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ENDOTHELIN ET_B RECEPTORS ARE INVOLVED IN THE RELAXATION OF THE PIG URINARY BLADDER NECK: A POSSIBLE THERAPEUTICAL TARGET FOR URINARY INCONTINENCE PRODUCED BY INTRINSIC SPHINCTERIC DEFICIENCY.

Hypothesis / aims of study

The knowledge of the mechanisms involved in the control of the bladder neck smooth muscle tone is essential for the treatment of type III stress urinary incontinence due to intrinsic sphincteric deficiency [1]. The fact that bladder endothelin receptor expression and activities change under pathophysiological conditions, such as urethral obstruction suggests that endothelin receptors and/or their downstream intracellular mechanisms may be useful as targets in the treatment of urinary obstruction symptoms associated with benign prostatic hypertrophy, as well as in urinary incontinence [2, 3]. The mediation of endothelin ET_A receptors in the contraction of the lower urinary tract smooth muscle is well known. However, scarce information exists about the role of ET_B receptors producing relaxation of bladder outlet region. Therefore, the current study investigates the possible presence of ET_B receptors involved in the relaxation of the pig urinary bladder neck.

Study design, materials and methods

ET_B receptor expression was determined by both immunohistochemistry and Western blot by using a rabbit anti-ET_B antibody. For functional studies, urothelium denuded bladder neck strips 4-6 mm long and 2-3 mm wide were suspended horizontally with one end connected to an isometric force transducer (Grass FT 03C) and the other one to a micrometer screw, in 5 ml organ baths containing physiological saline solution at 37° C gassed with carbogen (95% O₂ and 5% CO₂) to obtain a final pH of 7.4. The signal was continuously recorded on a polygraph (Graphtec Multicorder MC 6621). Passive tension of 2 g was applied to the strips and they were allowed to equilibrate for 60 min. On 1 μM phenylephrine-induced tone, cumulative concentration-response relaxation curves (CRC) to BQ3020 were obtained by increasing the organ bath concentration in half log unit steps. Since CRC to this agonist were not reproducible in two consecutive curves, bladder neck strips from the same animal were run in parallel, one of them used as control and the other one assessed for the specific treatment for 30 min.

Results

ET_B receptor expression (Western blot) was observed in the muscular layer and urothelium. A strong ET_B-immunoreactivity (ET_B-IR) was identified within nerve fibres among smooth muscle bundles. BQ3020, an ET_B receptor agonist, produced concentration-dependent relaxations of bladder neck preparations, which were reduced by the selective ET_B receptor antagonist BQ788. These responses, however, were not modified by ω-conotoxin GVIA, N^G-nitro-L-arginine, 1H-[1,2,4]-oxadiazolo[4,3-a]quinoxalin-1-one and indomethacin, blockers of neuronal voltage-gated Ca²⁺ channels, nitric oxide (NO) synthase, soluble guanylyl cyclase and cyclooxygenase (COX), respectively.

Interpretation of results

These results suggest that BQ3020 produces relaxation of the pig bladder neck via activation of smooth muscle endothelin ET_B receptors through a mechanism independent of NO/cGMP or COX pathways.

Concluding message

Endothelin ET_B receptors may be useful as target for urinary incontinence treatment produced by intrinsic sphincteric deficiency.

References

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- Ukai et al, Eur J Pharmacol 580: 394, 2008.

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What were the subjects in the study?	ANIMAL
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	No
Statement that no ethical approval was needed	No ethical approval was needed