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Agonist-dependent desensitization of the β-adrenoceptor-mediated rat urinary bladder relaxation

Wim Vrydag, Martin C. Michel

Acedemic Medical Center, Amsterdam, Netherlands

Overactive bladder syndrome is a prevalent condition in the adult population and markedly reduces the quality of life of the afflicted patients. Multiple β_3-adrenoceptor agonists are currently in development for the chronic symptomatic treatment of this syndrome (Colli *et al.* 2007). The long term clinical efficacy of agonists can be limited by receptor desensitization. Data from cell experiments indicate that the β_3-adrenoceptor desensitization is cell specific (Chaudhry & Granneman 1994). Therefore, we have explored the presence and possible mechanisms of such desensitization in the rat urinary bladder.

Male Wistar rat (280-320 g) bladder strips were pre-treated in organ baths for 6 h in Krebs buffer or 24 h in culture medium in the absence or presence of isoprenaline (non selective β-adrenoceptor agonist), fenoterol (β_2-adrenoceptor selective agonist) or the β_3-adrenoceptor selective agonists YM178 ((R)-2-(2-aminothiazol-4-yl)-4'-{2-[(2-hydroxy-2-phenylethyl)amino]ethyl} acetanilide) and CL 316,243 (disodium 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,3-benzodioxole-2,2-dicarboxylate). After wash out, relaxation curves with fresh agonists were generated against a tone induced with 50 mM KCl. Data are means ± S.E.M. of ≥ 3 experiments, and a $p<0.05$ (ANOVA) was considered significant.

The maximum relaxation by isoprenaline was reduced with 54% after 24 h pre-treatment with isoprenaline, but due to deterioration of contraction and relaxation responses further experiments were performed after 6 h pre-treatment. Isoprenaline-induced relaxation was compared with vehicle (E_{max} 50 ± 5%) reduced after pre-treatment with isoprenaline (27 ± 4%), fenoterol (27 ± 6%), YM178 (34 ± 3%) or CL 316,243 (33 ± 2% all $p<0.05$). The fenoterol-induced relaxation was reduced by pre-treatment with isoprenaline (44 ± 4% vs. 23 ± 2%) but not with YM178 or CL 316,243. CL 316,243-induced relaxation was desensitized by pre-treatment with isoprenaline (32 ± 5% vs 13 ± 4%) and to a lesser extent with CL 316,243 (32 ± 5% vs. 22 ± 2%), whereas the YM178-induced relaxation was not affected by pre-treatment with isoprenaline or YM178.

We conclude that relaxation by β-adrenoceptor agonists in rat bladder can desensitize but this mainly involves the β_2-component (fenoterol response). Relaxation responses to β_3-agonists exhibit compound-specific desensitization with CL 316,243 being sensitive to desensitization and YM178 not. Our data do not provide evidence that long term treatment with YM178 carries a risk of desensitization.

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Chaudhry & Granneman, J. Pharmacol. Exp. Ther., 1994, 271, 1253-8

Colli *et al*, Expert Opin. Investig. Drugs, 2007, 16, 999-1006