Potency ratio between the β-adrenoceptor stimulants isoprenaline and terbutaline on rabbit detrusor muscle

It is well established that the urinary bladder detrusor muscle of the rabbit contains β-adrenoceptors which mediate relaxation (Ahlquist, 1948; Edvardsen & Setekleiv, 1968; Anderson, Pierce & others, 1971). As proposed by Lands Luduena & Buzzo (1967), who studied the rank order of potency of β-receptor stimulating amines in various organs, it seems that there are different kinds of β-receptors (β_1- and β_2-receptors). This view has been substantiated by the recent synthesis of β_2-receptor selective agonists such as terbutaline (Persson & Olsson, 1970) and antagonists such as H 35/25 (Levy & Wilkenfield, 1969). Using terbutaline, it has been confirmed that the uterus (Olsson & Persson, 1971), the vascular system (Persson & Olsson, 1970) and the skeletal muscle (unpublished observations) probably contain β_2-receptors. This study is concerned with the relaxing potency of terbutaline and isoprenaline on rabbit detrusor. The effect of the β-receptor antagonists H 35/25 and practolol are also studied.

Five rabbits (2·0–2·5 kg) were stunned with a blow on the head and bled. Strips (20–30 × 3 mm) were cut over the apex of the bladder as described by Edvardsen & Setekleiv (1968). The method was slightly modified in that the strips were freed from serosal and mucosal coverings. The preparations were mounted in a 25 ml organ bath containing Krebs solution at 37° gassed with 5% CO_2 in oxygen. The load on the strips was 0·5 g. The isometric tension was recorded on a Grass polygraph, through a force displacement transducer (FT 03). After at least half an hour of stabilization in the bath, maximum relaxation was determined by adding a supramaximal dose of isoprenaline to the bath (1 μg ml^{-1}). Dose-response relations were then achieved by adding the drugs cumulatively to the bath in a geometric progression. Seven detrusor preparations were used. Various degrees of spontaneous activity occurred in five of the strips. Threshold effects of the β-stimulators were recorded as a decrease in basal tension, and the frequency and amplitude of contractions gradually diminished during increased doses of the β-adrenoceptor stimulating agents except in

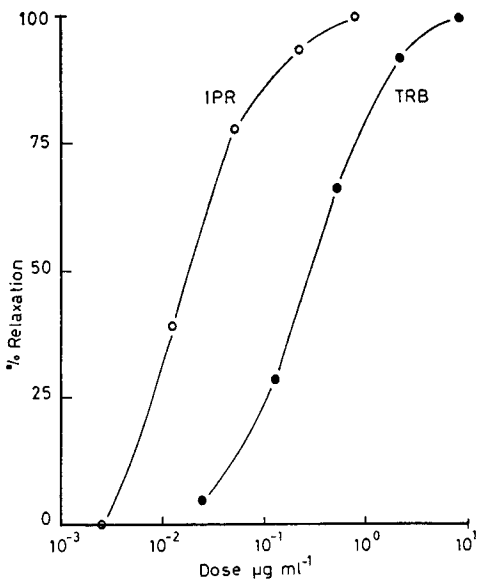

FIG. 1. The results from an experiment showing the response (% relaxation) of the detrusor muscle to isoprenaline (○) and terbutaline (●), evaluated in the same strip.

one preparation where a transient increase in amplitude (decrease in frequency) was recorded along with the decrease in basal tension. A similar effect has been reported to occur when other isolated smooth muscle is affected by β-adrenoceptor stimulating agents (Hawkins, 1964; Anderson & others, 1971; Persson, 1972). Inhibitory responses in all preparations were evaluated by measuring the decrease in basal tension. Terbutaline and isoprenaline relaxed the detrusor muscle to the same degree and the dose-response curves of the two amines seemed to be parallel for the whole effective dose-range, (Fig. 1). The ED50 was for isoprenaline 0·014 $\pm$ 0·003 μg ml^{-1} (mean $\pm$ s.e.), and for terbutaline 0·24 $\pm$ 0·05 μg ml^{-1} (mean $\pm$ s.e.), so that isoprenaline is about 16 times as active as terbutaline on molar basis. To obtain a 50% inhibition of the relaxation of equi-effective doses (ED75) of isoprenaline and terbutaline, less than 0·1 μg ml^{-1} of H 35/25 was needed. Doses up to 5·0 μg ml^{-1} of the β_1-selective antagonist practolol were used without inhibiting effect.

The results support the view that rabbit detrusor muscle contains β-adrenoceptors which are active in its relaxation. Terbutaline is known to be a selective β-receptor stimulating agent and has been shown to have about 1/20 of the activity of isoprenaline in isolated bronchial, biliary and uterine smooth muscle preparations (Persson & Olsson, 1970; Persson, 1973; Olsson & Persson, 1971; Andersson, Ingemarsson & Persson, 1973). This ratio differs considerably from the potency ratio between terbutaline and isoprenaline in isolated heart preparations where, specifically in rabbit hearts isoprenaline was more than 1000 times as active as terbutaline (Persson & Olsson, 1970). The present findings show that the β-adrenoceptors of the rabbit detrusor muscle are sensitive to stimulation by a β_2-selective agent, terbutaline and to blockade by a β_2-selective blocker, H 35/25. Further studies are, however, needed to generally characterize the subtype of β-adrenoceptors present in the urinary bladder wall.

The following drugs were used: ($\pm$) isoprenaline hydrochloride (Sigma Chemical Company, USA), ($\pm$)-terbutaline sulphate (AB Draco, Sweden), H 35/25, 1-(4'-methylphenyl)-2-isopropylamino-propanol (AB Hässle, Sweden) and practolol (ICI, U.K.). The drugs were dissolved in fresh glass-distilled water before each experiment.

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