INVOLVEMENTS OF CYCLOOXYGENASE-2 AND NITRIC OXIDE SYNTHASE IN KETAMINE-INDUCED CYSTITIS IN RATS

Hypothesis / aims of study
The major aims of the present study were to investigate urodynamic functions after acute and chronic ketamine treatments and to evaluate the expression and localization of cyclooxygenase-2 (COX-2) and different nitric oxide synthase (NOS) isoforms in the urinary bladder after ketamine treatment.

Study design, materials and methods
Sprague-Dawley (SD) rats received intraperitoneal (IP) ketamine (25 mg/kg/day) or saline daily injection for a period of 14 and 28 days, respectively. Cystometry was performed in each group and cystometry parameters were determined. Paraffined sections were stained with Masson’s Trichrome stain for histological studies. Western blot analyses were performed for COX-2 and different NOS isoforms expressions. Immunofluorescence study was carried out to examine the expressions of COX-2 and ED-1 (macrophage markers).

Results
Ketamine treatment resulted in bladder hyperactivity with increases in filling, threshold, and micturition pressures. Non-voiding contraction was significantly increased, while the bladder capacity was decreased. Ketamine treatment also caused morphological changes characterized by ulcerated urothelium and erythematous patches in lamina propria with mononuclear cells infiltration. In addition, the expressions of COX-2, iNOS and eNOS isoforms were increased. No significant changes were observed in nNOS expressions at different time points. Immunofluorescence study showed COX-2 positive-stained cells were significantly increased, and most of the COX-2 expression cells were co-stained with macrophage marker.

Interpretation of results
Ketamine treatment stimulates macrophage infiltration, induces COX-2 expression and enhances iNOS activity, which could contribute to bladder damages and altered micturition reflex. On the contrary, up-regulated eNOS expressions after ketamine injection may have protective effects on regulating bladder microcirculation. Clinically, the elucidation of the changes in the level of NO and the utilization of NOS and/or COX inhibitor may have potential therapeutic value for ameliorating bladder dysfunction in ketamine abused population.

Concluding message
Ketamine injection significantly increased micturition frequency and non-voiding contractions, while decreased bladder capacity. Ketamine enhanced bladder interstitial fibrosis, decreased urothelium thickness, and accelerated macrophages infiltration. The expressions of COX-2, iNOS and eNOS in the urinary bladder were up-regulated in ketamine-induced cystitis with little changes in nNOS level.

Disclosures
Funding: This research is supported in part by the Department of Medical Research, Kaohsiung Medical University Hospital grant (KMUH-100-0R44), in part by the Kaohsiung Medical University grant (KMU-Q098015) and Kaohsiung Municipal Hsiao-Kang Hospital grant (KNHK-100-025). Clinical Trial: No Subjects: ANIMAL Species: Rat Ethics Committee: Animal Care and Treatment Committee of Kaohsiung Medical University.