Executive summary

Long-term ketamine abuse is known to be associated with impairments in various cognitive functions and lead to bladder contracture and severe lower urinary tract symptoms, clinical called ketamine-induced cystitis (KIC). A clinical empirical Chinese medicine formula (CECMF) in this study contains 12 Chinese herbal medicines. Most of the constituents of CECMF have been reported to have potential neuroprotective effects against cognitive deficits in animal or in patients, and have been widely used to treat acute cystitis in clinic. In this follow-up investigation, we endeavored to illuminate the potential benefit of CECMF on long term ketamine-induced cognitive damages and cystitis in Sprague-Dawley (SD) rats and decipher the mechanism of action.

Firstly, our result illustrated that CECMF treatment significantly ameliorated cognitive impairments induced by ketamine in both adult and neonatal male rats. CECMF markedly increased the expressions of Bcl-2 and reduced the levels Bax and cleaved caspase 3 in ketamine treated rats. CECMF treatment also evidently ameliorated the synaptic transmission plasticity in ketamine treated rats, enhanced expressions of GluN2A, GluN2B, GluA1, GluA2, PSD93, PSD95, SYN1 and SYT in the hippocampus of ketamine-treated rats. Moreover, CECMF modulated CaMKIIβ-ERK1/2-CREB/NF-κB pathway in brains of ketamine-treated adult and neonatal rats.

Secondly, our results demonstrated that CECMF obviously relieved frequent micturition, reduced the levels of NO and APF and improved the levels of GP51 in KIC rats. CECMF also overtly lowered urothelial monocyte/macrophage infiltration, lessened interstitial fibrosis deposition, and reduced inflammation (IL-1β, IL-6, TNF-α, and COX-2) and fibrogenesis (ICAM-1, TGF-β1, Type I collagen, Type III collagen and fibronectin) in the bladders of KIC rats. CECMF treatment significantly attenuated urothelial neuroreceptors alteration, decreased the levels of TRPV1, M2-mAChR, M3-mAChR, purinergic receptor P2X1, P2X2, and P2X3 in the bladders of KIC rats. Furthermore, CECMF prominently activated Nrf2/HO-1 and suppressed NF-κB pathways in bladders of KIC rats.

Finally, the results of the acute toxicity demonstrated that CECMF at up to the dose of 128 g/kg, which was the maximum tolerable dose of CECMF in mice, did not exert any overt toxicity. The results of sub-chronic toxicity study demonstrated that CECMF (5, 10 and 20 g/kg) did not affect the body weight, relative organ weights, the functions of liver and kidney and hematological analysis in male and female rats after treatment with CECMF for 90 days or 30 post drug withdraw. These results indicated that CECMF held promising potential to be further developed into an innovative Chinese medicine-based for treatment of cognitive deficits and cystitis induced by ketamine.