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Protective effects of polysialic acids (PSAs) and its mimics on the nervous system after injury

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Abstract

Polysialic acid (PSA), a polymer of alpha-2,8 linked sialic acid residues, is a negatively charged macromolecular glycan mainly attached to neural cell adhesion molecules (NCAM). Studies have shown that PSA is not only essential for the development of normal brain circulation, but also for synaptic plasticity, learning and memory in adults. Although the occurrence, features, biosynthesis, and physiological roles of PSA and related effects on related diseases, including schizophrenia, bipolar disorder, neurodegenerative diseases and cancer, have been well reviewed, the important roles of PSA and its mimics in the regeneration of the nervous system following injury have not been well discussed. As a consequence, this article comprehensively reviews the effects of small organic compounds that simulate PSA, such as tegaserod and 5-nonyloxytryptamine (5-NOT), on the nervous system of mammals, suggesting that these mimetics may have tremendous therapeutic potential, especially for strategies aimed at tissue repair after injury of the nervous system.

Keywords: Polysialic acid; nervous system impairment; tegaserod; 5-NOT; neural regeneration

INTRODUCTION

Polysialic acid (PSA), a kind of unique carbohydrates, is a linear, homogenous poly alpha-2,8-linked sialic acid mainly attached to the neural cell adhesion molecules (NCAM) of the vertebrate nervous system through the typical N-linked glycosides.[1] In the developing and adult nervous system in higher vertebrates PSA can be expressed by migrating cells, such as olfactory interneuron precursors[2], or dynamically expanding processes of Schwann cells or neurons in the synaptic plasticity region, and in stem cells in the subventricular zone.[3-5] PSA participates in learning, memory and synaptic plasticity, promotes cell motility and axon orientation and targeting, and mediates the interaction of NCAM with other molecules, such as brain-derived neurotrophic factors (BDNF)[6], α-amino-3-hydroxy-5-methyl-4-isoxazolepropionicacid (AMPA) receptors[7], heparin sulfate proteoglycan (HSPG)[8], histone H1[9], N-methyl-D-aspartate (NMDA) receptor[10], and myristoylated alanine-rich C kinase(MARCKS) substrate.[11] These functions of PSA are vital for the treatment of nervous disorders. Previous review first comprehensively outlines the occurrence, features, biosynthesis, and physiological roles of PSA, such as PSA formations of attractive filed for neurotrophic factors, growth factors, cytokines and proteins, and subsequently focuses on the related diseases, such as schizophrenia, bipolar disorder, neurodegenerative diseases and cancer.[12] In the current review, we mainly concentrate on the effect of PSA and its mimics on the nervous system after injury.

When over-expressed in endogenous astrocytes and transplanted Schwann cells, virus-mediated PSA expression can enhance the formation of dendrites in Purkinje cells after injury and improve axonal regeneration after spinal cord injury (SCI).[13] However, treatment with PSA transduction virus or application of PSA-expressing cells as therapeutic strategies has the disadvantages that PSA can be cleaved in vivo by neuraminidase and sialidase, such as sialidase NEU4 that is highly expressed in the central nervous system.[14] In addition, it is sometimes difficult to isolate, purify, or produce

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PSA from biological sources, especially when a defined PSA with a certain number of sialic acid residues is needed.[15] Therefore, compounds that structurally and functionally mimic PSA from small organic molecular libraries play a key role in promoting functional recovery and plasticity after peripheral and central nervous system injury.

THE DEFINATION AND BASIC STRUCTURE OF POLYSIALIC ACID

Sialic acid, a derivative of neurominic acid, is an acidic amino sugar containing 9 carbon atoms and a pyranose structure.[16] The PSA is a linear homopolymer of sialic acid monomers linked by α-2,8 ketosidic linkages.[17] The two monomers of the PSA terminal, which are next to each other and connected by the alpha ketone bond, form the lactone[18] and play a certain role in the stability of PSA. The biochemical properties of PSA such as carrying of negative charges, space occupancy, and carrying of water and other ions, mainly depend on the carboxyl groups of sialic acid. Studies have shown that PSA is involved in cell adhesion, migration, neurite outgrowth, nerve bifurcation, neuronal orientation, synapse formation, neuritogenesis and other functions.[19,20] The migration promoting effect of PSA is more common at the developmental stages of brain. For example, the migration of the luteinizing hormone releasing hormone (GnRH) cells to the forebrain depends on polysialic acid.[21] (Figure 1)

MOLECULES INTERACTING WITH POLYSIALIC ACID AND THE SIGNALING PATHWAY

PSA can regulate the activity of many cell adhesion molecules such as integrins, cadherins, and other immunoglobulin superfamily molecules involved in neuronal cell adhesion[21], while it mainly attaches to NCAM.[24] NCAM is a cell surface glycoprotein composed of five immunoglobulin (Ig)-like domains and two fibronectin III repeat units. PSA is linked to NCAM by glycosides on the N-glycosylation site on Ig-5.[21] PSA can form a larger hydration radius as it is hydrophilic and carries many negative charges.[25] The presence of PSA increases the distance between cell membranes during NCAM-NCAM interaction, causing other adhesion molecules on the membrane to lose adhesion ability due to

