797

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DO ALPHA-BLOCKERS EXERT THEIR EFFECT VIA THE PROSTATE, THE BLADDER OR BOTH? A STUDY OF POST-TAMSULOSIN CHANGES IN THE PROSTATE AND BLADDER OF MEN WITH BENIGN PROSTATE ENLARGEMENT (BPE) AND OVERACTIVE BLADDER (OAB) SYMPTOMS

Hypothesis / aims of study

Lower urinary tracts symptoms (LUTS), benign prostatic enlargement (BPE) and overactive bladder (OAB) are interrelated. The underlying pathophysiologic mechanisms have not been fully elucidated. Additionally, OAB symptoms may appear in the absence of bladder outlet obstruction or may persist after prostatectomy. Administration of alpha-blockers remains the recommended first-line treatment while co-administration with anticholinergics is proposed for those who don't get adequate symptomatic relief from monotherapy. However the exact mechanism and the extent to which various pathways are involved in the pathophysiology of OAB in men with BPE as well as how they are influenced by pharmacotherapy are not known.

We aimed to explore whether the mechanism of action of alpha-blockers in the treatment of male LUTS, in particular BPE-OAB, is exerted via an effect on the prostate, the bladder or both. In parallel, we examined possible correlations between clinical parameters and the expression of receptors which have been associated with the pathophysiology of either BPE or OAB in both the prostate and the bladder of these patients.

Study design, materials and methods

We compared two groups of men above 50 years of age with BPE and predominately storage LUTS as defined by IPSS (storage subscore ≥ voiding subscore and score ≥3 in the urgency question). Study participants had prostate volume >30ml, maximum flow rate (Qmax) ≥10ml/s, post-void residual (PVR) <100ml, PSA ≤10ng/ml and at least 3 urgency episodes per 24h in a 3-day bladder diary. The first group included symptomatic treatment-naïve men before any pharmacological intervention (baseline group) and the second group men who presented with storage LUTS and were submitted to prostatectomy following treatment with tamsulosin for at least 6 months (post-monotherapy group). All recruited patients filled the IPSS (International Prostate Symptom Score) questionnaire and had transrectal and transabdominal ultrasonography (measured parameters: prostate and adenoma volume, PVR, detected vessel surface). Patients with neurogenic bladder or a history of urinary tract malignancy were excluded. Patients with positive digital rectal examination as well as PSA values 4-10ng/dl were included only after negative prostate biopsy. Bladder and prostatic tissues were obtained either during prostatectomy or transrectal ultrasonographic guided biopsy (TRUSgbx) of the prostate for elevated PSA. The latter were obtained from the transitional zone. The Institutional Review Board and the University Ethics Committee approved the study and all patients gave written informed consent.

Real–time polymerase chain reaction (RT-PCR) and Western Blotting techniques were employed to examine the mRNA (gene) and the protein expression of the muscarinic receptors M1, M2, M3, the adrenergic α1A and α1D receptors, the androgen and the TRPV1 receptor. Expression levels of transcripts were normalized to GAPDH (for gene expression) or actin (for protein expression) as endogenous control.

The paired t-test and Mann-Whitney test were used for intra- and intergroup variability of examined parameters. Pearson and Spearman correlation coefficients were used depending upon the uniformity of distribution. The statistical analysis was performed on SPSS 21.0 software (Armonk, NY: IBM Corp).

Results

Fifteen patients were allocated at each group. At baseline, both groups were comparable for age (72.5 vs. 70.1 years), total IPSS (16.9 vs. 18.1), storage (8.9 vs. 9.6) and voiding subscores (6.7 vs. 7.2). The treatment naïve group had somewhat larger prostate (58.5 vs. 51.3) and adenoma volumes (38.8 vs. 32.9) butwithout reaching statistical significance.

Statistically significant differences in the ***protein expression*** of bladder M2, TRPV1 and α1A receptors were found between the two groups, with decreases noted in the post-tamsulosin group. The protein expression for M2 receptor was 1.07 ± 0.20 vs. 0.29 ± 0.11 (p=0.005), for TRPV1 1.59±0.41 vs. 0.42±0.27 (p=0.016) and for α1A receptor 2.72±0.60 vs. 1.37±0.65 (p=0.05). The protein expression of prostatic α1A and α1D receptors was also significantly different between the two groups: protein expression of α1A was found to be higher in the baseline group (0.58 ± 0.06 vs. 0.04 ± 0.01, p=0.000) while α1D expression was higher in the tamsulosin group (0.15 ± 0.10 vs. 1.39 ± 0.23, p=0.034).

Gene (mRNA) expression of bladder M2, M3 and TRPV1 receptors appeared to be higher in the tamsulosin group (1.23±0.41 vs. 3.45±0.99, 0.90±0.65 vs. 2.28±0.75 and 1.97±0.91 vs. 5.15±2.25), yet statistical significance was not reached (p=0.419, p=0.668, p=1.0). Muscarinic, adrenergic and androgen receptors mRNA expression levels in prostatic tissue were also no different between the two groups.

Correlations between clinical and molecular characteristics: bladder mRNA expression of muscarinic M1 and M3 receptors of treatment-naïve patients showed a negative correlation with the storage IPSS score (r=-0.669, p=0.034), while M2 protein expression reveals positive correlation with prostate volume of the patients on tamsulosin (r=0.56, p=0.046). TRPV1 gene expression in the bladder of tamsulosin patients has a positive correlation with storage IPSS score (r=0.734, p=0.016). The bladder androgen receptor showed a positive correlation with storage and total IPSS score (r=0.867, p=0.012) in the tamsulosin group only.

The gene expression of α1A adrenergic receptor in the prostate showed significant correlations with the storage (r=0.949, p=0.051), voiding (r=1.0, p<0.05) and overall IPSS (r=1.0, p<0.05) scores in treatment-naïve patients, while prostate protein expression of α1D receptor showed negative correlation with voiding IPSS score and total IPSS score in the tamsulosin group. Finally, prostate expression of the androgen receptor showed a negative correlation with prostate volume in this group (r=-0.624, p=0.03).

Interpretation of results

Changes in mRNA and protein expression of muscarinic, adrenergic and sensory receptors in the tamsulosin group suggest a multi-axial effect of alpha-blockers on sympathetic, cholinergic and sensory pathways of the bladder and the prostate. Strong correlations between the expression of α1A receptor in the prostate of treatment naive patients with the IPSS total score and storage subscores together with a lower protein expression in the treatment group suggest a role for α1A in the pathogenesis of BPE/OAB, as well as a potential role in bladder sensory pathways. Expression of the muscarinic, the TRPV1 and the androgen receptor also showed correlations with storage IPSS subscores, implicating their involvement in the pathogenesis of OAB in patients with BPE

Concluding message

Results of this pilot study suggest involvement of adrenergic, muscarinic and sensory receptors in the pathogenesis of BPE-associated OAB. Changes in mRNA and protein expression of muscarinic, adrenergic and sensory receptors in the tamsulosin group suggest that alpha-blockers may exert their effect via sympathetic, cholinergic and sensory pathways of both the bladder and the prostate.

Disclosures

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