Cell Surface Engineering of Glycosaminoglycan Mimetics for Targeting Parkinson's Disease

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The reduction of dopamine levels due to the malfunction of dopaminergic neurons results in Parkinson's Disease (PD). Current treatments, lacking neuroprotective functions, face challenges in endogenous dopamine production. Thus, enhancing neuroprotective pathways for survival of dopaminergic neurons is key in advancing treatments for PD. Glial cell line-derived neurotrophic factor (GDNF) is a growth factor shown to enable neurite outgrowth and is thus vital to development of dopaminergic neurons. GDNF requires Heparan Sulfate (HS), a class of glycosaminoglycans (GAGs) to activate its c-Ret receptor, making HS a potential therapeutic. However, homogenous HS is difficult to access from natural sources, limiting applications. Since sulfation patterns of HS give rise to protein specific HS-GDNF interactions, current GAG mimetics, lacking precise control of sulfate presentation, limit tailored GAG-mediated signaling. To overcome such challenges, a novel GAG mimetic was synthesized, achieving optimal GDNF recognition by precisely controlling spatial arrangements of sulfated motifs via a structurally well-defined polyproline scaffold, characterized by Circular Dichroism Spectroscopy. Surface Plasmon Resonance study has shown that the mimetic binds to GDNF with high affinity due to good geometrical fit of sulfate groups to postulated HS-GDNF binding sites identified through computational studies. The mimetic's ability to increase GDNF-mediated neuronal signaling was further proven by successfully introducing mimetic onto PC12 cell surface and enhancing neurite outgrowth on PC12 cells through GDNF-GFRα1 mediated pathway. The findings of this study reflect a promising strategy for engineering GAG mediated neural processes and a novel therapeutic agent for Parkinson's disease.

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