362

Juan Y[1], Li Y[2], Chuang S[3], Chang C[4], Shen J[5], Jang M[5], Wu W[1]
1. *Department of Urology, Kaohsiung Medical University Hospital; Department of Urology, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung, Taiwan,* ***2.*** *Department of Urology, Chi-Shan Hospital, Department of Health, Executive Yuan, Kaohsiung,* ***3.*** *Yuh-Ing Junior College of Health Care and Management,* ***4.*** *Department of Physiology, College of Medicine, Kaohsiung Medical University,* ***5.*** *Department of Urology, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung, Taiwan;*

UROTHELIAL DYSFUNCTION AND INCREASED APOPTOTIC PATHWAY IN KETAMIN-INDUCED ULCERATIVE CYSTITIS

Hypothesis / aims of study
The aims of the present study were to investigate the relation of chronic ketamine administration induced ulcerative cystitis to bladder urothelial cells apoptosis and urothelium barrier dysfunction.

Study design, materials and methods
Thirty *Sprague-Dawley* (SD) rats were distributed into three groups which received saline or ketamine (25 mg/kg/day) for a period of 14 and 28 days. In each group cystometry was performed weekly. Western blot analyses were carried out to examine the expressions of apoptosis-associated protein (*Bcl-2* and caspase 3), oxidative stress markers (nitrotyrosine and protein carbonylation), and urothelial tight junction proteins (zonula occludin-1 and claudin-4) in bladder tissues. An immunofluorescence study was done to evaluate urothelial barrier functions and the TUNEL assay was performed to evaluate the distribution of apoptotic cells.

Results
Chronic ketamine treatment resulted in bladder hyperactivity with a significant increase in non-voiding contractions.The expressions of pro-apoptotic protein and oxidative stress markers significantly increased after long term ketamine treatment. There were also significant increases in urothelial and smooth muscle cells apoptosis after long-term ketamine treatment. Meanwhile, loss of urothelial barrier function and decreased urothelial tight-junction proteins were present in ketamine-administrated groups.

Interpretation of results
These alterations in lower urinary tract dysfunction and tissue constituents were accompanied by increases in the expressions of pro-apoptotic protein and oxidative stress markers. Ketamine resulted in a significant increase in oxidative stress and bladder tissue damages. Loss of urothelial barrier function and decreased urothelial tight-junction proteins were present in ketamine-administrated groups, showing urothelial dysfunction may play an important role in ketamine-induced bladder pain and overactivity.

Concluding message
Chronic ketamine administration induced bladder dysfunction by increasing urothelial apoptosisandenhancing oxidative stress accompanied with urothelial lining defects. Defects in the urothelial barrier and increased oxidative stress may result in bladder overactivity.

Disclosures
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