A BBB-permeable neurotrophic polysaccharide, midi-GAGR

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Research Abstract

There have been enormous efforts to find an effective therapeutic agent for the treatment of neurodegenerative diseases such as Alzheimer’s disease while a disease-modifying treatment is not found yet. Compared to the conventional treatments, neurotrophic peptides appear to be able to slow neurodegeneration by regenerating neuronal structures and increasing neuron

survival. However, the short plasma half-life and poor blood-brain-barrier (BBB)-permeability of neurotrophic peptides lower their in vivo efficacy. Thus, researchers have searched for a neurotrophic agent that has longer plasma half-life and better BBB-permeability. Recent studies showed that a subset of polysaccharides could protect neurons from the oxidative insults of free reactive radicals and amyloid peptide, raising the possibility of their use for the treatment of neurodegenerative diseases. However, their BBB-permeability was not demonstrated. This possibility prompted us to search for a BBB-permeable neurotrophic polysaccharide. Our effort discovered the BBB-permeable, neuroprotective, and neurotrophic polysaccharide, midi-GAGR. Midi-GAGR is a cleavage product of low acyl gellan gum that has few side effects in human and is already approved by FDA for human use as food additive. In our study, midi-GAGR (1 ?M) protected rodent cortical neurons from the pathological concentrations of co-treated or post-treated free reactive radicals and A?42 peptide. Midi-GAGR also protected rodent cortical neurons from activated microglial cells. Moreover, midi-GAGR showed a strong neurotrophic property; it enhanced neurite outgrowth and increased phosphorylated cAMP-responsive element binding protein (pCREB) in the nuclei of primary cortical neurons. Importantly, intra-nasally administered midi-GAGR entered the brain through the BBB, exerted its neurotrophic effects, and maintained its structural intactness for >12 h after one-time administration. We also found that midi-GAGR strongly bound to fibroblast growth factor receptor 1 (FGFR1), a known neurotrophic receptor. Taken together, midi-GAGR is a good drug candidate for the treatment of neurodegenerative diseases since it has good BBB-permeability, strong neuroprotective and neurotrophic effects, and >12 h plasma half-life. The goals of our proposed research are to identify the mechanism underlying the neuroprotective and neurotrophic effects of midi-GAGR and to examine its efficacy in slowing neurodegeneration in animal. The outcome of this research will provide a solid pre-clinical basis for the clinical development of midi-GAGR.

Further information available at:

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