Targeting both the dynamic and static components of LUTS/BPH using a soluble guanylate cyclase stimulator compared to vardenafil: preclinical evidences

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BACKGROUND

In randomized clinical trials, PDE5 inhibitors improve LUTS related to BPH.

Soluble guanylate-cyclase (sGC) stimulators bypass the need for an NO drive while activating the same signaling pathway. We have assessed and compared BAY 41-2272, a sGC stimulator, to vardenafil with respect to their relaxing effects on human prostate and their antiproliferative/pro-apoptotic effects on prostate growth induced by testosterone supplementation in the rat.

OBJECTIVES

- To assess and compare BAY 41-2272, a sGC stimulator, to vardenafil with respect to their relaxing effects on human prostate
- To evaluate quantitatively the chronic effects of the sGC stimulator, BAY 41-2272, and vardenafil on proliferation and apoptosis markers in the testosterone-induced rat model of BPH

MATERIALS & METHODS

Human prostate samples were obtained from 12 patients (67±2.8 years old) undergoing cystoprostatectomy for infiltrating bladder cancer. Prostatic strips were mounted isometrically in organ baths filled with Krebs-HEPES buffer containing indomethacin (10−5 M) and dexamethasone (10−5 M) maintained at 37°C and bubbled with 95% O2 and 5% CO2, pH 7.4. Firstly, cumulative concentration-response curves were performed in order to evaluate and compare the effects of BAY 41-2272 and vardenafil on PHE (10−4 M)-precontracted or KCl (50 mM) precontracted human prostatic strips. Secondly, the potential enhancing effect of BAY 41-2272 on SNP-induced relaxations of PHE-precontracted prostatic strips was determined after exposure of the strips to BAY 41-2272 (10−6 or 10−3 M) for 20 min. Relaxation responses are expressed as a percentage of inhibition of the contractile response to PHE or KCI. For each GRC, a pD2 value (log concentration of compound that produces 50% reduction of the maximal response) and a mean maximal effect (Emax) are determined using the four parameters logistic regression using GraphPad Prism® 5.04 software.

RESULTS

Ex vivo experiments on human prostate samples

Concentration-effect curves (log M vs log pEC50) comparing Emax and pD2 of BAY 41-2272 and vardenafil on human prostatic strips. The drugs were tested at 10−9 M to 10−6 M in the presence or absence of 10−5 M SNP. Statistical analysis was performed using two way ANOVA followed by Bonferroni test.

In vivo experiments in testosterone-supplemented rats

Neither vardenafil nor BAY 41-2272 modified prostate weight in testosterone-treated rats.

CONCLUSIONS

- In addition to a potential relaxant effect on prostate smooth muscle fibers (dynamic component), sGC stimulation might favor prostate regression (static component).
- Of note, the effects of sGC stimulation on urethral pressure and voiding efficiency are still unknown.
- sGC stimulation could thus represent a novel promising pharmacological mechanism of action for the treatment of LUTS related to BPH.

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