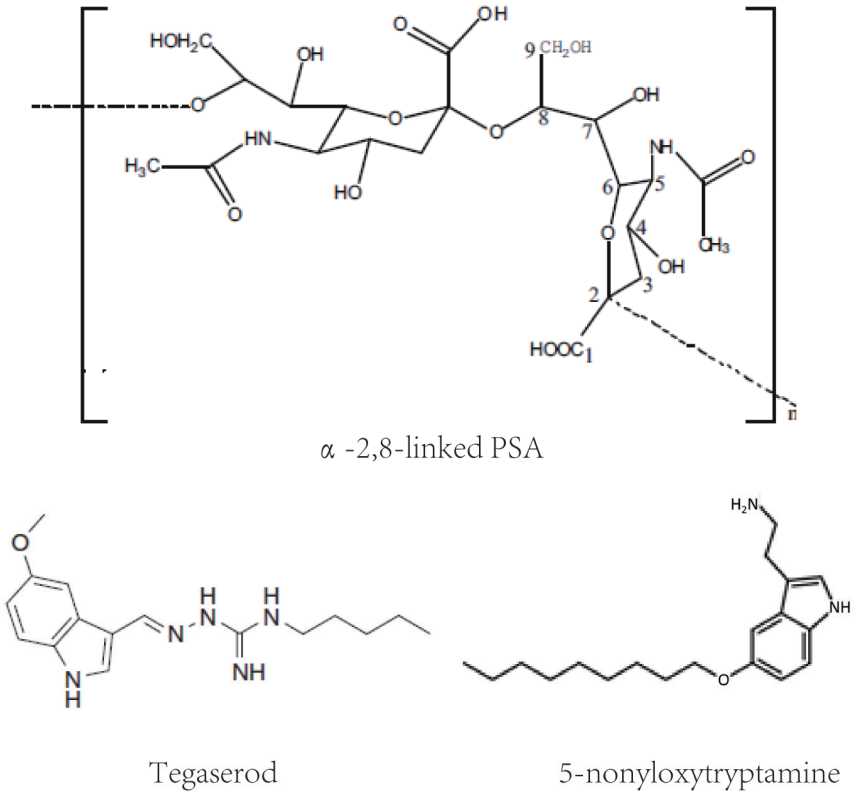

Figure 1. Structures of α-2,8-linked PSA, tegaserod and 5-nonyloxytryptamine[22, 23].

excessive distance, thus reducing the adhesion between cell membranes. However, deletion of PSA by specific exonuclease EdnoN can enhance the adhesion between membranes.[26] Therefore, the presence or absence of PSA can directly or indirectly regulate the adhesion between cell membranes. Since PSA is expressed only in the postembryonic and early postnatal stages, it plays an important role in regulating the development of the nervous system.[27] (Figure 2).

REPARING EFFECT OF POLYSIALIC ACID MIMICS ON NERVOUS SYSTEM INJURY

PSA mimetic peptides have been well developed by performing phage display screening[28], and may have therapeutic effect. (Figure 3) The peptides and small compound mimics of PSA have a multiple of advantages in drug development for therapies in the treatment of human diseases. Purified synthetic compounds are non-xenogeneic as compared to proteins or molecules purified from animals and bacteria or recombinantly generated in *E. coli*, insect or mammalian cells. Application of PSA mimetic peptides discovered by screening of phage display libraries with PSA monoclonal antibodies[28,29] or small molecules can promote functional recovery and plasticity after SCI and femoral nerve injury.[2,24,29-32]

Tegaserod, a FDA-approved drug for treatment of irritable bowel syndrome and constipation[33] by stimulating the 5-HT_4 receptor on enteric neurons[34,35], has been screened as a specific PSA mimicking small organic compound from a library of small organic molecules.[28] Two different functions of tegaserod can be functionally distinguished from each other.[24] PSA mimicking activity of tegaserod was confirmed in the primary culture of neurons and Schwann cells from both central and peripheral nervous systems of mice, and this effect was independent of its original function as the 5-serotonin (5-HT) receptor agonist.[32] Also, tegaserod can enhance locomotor recovery and regrowth sprouting of axons when applied at the lesion site of mice with a femoral nerve injury of the peripheral nervous system *in vivo*.[32] In a mouse model of severe compression-induced SCI, the regenerative function of the mice treated with tegaserod was significantly enhanced when compared to the control-treated mice.[24] These experiments validate the potential of tegaserod in treating nervous system injuries in mammals.

