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INVESTIGATIONS OF HIGH FAT AND HIGH SUGAR AND SURGICAL MENOPAUSE - INDUCED OVERACTIVE RAT BLADDER AND THE BENEFICIAL EFFECT OF EPIGALLOCATECHIN GALLATE

Hypothesis / aims of study
The pathophysiology mechanism of menopause in the metabolic syndrome associated bladder dysfunction is still not clear. The major aims of the present study were to examine high fat and high sugar (HFHS) and surgical menopause - induced metabolic syndrome by elucidating the critical role of oxidative stress as well as the beneficial effect of epigallocatechin gallate (EGCG) in overactive bladder (OAB).

Study design, materials and methods
Sprague-Dawley rats were divided into five experimental groups. These included: (a) normal rat chow diet (the control group), (b) purified HFHS diet (the HFHS treated group), (c) bilateral with HFHS diet (the OVX-HFHS treated group; surgical menopause with metabolic syndrome), (d) OVX combined with HFHS diet and antioxidant EGCG injection (the OVX-HFHS-EGCG treated group), and (e) HFHS diet with EGCG (the HFHS-EGCG treated) group. The ovariectomized rat model was employed to mimic the physiological conditions of ovarian hormone deficiency or the postmenopausal state to induce OAB symptoms. The serum estradiol concentration was determined by ELISA assay 2 weeks after surgical bilateral ovariectomy. At six months after HFHS feeding, cystometrogram, physical indicator, urine and serum biochemistry parameters were measured monthly. Immunofluorescence studies were carried out to show the expression and localization of neurofilament and muscarinic receptors. Western blots were carried out to examine the expressions of muscarinic and purinergic receptors, fibrosis-associated proteins, mitochondria and ER stress markers and mitochondrial respiratory subunits enzymes.

Results
Metabolic syndrome induced by surgical menopause combined with HFHS feeding was found to display bladder hyperactivity. Such bladder hyperactivity was accompanied by bladder interstitial fibrosis as well as increases in the expressions of bladder muscarinic (M2 and M3) and purinergic (P2X3) receptors. Besides, the expressions of mitochondria respiratory subunits enzymes were significantly increased in OVX-HFHS treated and OVX-HFHS-EGCG groups. These results revealed that surgical menopause enhanced the generation of oxidative stress mediated by mitochondria and ER - dependent pathways, and consequently attributed to bladder apoptosis, denuded urothelial mucosa as well as defective and thinning urothelium. These data confirmed that ovary hormone deficiency induced overactive bladder dysfunction via over-expression of muscarinic and purinergic receptors. EGCG was found to lessen bladder dysfunction in HFHS feeding - induced metabolic syndrome through its antioxidant effects.

Interpretation of results
Ovariectomy could enhance HFHS -induced bladder overactivity. Such HFHS-induced increase in the expressions of mitochondria respiratory enzyme complexes suggested that HFHS with OVX caused an enhancement in the generation of oxidative stress. EGCG could eliminate HFHS-induced bladder overactivity through its antioxidant, antiapoptosis and antifibrosis effects.

Concluding message
HFHS feeding and surgical menopause enhances the generation of ROS mediated by mitochondria and ER, leading to inducing oxidative stress in accompanying with enhanced bladder apoptosis and interstitial fibrosis. Such effects on the increased apoptosis as well as the urothelial barrier dysfunctions are potential factors underlying bladder over-activity and inflammatory process in metabolic syndrome. EGCG could eliminate HFHS-induced bladder overactivity through its antioxidant, antiapoptosis and antifibrosis effects.

Disclosures
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