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EXPRESSION PROFILES OF ATP-SENSITIVE AND CALCIUM-ACTIVATED POTASSIUM CHANNELS IN RAT BLADDER SECONDARY TO PARTIAL OUTLET OBSTRUCTION

Hypothesis / aims of study

Altered potassium channel activities of detrusor myocytes have been suggested to contribute to the etiology of bladder overactivity, and ATP-sensitive potassium channels (K_{ATP}) openers have shown to exert potent relaxant activity on bladder detrusor muscle (1, 2). In addition there has been growing interest in the therapeutic potential of modulators of large conductance calcium-activated potassium channel (BK_{Ca}) (2), however, the clinical trials of these channel modulators have been limited as a result of side effects (3). Finally, very little is known of the identities K_{ATP} and K_{ca} expressed in rat bladder. Therefore, to address this question, reverse transcriptase- real time polymerase chain reaction (RT-real time PCR) was used to assess the expressions of subfamilies of K_{Ca} and K_{ATP} in rat bladder. In addition, we also investigated whether short-term partial bladder outlet obstruction (PBOO) has any effect on mRNA expressions of these channel subtypes.

Study design, materials and methods

Male Sprague-Dawley rats of 260 to 280gm body weight, twelve for sham-operation and eighteen for outlet obstruction, were anesthetized with enflurane, and the bladder and urethra were exposed through a midline incision. A 24-gauge infusion needle was placed parallel to the urethra, and 4-0 silk ligature was tied around the urethra and the needle. The needle was then removed, resulting in partial obstruction. Three, six, and ten days post-obstruction, the bladder was exposed again through a midline incision, quickly removed and frozen in liquid nitrogen for mRNA measurement. Total RNA was extracted using Trizol reagent and mRNA levels of K_{ATP} and K_{ca} subtypes were measured by RT-real time PCR

Results

In rat bladder, mRNA expressions of BK_{Ca}, intermediate conductance calcium-activated potassium channel (IK_{Ca}), and three isoforms of small conductance calcium-activated potassium channels (SK_{Ca}) were confirmed. We also confirmed the presence of mRNAs of inward rectifier potassium channel (Kir) 6.1, Kir 6.2, and its regulatory subunit, SUR 2B. Thus, in rat bladder, K_{ATP} was composed of either Kir 6.1 or Kir 6.2 with SUR 2B. Gene expression of BK_{Ca} was significantly increased comparing with that of sham-operation at 3 and 6 days secondary to PBOO. In case of SK_{Ca}, type 2 mRNA levels were increased significantly at 10 days after PBOO and type 3 mRNA levels were elevated profoundly at 3 and 6 days after PBOO, whereas mRNA levels of type 3 SK_{Ca} and IK_{Ca} were not changed significantly by PBOO. In addition, gene expressions of Kir 6.1 and SUR 2B were prominently increased at 3, 6, and 10 days post-obstruction. In bladder, mRNA level of Kir 6.2 was lower than that of Kir6.1 and it was elevated only at 10 days after PBOO.

Concluding message

In present study, gene expressions of several K_{ATP} and K_{ca} subtypes were increased secondary to short-term PBOO. These results suggest that expressions of K_{ATP} and K_{ca} subtypes are differentially regulated and may contribute to the abnormal bladder detrusor activity during the progression of PBOO.

References:

(1) K-ATP opener-mediated attenuation of spontaneous bladder contractions in ligature-intact, partial bladder outlet obstructed rats. Life Sci. 2003 Mar 14;72(17):1931-41.
(2) Bladder instillation of "naked" hSlo/pcDNA3 ameliorates detrusor hyperactivity in obstructed rats in vivo.Urology. 2001 Jun;57(6 Suppl 1):111.
(3) In vivo evaluation of the potency and bladder-vascular selectivity of the ATP-sensitive potassium channel openers (-)-cromakalim, ZD6169 and WAY-133537 in rats. BJU Int. 2003 Feb;91(3):284-90.