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Direct vasomotor effects of theophylline and enprofylline on human coronary artery in-vitro: comparison with feline coronary and cerebral arteries

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The vasomotor effects of theophylline and enprofylline were investigated on circular segments of human coronary artery taken 6 h after death. Isolated arterial segments were examined using a sensitive myograph and isometric contractions were recorded with Grass transducers. The results were compared with those obtained in feline coronary and cerebral arteries. Theophylline and enprofylline induced pronounced relaxation of all types of precontracted arteries. In feline cerebral arteries the potency for eliciting relaxation was slightly higher for theophylline compared with enprofylline, while there was no difference in potency for the methylxanthines in coronary arteries. Prostaglandin $F_{2\alpha}$ frequently induced rhythmic contractions in human, but not in feline coronary arteries. Theophylline increased the amplitude of the rhythmic contractions while this was not seen following administration of enprofylline. Whether this mode of activity by theophylline contributes to its arrhythmogenic properties in-situ requires clarification.

Xanthine derivatives have been reported to reduce coronary vascular resistance, increase heart rate and to induce cardiac arrhythmias (Hendeles et al 1977; Andersson & Persson 1980; Benditt et al 1983; Persson et al 1983). Furthermore, theophylline and enprofylline have a weak inotropic effect in-vivo (Persson et al 1983; Conradson 1986). Recently the two xanthine derivatives have been found to relax human placental arteries in-vitro (Nielsen-Kudsk 1985a, b). The severity of the extrapulmonary toxicity of theophylline has been shown to be correlated with its plasma concentration (Hendeles et al 1977). However, the mechanisms behind the vasomotor activity of xanthine derivatives are not fully understood; both a direct and an indirect catecholamine-mediated effect may be involved (Rutherford et al 1981).

There are pharmacological and clinical differences between the two most commonly used xanthine derivatives, theophylline and enprofylline. Enprofylline appears to lack adenosine-antagonistic properties; it is less prone to cause CNS and diuretic side-effects compared with theophylline (Persson et al 1982, 1983). In view of the differences in the action profile of theophylline and enprofylline and due to their reported cardiovascular effects, we found it worthwhile to examine the vasomotor activity of these agents in segments of human coronary artery taken post mortem. The responses are compared with those noted in feline coronary and cerebral arteries.

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Materials and methods

The left epicardial artery was taken from a 63 years old female 6 h after death which occurred due to a cerebral stroke. Segments, approximately 600 μm wide and 3 mm long, were dissected free from all connective tissue using an operation microscope. Epicardial coronary and middle cerebral arteries were taken from 8 cats, 2·4–3·5 kg, killed under pentobarbitone anaesthesia (30 mg kg^{-1} i.p.); segments approximately 200–300 μm wide and 2–3 mm long, were prepared as described above. The vessel segments were immediately mounted on two parallel L-shaped metal hooks in tissue baths containing a buffer solution kept at 37 °C. A gas mixture of 95% O_2 and 5% CO_2 was bubbled through the bath resulting in a pH of 7·3–7·4. Isometric contractions and relaxations were recorded by FT O3 C Grass transducers and displayed on a Grass polygraph. The arterial segments were given a passive load of 4 mN and allowed to stabilize at this level of tension for at least 1·5 h. The buffer medium was changed to fresh solution every 15 min. For further details of the method, see Högestätt et al (1983).

The vessel segments were incubated in standard buffer solution (see below). The contractile capacity of the individual segments was checked by exposure to a buffer containing 124 mM potassium. When the contraction was stable, i.e. after 2–4 min, theophylline and enprofylline were administered in a cumulative manner and concentration-response curves were obtained. Prostaglandin $F_{2\alpha}$ (3 μM) frequently induced a rhythmic contractile activity in human coronary arteries. The effect following the cumulative addition of theophylline and enprofylline was investigated also in the presence of this rhythmic activity.

