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THE EFFECTS OF ENDOTHELIN-1 AND YM598, A NOVEL SELECTIVE ENDOTHELIN ETA RECEPTOR ANTAGONIST, ON THE LOWER URINARY TRACT IN VITRO AND IN VIVO

Hypothesis / aims of study

The role of endothelins in the lower urinary tract is still uncertain. In this study, we investigated the contractile responses of endothelin-1 in the lower urinary tract both in vitro and in vivo. We also assessed the effects of a novel selective endothelin ET_A receptor antagonist, YM598, on the endothelin-1-induced contractile responses.

Study design, materials and methods

In the *in vitro* studies, isolated rabbit bladder base, urethra, and prostate tissues were used. Segmental strips of these tissues were vertically suspended in an organ bath, and various agonists (endothelin-1, sarafotoxin S6c, phenylephrine, and acetylcholine) were added to obtain concentration-response curves. The inhibitory effects of YM598 on endothelin-1-induced contractile responses were also investigated, and the negative logarithm of the molar concentration of antagonist required to produce a 2-fold rightward shift of the concentration-response curves to agonist (pA_2) were calculated.
In the *in vivo* studies, the prostatic urethral pressure (PUP) was measured in anesthetized male beagle dogs. A balloon catheter was placed in the urethra at the prostatic site through the external urethral meatus, and endothelin-1 (0.006-0.8 g/kg, i.a.) and phenylephrine (0.06-8 g/kg, i.a.) were administered just above the branches of the external iliac artery. The inhibitory effects of YM598 (0.1-3 mg/kg, i.v.) on the endothelin-1 (0.2 g/kg, i.a.)-induced elevation in PUP was also investigated, and the dose causing 50% of the maximal inhibition (ID_{50}) value was calculated. Additionally, the effects on the urethral pressure profile (UPP) were also investigated in anesthetized male beagle dogs. To measure the UPP, a catheter was inserted into the urinary bladder through the external urethral meatus, and physiological saline infusion was started at a rate of 1.91 mL/min. The catheter was then withdrawn at a rate of 25 mm/min.

Results

In the *in vitro* studies, endothelin-1, phenylephrine, and acetylcholine, but not sarafotoxin S6c, caused the bladder base, urethra, and prostate tissue isolated from rabbits to contract in a concentration-dependent manner. Whereas the maximal responses induced by endothelin-1 were smaller than those induced by other agonists, sensitivities to endothelin-1 were about 200 to 300 times higher than to other agonists in all preparations. Pre-incubation of YM598 shifted the concentration-response curves of endothelin-1 to the right. The pA_2 values of YM598 were 6.6 in the bladder base, 6.7 in the urethra, and 6.5 in the prostate, respectively.
In the *in vivo* study, both endothelin-1 (0.006-0.8 g/kg, i.a.) and phenylephrine (0.06-8 g/kg, i.a.) elevated the PUP in anaesthetized dogs in a dose-dependent manner. The maximal response induced by endothelin-1 was about half of that induced by phenylephrine. YM598 (0.1-3 mg/kg, i.v.) inhibited the endothelin-1 (0.2 g/kg, i.a.)-induced elevation in PUP in a dose-dependent manner, with an ID_{50} value of 0.13 ± 0.07 mg/kg. In the experiment where was measured measuring UPP, endothelin-1 (1 mg/kg, i.v.) elevated urethral pressure at not only the prostatic site but also non-prostatic sites. YM598 (1 mg/kg, i.v.) completely inhibited the endothelin-1 (1 mg/kg, i.v.)-induced elevation in urethral pressure.

Interpretation of results

Endothelin-1 induced contractile responses in the lower urinary tract both *in vitro* and *in vivo*. Though the maximal responses were smaller than those induced by phenylephrine, the sensitivities to endothelin-1 were much higher than those to phenylephrine. Because selective endothelin ET_B receptor agonist sarafotoxin S6c did not induce a contractile response, and endothelin-1-induced contractile responses were fully inhibited by selective endothelin ET_A receptor antagonist YM598, endothelin-1 might induce contractile responses mainly through endothelin ET_A receptors in the lower urinary tract.

Concluding message

Endothelin-1 might take part in the pathogenesis of various urinary tract dysfunctions involving urinary tract contractions, like benign prostate hyperplasia, through endothelin ET_A receptors. A selective endothelin ET_A receptor antagonist, YM598, may have ameliorating effects on various urinary tract dysfunctions, including benign prostate hyperplasia.