

NEURAL AND MUSCULAR β_3 -ADRENOCEPTORS IN RAT AND HUMAN DETRUSOR SMOOTH MUSCLE: DIFFERENCES DISCLOSED BY SELECTIVE AGONISTS

Hypothesis / aims of study

Evidence for a role of β_3 -adrenoceptors in the relaxation of detrusor smooth muscle comes from pharmacological studies using selective agonists and antagonists (1). To compare the functional importance of β_3 adrenoceptors on rodent and human urinary bladder, we investigated the effect of the non selective β adrenoceptor agonist, (-) Isoprenaline, as well as of the selective β_3 -agonists, SR58611 and SAR150640 (2) on *in vitro* preparations of detrusor muscle.

Study design, materials and methods

Rat detrusor muscle strips were removed from male CD rats (200-250g) and dissected longitudinally. Macroscopically healthy specimens of human urinary bladder were obtained from patients undergoing radical prostatectomy or for clinically localized bladder cancer; patients were not treated with any neo-adjuvant anti-androgen. The strips were mounted in a 20 ml organ-bath containing warm (37°C) Krebs solution aerated with 95% O₂ and 5% CO₂, under constant tension of 0.5 g. Isotonic contractions were evoked by sub-maximal electrical field stimulation (EFS) or by carbachol (1 μ M). EFS essentially activated rat and human cholinergic neurons, since atropine or tetrodotoxin, abolished the evoked twitch contractions. Agonists cumulative concentration-response curves (1nM-0.1mM) were applied for each strip. Their inhibitory responses (IC₅₀, %Emax) were expressed as per cent of the maximal effect of 1 μ M atropine (EFS) or 0.1mM papaverine (carbachol pre-contraction) added at the end of the assay. IC₅₀ is the concentration of the agonist producing half of its maximal response. (-)Isoprenaline was tested in presence of 1 μ M CGP20712 (selective β_1 -adrenoceptor antagonist) and ICI118551 (selective β_2 -adrenoceptor antagonist).

Results

Results are shown in the table.

| | Rat (<i>n</i> =3-5) IC ₅₀ μ M (95% confidence limits) (% Emax) | | Human (<i>n</i> =3-5) IC ₅₀ μ M (95% confidence limits) (% Emax) | |
|-----------------|--|--------------------------|--|--------------------------|
| | EFS | Carbachol | EFS | Carbachol |
| (-)Isoprenaline | 0.09 (0.07-0.13) (98) | 0.74 (0.56-0.98) (76) | 3.0 (0.98-9.95) (29) | 0.13 (0.03-0.56) (91) |
| SR58611 | 0.04 (0.01-0.18) (85) | 2.4 (1.41-4.15) (44) | >10 | ~5.0 (40) |
| SAR150640 | 11 (4-29) (89) | 69 (48-99) (53) | 1.0 (0.31-3.77) (49) | 0.25 (0.04-1.54) (80) |

Interpretation of results

In human preparations all β -adrenoceptor agonists were more potent on muscular than neural contractions. By contrast, in rat they showed an opposite profile. SAR150640 was more potent in human whereas SR58611 in rat.

Concluding message

These results suggested the presence of functional neural and muscular β_3 adrenoceptors in detrusor smooth muscle of rat and human. Their role involved mostly neural transmission in rat and a direct myogenic activity in human. Selective β_3 agonists showed a different profile of activity in rat and in human tissues: SR58611 was more potent and effective in rat whereas SAR150640 in human. The recognition of the differences between rodent and human β_3 adrenoceptors and their sensitivity to selective agonists are important findings to be considered in pharmacological studies where pathophysiological models of overactive bladder are investigated.

References

1. Igawa et al, Korean J Urol 2010, 51, 811-8
2. Croci et al, J Pharmacol Exp Ther 2007, 32,1118-26

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| Specify source of funding or grant | No funding and no grant |
| Is this a clinical trial? | No |
| What were the subjects in the study? | ANIMAL |
| Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained? | Yes |
| Name of ethics committee | Sanofi-Aventis Milan animal welfare committee (AWC). Animal care was in accordance with the Sanofi-aventis international ethical code and the international principles governing the care and treatment of laboratory animals (E.E.C. Council Directive 86/609, DJL358, 1, Dec.12, 1987). |