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KETAMINE-INDUCED ULCERATIVE CYSTITIS IS ASSOCIATED WITH INCREASED EXPRESSION OF TRANSFORMING GROWTH FACTOR-B AND ENHANCED INTERSTITIAL FIBROSIS IN RAT

Hypothesis / aims of study

To investigate if the expression of transforming growth factor-β (TGF-β) is up-regulated and further evaluate the progression of interstitial fibrosis after long-term ketamine treatment by using a ketamine addiction rat model.

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 and metabolic cage micturition pattern study were performed weekly. Western blot analyses were carried out to examine the expressions of inflammatory protein (TGF-β), fibrosis proteins (fibronectin and type I collagen) and extracellular signal-regulated kinase 1/2 (ERK1/2) in bladder tissues. Immunofluorescence study was done to evaluate the intramural nerve densities.

Results

Chronic ketamine treatment resulted in bladder hyperactivity with a significant increase in micturition frequency and decrease in bladder compliance. These alterations in micturition pattern were accompanied by increases in the expressions of inflammatory and fibrosis markers, TGF-β, fibronectin and type I collagen after long-term ketamine treatment. Mason trichrome's stain showed ketamine treatment decreased urothelium thickness while increased collagen to smooth muscle ratio and exacerbated interstitial fibrosis. Ketamine treatment significantly decreased intramural neurofilaments stainings by immunofluorescence study, indicating ketamine resulted in bladder partial denervation.

Interpretation of results

Chronic ketamine treatment significantly increased bladder interstitial fibrosis. Increased interstitial fibrosis might resulted in decreased bladder compliance and increased micturition frequency. The expression of TGF-β, which was a potent pro-fibrotic cytokine, also significnatly increased. The increased expression of TGF-β is capable of stimulating fibroblast collagen and fibronectin biosynthesis. Persistent activation of ERK1/2 may induce oxidative stress with subsequent induction of COX-2 expression.

Concluding message

Ketamine administration results in frequent bladder contractions and decreased bladder compliance. These overactive bladder symptoms are associated with an increase in TGF-β and enhanced bladder interstitial fibrosis. Ketamine –induced bladder overactivity was also related with a decrease in intramural nerve densities and ERK1/2 activation.

Disclosures

Funding: We are grateful to Professor Chang-Hwei Chen of the University at Albany for his valuable comments on this manuscript. This research is supported in part by the grant from Department of Health, Executive Yuan, in part by Department of Medical Research, Kaohsiung Medical University Hospital grant (KMUH-100-0R44, KMUH101-1R43), and Kaohsiung Municipal Hsiao-Kang Hospital grant (Kmhk-100-029,Kmhk-100-025,Kmhk-101-017 and Kmhk-101-016). **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** Kaohsiung Medical University