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BETA-3 RECEPTOR AGONIST, MIRABEGRON RELAXES ISOLATED PROSTATE FROM HUMAN AND RABBIT: NEW THERAPEUTIC INDICATION

Hypothesis / aims of study

Lower urinary tract symptoms (LUTS) secondary to benign prostate hyperplasia (BPH) is one of the most prevalent disorders affecting elderly man. Clinical studies have been demonstrating that LUTS and BPH are being considered risk factors for erectile dysfunction (ED). Recently, the Food and Drug Administration has approved mirabegron, a beta-3 adrenoceptor (β_3 -AR) agonist for the treatment of overactive bladder. Stimulation of β_3 -AR relaxes detrusor smooth muscle, decreases afferent signaling from bladder, improves bladder compliance and increases bladder capacity in patients. Therefore, this study is aimed to evaluate by means of functional and immunohistochemical assays the role of β_3 -AR activation in isolated prostate from rabbit and human.

Study design, materials and methods

Patients-Human tissue prostate were obtained from 7 patients who had undergone transurethral resection or open prostatectomy. Animals-Male New Zeland rabbits (weighing 3–4 kg).

Functional assays : Four to six tissues segments excised from human prostate transition zone or rabbit prostate were placed immediately in Krebs-Henseleit solution mounted in organ bath and continuously bubbled with a mixture of 95%O₂ and 5% CO₂ (pH 7.4) at 37°C. A resting tension of 1 g was applied to each strip. After the equilibration period, tissues were challenged with 80 mM KCl to check tissue viability.

In human prostate, cumulative concentration-response curve to phenylephrine (PE, 0.0001-3 mM) were carried out in the absence (control) and presence of beta-3 adrenoceptor agonist, mirabegron (1 or 10 μ M, 30 minutes).

In rabbit prostate, concentration response curve to mirabegron (0.001- 300 μ M) was carried out in tissues pre-contracted with PE (10 μ M) in the absence (control) and presence of beta-1- (atenolol, 3 μ M), beta-2- (ICI 118,551, 1 μ M), beta-3-receptor antagonists (L 748,337, 300 nM), inhibitors of nitric oxide synthase (L-NAME, 100 μ M) or sGC (ODQ, 10 μ M) and blockers of potassium channel (tetraethylammonium [1 mM], charibdotoxin [100 nM], apamin [1 μ M] and glybenclamide [10 μ M]). Second, electrical field stimulation induced contraction were carried out in the absence (control) and presence of mirabegron (1 or 10 μ M).

Results

In rabbit prostate, phenylephrine (PE, 10 μ M) induced sustained contraction (3,27 \pm 0,68 mN n=7). Cumulative addition of mirabegron (0.001-300 μ M) induced concentration-dependent relaxation with pEC₅₀ and E_{max} values of 6.2 \pm 0.12 and 77 \pm 3%, respectively (n=4). In human prostate, PE induced concentration-dependent contraction with pEC₅₀ and E_{max} values of 5.23 \pm 0.09 and 90 \pm 6 %, which was significantly reduced by, approximately, 32 % (1 μ M, n= 5, P<0.05) and 52 % (10 μ M, n=5, P<0.05) in the presence of mirabegron.

Electrical field stimulation (EFS, 1-32 Hz, 50V) induced frequency-dependent contraction in rabbit prostate with maximal contraction being reached at 32 Hz. One μ M of mirabegron did not reduce significantly EFS-induced contraction, whereas 10 μ M reduced by 63% this response at 8, 16 and 32 Hz.

Interpretation of results

The blockade of beta-1 and beta-2 adrenoceptor by atenolol (1 μ M) and ICI 118,551 (1 μ M) did not affect the relaxation induced by mirabegron. On the other hand L 748,337, a beta-3 adrenoceptor blocker (300 nM) caused a 6-fold rightward shifts in the relaxation induced by mirabegron.

There exist evidence that beta-3 adrenoceptor activation would lead to nitric synthase activation mainly on cardiomyocytes and vessels. However, neither L-NAME (100 μ M) nor ODQ (10 μ M) interfered on mirabegron-induced relaxation in rabbit prostate.

Concluding message

Clinical studies have shown the efficacy of pharmacology treatment to reduce the incidence of complications of BPH, the need for surgery and the progression of prostate cancer. Mirabegron is already approved for the treatment of overactive bladder and may constitute a new therapeutic option for the treatment of LUTS secondary to BPH. However, larger scale, randomized placebo-controlled trials are needed to ascertain the safety, efficacy and cost-effectiveness of β_3 -AR agonists in the treatment of prostatic disorders in comparison to the current therapy.

References

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Disclosures

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