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MECHANISMS OF (-ADRENERGIC RELAXATION IN DETRUSOR MUSCLE

Aims of Study

Recently, attention has focused on β-adrenoceptor (β-AR) as a potential target for the pharmacological treatment of overactive bladder. The activation of β-AR is known to relax detrusor muscle in many mammals, including humans. This effect has been considered to be mediated by cAMP-dependent protein kinase (PKA). However, evidences suggest that in smooth muscle, a cAMP-independent coupling exists between β-AR stimuration and calcium-activated potassium channels (Kc_a channels) directly via Gs protein. This cAMP-independent mechanism may vary greatly between smooth muscles and remains to be elucidated in detrusor muscle.

In the present study, we investigate the cAMP-dependent and -independent mechanisms underlying β-AR mediated relaxation of detrusor muscle. In addition, the roles for the two mechanisms are also studied.

Methods

Detrusor muscle strips from male Sprague-Dawley rats (8 weeks, 200-250 gm wt.) was mounted in a 25ml organ bath containing Krebs solution oxygenated with 95% O_2 and 5% CO_2 at 37°C. The tension of the strips was measured isometrically. We studied β-AR agonists-induced relaxation and the effects of inhibitors on the relaxation in two different conditions of detrusor muscle, i.e., detrusor strips were contracted by 40mM KCl or the strips were only stretched until a basic tension of 1g was achieved. The drugs used in this experiment were as follows: isoproterenol (β-AR agonist), FR165101 (β3-AR agonist), SQ22536 (adenylate cyclase inhibitor), charybdotoxin, iberiotoxin (Kc_a channel inhibitors).

The cAMP activity in detrusor muscle was also measured when β-AR agonist was added. At each concentration of β-AR agonist, the detrusor strips were rapidly frozen in liquid nitrogen. The detrusor tissue was homogenized, and cAMP activity was assayed using a cAMP EIA system kit (Amersham).

Results

In rat detrusor strips precontracted by high K^+, isoproterenol and FR165101 (β3-agonist) relaxed detrusor muscle in a concentration-dependent manner (10^{-9} to 10^{-4}M). However, cAMP production reached a maximum at 10^{-7}M β-AR agonist and the production was not increased with a further increase in concentration (10^{-6} to 10^{-4}M), although the relaxant response advanced (Fig.1). SQ22536 (adenyrate cyclase inhibitor), charybdotoxin and iberiotoxin (K_{Ca} channel inhibitors) inhibited the relaxing effect of β-AR agonists significantly, but not completely.

In non-contracting detrusor muscle, the resting tension was also decreased with the increase in β-AR agonist concentration. In this condition, the dose response effect of β-AR agonists on cAMP production was found, and β-AR agonist-induced relaxation was suppressed completely by SQ22536, but not suppressed by K_{Ca} channel inhibitors (charybdotoxin and iberiotoxin).

Conclusions

These results suggest that in non-contracting detrusor, only cAMP-dependent mechanism may be involved in β-adrenergic relaxation while in contracting detrusor, both cAMP-dependent and -independent mechanisms via K_{Ca} channels may be exerting additional relaxant effects. Thus, the degree to which the two mechanisms contribute to the overall relaxation effect seems to depend on condition of detrusor activity (resting or contracting state). Clinical implication of this study is that β-AR agonist may be more effective for the treatment of overactive bladder because detrusor is always overactive in this pathologic condition.

Fig.1: Effects of isoproterenol on cAMP production and relaxation (KCl precontracted rat detrusor)