Studies have reported that PSA cyclic mimetic peptide (PR-21) can display PSA-like biological functions, including neurite outgrowth, fasciculation and guidance, and increased the migration of transplanted neural progenitors along the rostral migratory stream.[28] After dorsal hemisection at the T9 level of the adult mouse, delivery of PR-21 to the lesion site decreased the recovery time, enhanced motor functions, sensorimotor control, and coordination of the hindlimb with the forelimb when compared to the control peptide-treated mice.[31] At the cellular level, PR-21 increases the serotonergic

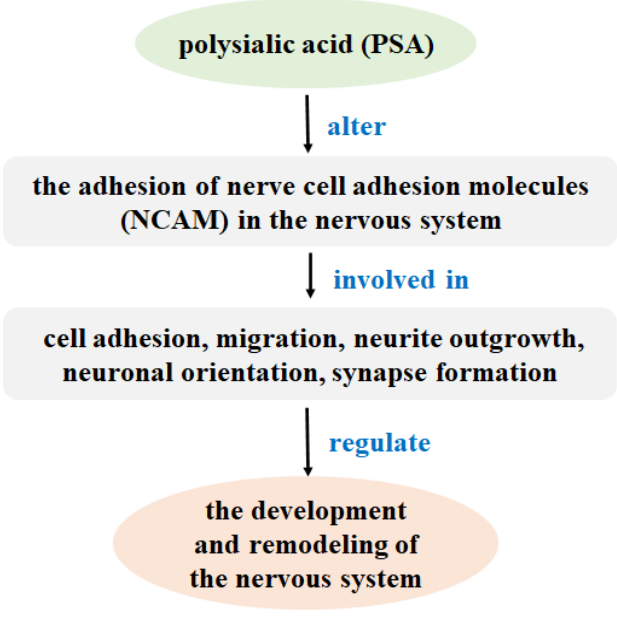

Figure 2. Physiological pattern of PSA.

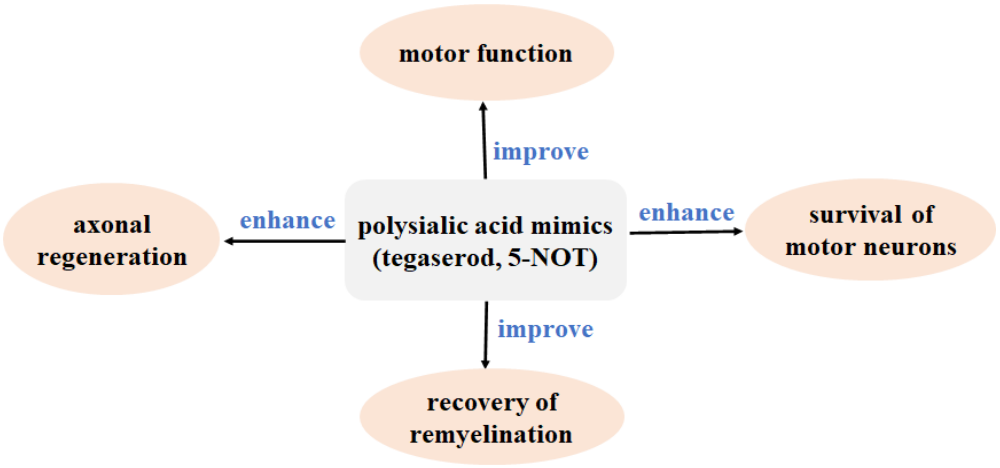

Figure 3. Schematic diagram demonstrating the therapeutic effect of PSAs mimics.

axon density at and caudal to the lesion site and reduces reactive gliosis in vivo. In an in vitro model of reactive astrocytes, PR-21 increased NCAM expression in enhanced glial fibrillary acidic protein (GFAP)-positive cells.[30]

The 5-nonyloxytryptamine (5-NOT), which was identified using a small organic molecule library, plays a similar role to that of colominic acid in the aspect of stimulating regeneration after SCI.[7] In addition, it is as effective as the PSA cyclic mimetic peptide (PR-21) in enhancing regeneration after SCI[30,31], and it can be applied at lower concentration and cannot be degraded by peptidases. In a mouse SCI model, the 5-NOT can yield an overall functional recovery of approximately 80%.[2] Based on the above findings, tegaserod and 5-NOT are expected to become candidate drugs for treatment of the nervous system injury (Figure 2).

CONCLUSION

PSA is not only an important glycan in the nervous system development and synaptic plasticity, but also in regeneration after injury. Studies indicate that PSA mimicking small organic compounds, such as tegaserod and 5-NOT, are potential drugs in the development of novel neurological therapies. Their application creates favorable conditions for axonal regeneration and remyelination to promote functional recovery after injury. Therefore, such compounds may be applied as a combined therapeutic strategy involved in the recovery promotion of acute nervous system injury and repair of neurodegenerative diseases, laying the foundation for PSA and the mimetic peptides as novel candidates for the treatment of the diseases related to neuronal injury in the future.

DISCLOSURE

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Conflicts of interest: None

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