641

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EFFECTS OF FESOTERODINE METABOLITE ON EXCITABILITY OF THE NEUROTRANSMITTER IN CULTURED UROTHELIAL CELLS FROM BLADDER OUTLET OBSTRUCTION (BOO) RAT

Hypothesis / aims of study
The urothelium is important to manifest the OAB symptoms in BOO and the expression changes of various urothelial signaling molecules, which contain receptors, are known to have a key pathophysiological role. In this study, we investigate the effect of 5-hydroxymethyl tolterodine (5-HMT, the active metabolite of fesoterodine) in the regulation of the urothelial messengers and signaling pathway that may improve OAB.

Study design, materials and methods
This study using female Sprague-Dawley rats was subdivided into control, BOO, and BOO+5-HMT groups. BOO was induced for 3 weeks and detrusour overactivity was confirmed with measuring intravesical pressure and intraabdominal pressure. 5-HMT (0.1 mg/kg body weight) was given intravenously three times per a week for 3 weeks. The urothelial layer was removed from smooth muscle layer and the expression of different extracellular signals (BNDF, NRG, NGF and G-CSF) was detected by RT-PCR and intracellular cascades (PKA, CREP, CRE-P, ERK, ERK-P, AKT, AKT-P) was confirmed by Western blotting. Primary cultured urothelial cells (UCs) of PBOO were exposed to various concentrations of 5-HMT (1-1000μM) for up to 24hr. Single cell RT-PCR was conducted for change the neurotransmitters of UCs.
Results
On RT-PCR and Western blotting, the urothelial expression of NRG and NGF was significantly increased in the BOO group than control group. In addition, the expression of ErbB2 receptors, PKA, CREP, ERK, and AKT was also increased in the BOO group. Interestingly, 5-HMT treatment produced down-regulation of these neurotransmitters and inhibited the downstream signals. Finally, we observed that expressions of BNDF, NGR, NGF and G-CSF in the UCs was inhibited by exposure of 5-HMT in cultured UCs in vitro.

Interpretation of results
Fesoterodine inhibited signaling of NRG and NGF to ErbB receptors which transduce multiple downstream signals including MAPK and PKA pathway via the modulation of expression and activity of different functional proteins in the BOO model.

Concluding message
These results suggest that fesoterodine might improve OAB by inhibiting the abnormal urothelial release of neurotransmitters and downstream signal cascades.

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Disclosures
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