The standard buffer solution consisted of (mM): NaCl 119, KCl 4·6, $CaCl_2$ 1·5, $MgCl_2$ 1·2, $NaHCO_3$ 15, NaH_2PO_4 1·2 and glucose 11. When NaCl was replaced by the equivalent amount of KCl, a solution with a high potassium content (124 mM) was obtained. The following drugs were used in the experiments; theophylline (Draco, Sweden), enprofylline (Draco, Sweden) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, Amoglandin, Astra, Sweden).

Mean values are given as mean ± s.e.m. Differences between mean values were assessed by Student's unpaired *t*-test. *P* values of less than 0·05 (*) were considered as significant.

Results

The xanthine derivatives (0·01–1 mM) produced only small reductions in resting arterial tone of arterial segments from either species. Contractions were never observed. Potassium (124 mM) always induced strong and stable contractions. Separate experiments revealed that contractions elicited by 124 mM potassium were stable for at least 30 min. The cumulative addition of theophylline or enprofylline to potassium-contracted arteries invariably resulted in concentration-dependent relaxations. Maximum relaxation observed in human coronary artery segments did not differ between the methylxanthines; being approximately 85% of the potassium-induced contractions (Fig. 1). A rhythmic contractile activity was frequently noted following the administration of 3 μM prostaglandin $F_{2\alpha}$ in human coronary arteries; however, this was never seen in feline coronary and cerebral arteries. The subsequent addition of theophylline (i.e. approximately 6 min after the administration of $PGF_{2\alpha}$) resulted in an increase of the amplitude of the rhythmic contractions (Fig. 2). Enprofylline (0·01–3 mM), on the other hand, had no such effect.

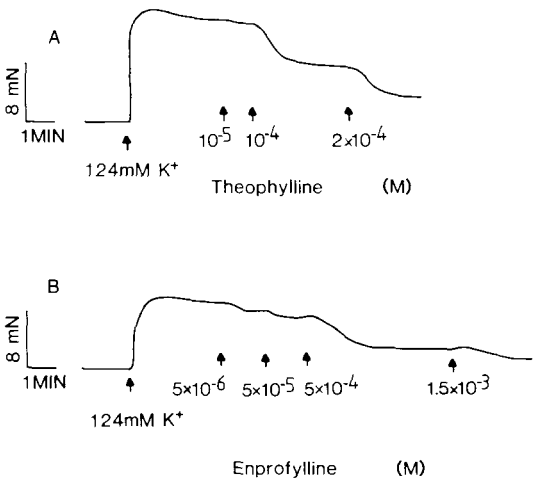

FIG. 1. Relaxations produced by cumulative addition of theophylline (A) and enprofylline (B) on isolated potassium-contracted (124 mM) segments of a post-mortem sample of human coronary artery.

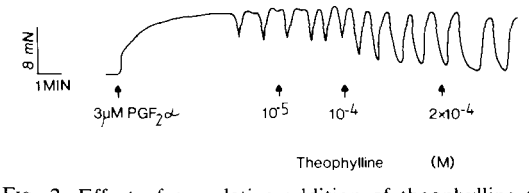

FIG. 2. Effect of cumulative addition of theophylline to $PGF_{2\alpha}$-induced rhythmic contractile activity in an isolated segment of a post-mortem sample of human coronary artery.

Theophylline and enprofylline relaxed precontracted (124 mM potassium) feline coronary and cerebral arteries in a concentration-dependent manner (Fig. 3). In cerebral arteries the potency for eliciting relaxation was somewhat higher for theophylline as compared with that of enprofylline, i.e. 0·6 and 1·4 mM, respectively, and produced relaxation of the same magnitude (i.e. 50% of potassium-induced precontraction). In coronary arteries there was no difference between the agents in potency (Fig. 3).

Discussion

Adenosine is considered to be a potent coronary vasodilator, acting primarily via adenosine receptors located on the smooth muscle cells (Olsson et al 1976; Schrader et al 1977; Merrill et al 1978). Theophylline has been shown in some tissues to counteract the dilator activity of adenosine (Olsson et al 1976; Merrill et al 1978). Enprofylline has been found to have a bronchodilating effect which is similar in magnitude to that of theophylline (Lunell et al 1983), but does not possess an adenosine antagonistic activity (Persson et al 1982; 1983).

