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THE MOLECULAR MECHANISM OF AUTOPHAGY VIA MITOCHONDRIAL AND ENDOPLASMIC RETICULUM PATHWAY IN KETAMINE-INDUCED ULCERATIVE CYSTITIS IN ANIMAL MODEL

Hypothesis / aims of study

To study the mechanism of bladder overactivity in ketamine-induced cystitis (KIC), we will elucidate whether ketamine-induced autophagy are mediated via the mitochondrial and endoplasmic reticulum (ER) pathway.

Study design, materials and methods

A ketamine-associated ulcerative cystitis model by intraperitoneally injecting ketamine (30 mg/kg) in rat was developed. Cystometry (CMG) and micturition frequency/volume studies were recorded for bladder function. Transmission electron microscopy (TEM) study was performed to evaluate the bladder morphology and evaluated the distribution of autophagosome and autolysosome. Quantitative real-time polymerase chain reaction analysis and western blot analyses were carried out to examine the expressions of autophagy-associated protein (mTOR (the mammalian target of rapamycin), Atg 12 (autophagy related gene 12), Atg 7, LC3 (Atg 8; microtubule-associated protein 1 light chain 3), Beclin 1 (Atg 6) , VPS 34 (vacuolar protein protein sorting 34) in bladder.

Results

Ketamine-treated rats showed bladder hyperactivity, however, ketamine with rapamycin treatment improved bladder function compared with ketamine. The bladder ultrastructure showed intact mitochondria and no autophagosome-like structure in the control group. However, in the ketamine group, some swelling and degraded mitochondria engulfed by autolysosome as well as apoptotic nuclear condensation and shrinkage. Whereas in ketamine with rapamycin group, some swelling and degraded mitochondria engulfed by double-membrane autophagosome. The mRNA and protein levels of autophagy related proteins (mTOR, Atg 12, Atg 7, Beclin1, LC3, and VPS 34) were elevated significantly after treatment. Additionally, the expression of the anti-apoptotic protein BCL-2 and BCL-XL in association with mitochondria in bladder tissues were significantly decreased in the ketamine and rapamycin treated groups. In contrast, the expressions of the pro-apoptotic proteins BAD, tBID, and BAX in association with mitochondria were significantly increased.

Interpretation of results

Autophagy and mitoptosis has important impacts on ketamine-induced bladder dysfunction and was correlated with mitochondria- and ER-dependent pathways.

Concluding message

This ketamine-induced ulcerative cystitis rat model could be useful for further investigating the associated mechanisms and for developing or refining therapeutic approaches especially for ketamine abusers.

Disclosures

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