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IMPROVEMENT OF DETRUSOR OVERACTIVITY BY ALPHA-1 ADRENOCEPTOR ANTAGONIST VIA SUPPRESSION OF ATP RELEASE FROM THE BLADDER EPITHELIUM IN AGED SPONTANEOUSLY HYPERTENSIVE RATS

Hypothesis / aims of study
Spontaneously hypertensive rats (SHRs) are characterized by hyperactivity of the sympathetic nervous system and show bladder dysfunction similar to that seen in patients with overactive bladder (OAB). Current evidence suggests that sympathetic overactivity and adenosine 5'-triphosphate (ATP) activity are also important factors in the development of OAB. Alpha-1 adrenoceptor (AR) antagonists are frequently prescribed therapeutic agents for OAB patients with BPH. However, how alpha-1 AR antagonists work to improve detrusor overactivity (DO) remains controversial. The aim of this study was to investigate the effects of naftopidil, an alpha-1 AR antagonist, on bladder function and ATP release from the bladder epithelium using aged SHRs and Sprague-Dawley (S-D) rats.

Study design, materials and methods
Two groups of aged male SHRs (58 weeks old, n = 8) and S-D rats (54 weeks old, n = 8) were used as experimental subjects. First, each rat was placed in a metabolic cage for 3 hours to assess voided volume per micturition and voiding frequency. Next, cystometrography with physiological saline in conscious rats was performed. A polyethylene catheter was inserted through the bladder dome under using halothane anaesthesia. We investigated the effects of intravenous naftopidil (0.01, 0.1, or 1mg/kg) on micturition reflex. Bladder contraction interval, bladder contraction pressure and number of non-voiding contractions (NVCs) per unit time were determined from each cystometry. Furthermore, the urinary ATP levels were determined before and after naftopidil administration during cystometry.

Results
Voided volume per micturition was significantly smaller and voiding frequency was significantly higher in SHRs than in S-D rats ($p<0.05$). Bladder contraction interval was significantly increased in both groups after intravenous administration of naftopidil ($p<0.01$). No significant differences in bladder contraction pressure were found between naftopidil and vehicle in either group. SHRs exhibited significantly more NVCs than S-D rats before naftopidil administration ($p<0.05$). Naftopidil administration significantly decreased the number of NVCs in SHRs (from 0.204 +/- 0.159 to 0.043 +/- 0.064 NVC/min, $p<0.01$), but such a change was not seen in S-D rats. The urinary ATP level before naftopidil administration was significantly higher in SHRs than in S-D rats ($p<0.05$). In SHRs, the ATP level was significantly decreased after naftopidil administration ($p<0.05$).

Interpretation of results
The data in the present study showed that intravenous naftopidil enlarged the bladder without decreasing bladder contraction pressure in SHRs and S-D rats, and decreased the number of NVCs in SHRs. The basal urinary ATP level was higher in SHRs with DO than in S-D rats, and decreased after naftopidil administration. Alpha-1 ARs are generally divided into alpha-1A, alpha-1B, and alpha-1D AR subtypes. Naftopidil is an alpha-1A and alpha-1D AR antagonist (a relatively selective alpha-1D AR subtype). The alpha-1D AR subtype is expressed in the detrusor, peripheral ganglia, and spinal cord in humans and rats. Recent experimental findings have shown that the alpha-1D AR subtype is involved in storage symptoms. The present study also revealed the inhibitory effect of intravenous naftopidil on the micturition reflex of conscious rats. ATP is a well-known intracellular energy carrier and is also recognized as an extracellular signaling molecule interacting with cell membrane purinoceptors (P). P2X3 receptors for ATP are abundant on nerve fibers running between urothelial cells, in the suburothelial plexus, perivascularly in the mouse bladder, and on suburothelial afferents in the rat bladder [1, 2]. It was reported that P2X3 receptor deficient mice have significantly reduced micturition frequency and significantly increased bladder capacity compared with P2X3 wild-type mice [3]. DO in aged SHRs may be explained by the increase of ATP release from the bladder epithelium. Furthermore, naftopidil's inhibitory effect on bladder activity may be via suppression of ATP release from the bladder epithelium.

Concluding message
We conclude from this study that (1) increased ATP release from the bladder epithelium may play a role in DO in SHRs characterized by sympathetic overactivity, and (2) alpha-1 AR antagonist naftopidil could improve DO via the suppression of ATP release from the bladder epithelium.

References
[1] Cell Tissue Res (2000) 300; 321-330.
[2] J Physiol (2005) 567; 621-639.
[3] Nature (2000) 407; 1011-1015.

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