Intra-arterial infusion of aminophylline, or the addition of xanthine derivatives to isolated arterial segments causes relaxation (Rutherford et al 1981; Nielsen-Kudsk 1985a, b), being in agreement with the findings of the present study (Figs 1 and 3). The mechanism behind this relaxant effect of xanthine derivatives is not fully understood; interaction with intracellular calcium binding and storage, and membrane permeability of calcium ions have been suggested (Nielsen-Kudsk 1985b). Intravenous administration of xanthine derivatives may, on the other hand, increase vascular resistance in cerebral, coronary and iliac vascular beds (Gottstein & Paulson 1972; Rutherford et al 1981). This effect has been suggested to be the result of an indirect action which involves α-adrenergic mechanisms (Rutherford et al 1981).

Rhythmic contractions in human coronary arteries in-vitro can be a spontaneous phenomenon, or it may be induced by $PGF_{2\alpha}$ administration (Fig. 2). The calcium entry blockers, nifedipine and diltiazem, have been reported to depress this $PGF_{2\alpha}$-induced rhythmic contractile activity of human coronary arteries (Weinheimer et al 1983; Kawasaki et al 1985). In the present study theophylline had an opposite effect; the amplitude of the phasic contractions was increased by the addition of theophylline (Fig. 2). Whether this action of theophylline contributes to the arrhythmogenic properties of theophylline in-situ requires further clarification.

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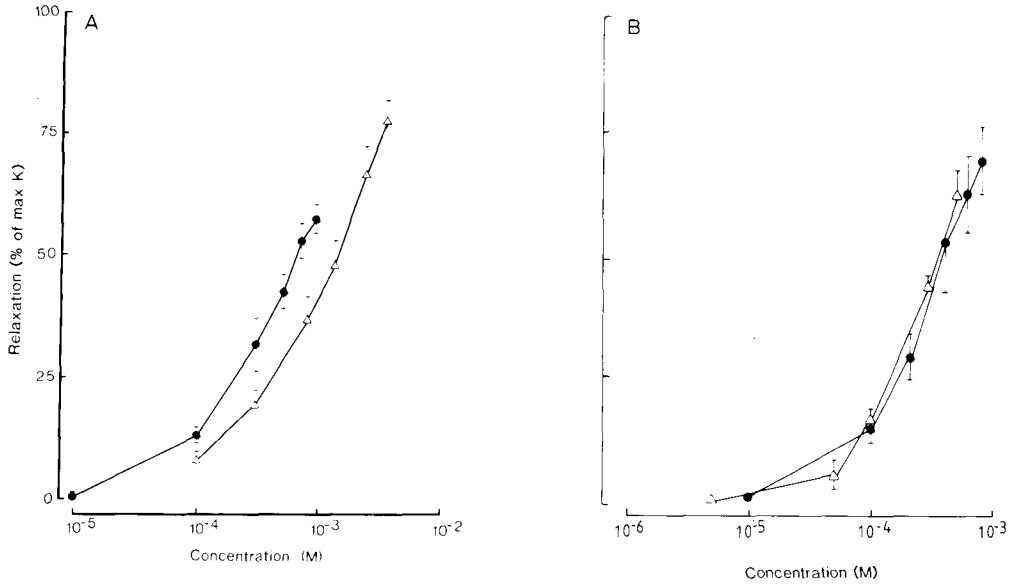

FIG. 3. Relaxation produced by theophylline and enprofylline of feline coronary (A) and cerebral (B) arteries precontracted by 124 mM potassium. Values are mean ± s.e.m. and indicate relaxation in % of potassium-induced precontraction (max K). Number of vessels investigated: 7–8. Key: ●, theophylline; △, enprofylline.

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