IGF-1 inhibits MPTP/MPP$^+$-induced autophagy on dopaminergic neurons through the IGF-1R/PI3K-Akt-mTOR pathway and GPER

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Background

Autophagy dysfunctions are involved in the pathogenesis of Parkinson's disease (PD). In the present study, we aimed to evaluate the involvement of G protein-coupled estrogen receptor (GPER) in the inhibitory effect of insulin-like growth factor-1 (IGF-1) against excessive autophagy in PD animal and cellular models. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment significantly induced mouse movement disorder and decreased the protein level of tyrosine hydroxylase (TH) in the substantia nigra (SN) and dopamine (DA) content in striatum. Along with the dopamine neuron injury, we observed significant upregulations of microtubule-associated light chain-3 II (LC3-II) and a-synuclein as well as a downregulation of P62 in MPTP-treated mice. These changes could be restored by IGF-1 pretreatment. Cotreatment with IGF-1R antagonist JB-1 or GPER antagonist G15 could block the neuroprotective effects of IGF-1. 1-Methy-4-phenylpyridinium (MPP$^+$) treatment could also excessively activate autophagy along with the reduction of cell viability in SH-SY5Y cells. IGF-1 could inhibit the neurotoxicity through promoting the phosphorylation of Akt and mammalian target of rapamycin (mTOR), which could also be antagonized by JB-1 or G15. These data suggest that IGF-1 inhibits MPTP/MPP$^+$-induced autophagy on dopaminergic neurons through the IGF-1R/PI3K-Akt-mTOR pathway and GPER.

Methods

PD mice model was established by intraperitoneal injection of MPTP and PD cellular model was prepared by MPP$^+$ treatment. IGF-1, IGF-1R antagonist JB-1 or GPER antagonist G15 were injected into the lateral ventricle through stereotaxic technique. Rotarod test were used to detect the behavior of mice. In order to explore molecular mechanism of the neuroprotective effect of IGF-1 through regulating autophagy, the content of dopamine (DA) were measured by high performance liquid chromatography (HPLC). Cell viability was detected by MTT method. Western blot was used to detect the markers of autophagy.

Results

(1) The results of rotarod test showed that MPTP significantly inhibited the movement of mice (P<0.001). IGF-1 significantly improved dyskinesia and significantly

increased the movement distance of mice (P<0.01), which could be blocked by JB-1 or G15 (P<0.05, P<0.01).

(2) HPLC results showed that IGF-1 obviously improved MPTP-induced decrease of DA content in striatum compared with MPTP group (P<0.05). This effect could be blocked by JB-1 and G15 (P<0.05).

(3) The results of autophagy-associated protein LC3-II and P62 showed that IGF-1 could inhibit MPTP-induced up-regulation of LC3-II and down-regulation of P62 (P<0.01, P<0.001), which could be blocked by JB-1 and G15 (P<0.01, P<0.05).

(4) IGF-1 could counteract MPTP-induced decrease of TH protein expressions and the increase of α-synuclein protein expression (P<0.001, P<0.05). These effects could be blocked by JB-1 and G15 (P<0.01, P<0.05).

Conclusion

IGF-1 inhibits MPTP/MPP^+-induced neuronal excessive autophagy and protects DA neurons. GPER is involved in the neuroprotective effect of IGF-1. The potential mechanism may be related to the IGF-1R/PI3k/Akt-mTOR signaling pathway.

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It was found that IGF-1 can protect DA neurons by inhibiting autophagy

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