at 37 °C gassed continuously with 5 % CO2 in oxygen. The tension of the strips was recorded isometrically with an electromechanical transducer (Statham model UC 3) and a potentiometric recorder. Before the experiments were started the preparations were allowed to equilibrate for 120–180 min in the bathing medium. During the equilibration period the resting tension was adjusted to about 400 mg and the solution was replaced every 15 min. Cumulative dose-response curves for noradrenaline and 5-HT were established using the method described by van Rossum (1963). Duration of exposure to a particular concentration depended on the time to reach equilibrium (the maximal response reached with that particular concentration). Thus there was no fixed interval at which time the concentration of the agonist was increased. Ergotamine caused a long lasting contraction of the arterial strips which could not be washed out. Increasing the ergotamine concentration in a cumulative way induced no further contraction of the arterial preparation. Thus dose-response curves for ergotamine were constructed from the mean effects of single doses and expressed as percentages of the preceding maximum response to 5-HT. It has been found previously that in canine saphenous arteries responses to single doses of noradrenaline or 5-HT did not significantly differ from those obtained with cumulative doses (Müller-Schweinitzer, 1976) and additional experiments have shown that identical pA2 values could be obtained with both dose-response techniques.

The following substances were used: noradrenaline hydrogen tartrate (Hoechst), serotonin creatininsulfat (Fluka), ergotamine tartrate and pizotifen hydrogenmalat (Sandoz), phentolamine hydrochloride (Ciba).

The stated concentrations are expressed throughout this paper as molar concentrations of the base of each compound.
RESULTS

**Antagonism by Phentolamine**

In the presence of $3.6 \times 10^{-7}$ and $3.6 \times 10^{-6}$ M phentolamine the cumulative log dose-response curve for noradrenaline was shifted to the right in a parallel fashion indicating competitive antagonism. From the shift at the 50% effect level of the control curve a $pA_2$ value of 7.4 was calculated for antagonism of noradrenaline by phentolamine. At concentrations of...