DOCTORAL THESIS

Glutamate antagonism as a potential treatment of Parkinson's Disease: a study in a rat model

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disease and the patients suffer serious motor disorder. Degeneration of dopaminergic neurons is the cause of PD. Glutamate excitotoxicity is known to contribute to the progressive dopaminergic denervation and it is one main cause of motor symptoms of PD. Attenuation of glutamate excitotoxicity may be a valuable mean in both treatment of motor symptoms and neuroprotection of dopaminergic neurons.

In the present study, two different strategies were employed to attenuate glutamate excitotoxicity by the reduction of glutamate receptor, NMDA receptor, overstimulation and the removal of synaptically released glutamate by the upregulation of glutamate transporter. First, a single dose of a small interfering RNA (siRNA) that targets N-methyl-D-aspartate receptor one (NR1) (siRNA-NR1) was employed to reduce the protein expression of functional NMDA receptor in the striatum. After administration of the siRNA-NR1 into normal rats, the NR1 protein was significantly down-regulated in both immunofluorescence experiment and Western blot analysis. After the application of the siRNA-NR1 to the 6-hydroxydopamine- (6-OHDA-lesioned rat, an animal model of PD, the grip strength and the number of contralateral rotation, which represented motor deficits, were found to be significantly reduced. The siRNA-NR1 was also found to decline the reduction of tyrosine-hydroxylase (TH)-positive cell ratio (lesion vs nonlesion) in SN of the 6-OHDA-lesioned rats.

Secondly, the effects of a neuroprotective antibiotic, ceftriaxone, was examined. Seven-day treatment of ceftriaxone was applied to the rats before the 6-OHDA lesion and five post-lesion time points were selected (day 2, 4 ,6 ,8 and 10) for analyses. By behavioral tests, ceftriaxone treatments were found to decrease both the grip strength and numbers of contralateral rotations in the 6-OHDA-lesioned rats. In addition, the reduction of tyrosine-hydroxylase (TH)-positive cell ratio (lesion vs nonlesion) in SN of the 6-OHDA-lesioned rats with ceftriaxone treatment was found to be decreased. Application of ceftriaxone enhanced the immunoreactivity and protein expression of GLT1. GLT1 is a major glial glutamate transporter and is responsible for re-cycling of synaptic glutamate. These results indicate that the up-regulation of GLT1 protein by the application of ceftriaxone inert neuroprotection of dopaminergic neurons.

In addition, co-administration of ceftriaxone and siRNA-NR1 was also applied in the 6-OHDA-lesioned rats. Significant reductions in both grip strength and the number of rotation were found in the co-treated animal groups when compared to the saline-treated animals. The degree of neuroprotection was similar between co-treatment and ceftriaxone treatment groups.

In conclusion, the present results as a whole have provided that glutamate antagonism

is beneficial to both amelioration of motor symptoms and neuroprotection of dopaminergic neurons. The present data can provide a basis for future development of non-dopaminergic therapies in treatment of PD.

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