Role of the Sulfation Pattern of Chondroitin Sulfate in its Neuritogenic Activities.

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Chondroitin sulfate (CS) is a representative sulfated glycosaminoglycan, which is covalently attached to a panel of core proteins to form proteoglycans (CSPGs), and is ubiquitously located in extracellular matrices and on cell surfaces in various tissues. CSPGs regulate diverse physiological phenomena such as cytokinesis, morphogenesis, and infections with viruses and bacteria. In particular, the pathologic functions of CS moieties of CSPGs as major axon growth-inhibitory molecules in the injured adult central nervous system (CNS) have attracted widespread attention, and prompted research aimed at overcoming their barrier effects on neuronal regeneration processes. Although axonal regeneration is indeed improved by the removal of CS moieties around lesion sites, CS does not always impede neurite outgrowth. For example, several CS preparations serve as stimulatory substrata for neurite outgrowth of cultured primary neurons.

The apparently contradictory actions of CS in the CNS are thought to be attributable to its structural diversity. CS is a linear polysaccharide that contains repeating disaccharide units consisting of glucuronic acid (GlcUA) and N-acetyl-D-galactosamine (GalNAc). The building blocks can be substituted with sulfate groups at various positions, thereby producing characteristic "sulfation codes". CS polysaccharides are divided into subclasses based on their disaccharide composition. The major CS subclasses found in mammalian tissues contain monosulfated disaccharide units, A [GlcUA-GalNAc(4-O-sulfate)] and C [GlcUA-GalNAc(6-O-sulfate)]. CS polysaccharides rich in A and C units are poorly permissive for neurite extension, probably reflecting the inhibitory nature of typical mammalian CS. In contrast, squid cartilage-derived CS-E polysaccharide possesses strong neuritogenic activity toward primary hippocampal neurons. CS-E is characterized by the predominant disulfated disaccharide E unit, [GlcUA-GalNAc (4,6-O-disulfate)]. We have recently demonstrated the involvement of a cell adhesion molecule, contactin-1, in CS-E-mediated neuritogenesis in a neuroblastoma cell line and primary hippocampal neurons. Our data provide the evidence for functional expression of CS through the CS receptor-mediated signaling pathway(s).

Hyaluronan As A Key Adhesion Molecule In The Liver

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White cells must attach to the vessel wall before they can emigrate into tissues. A series of molecules including selectins and integrins are needed to allow for recruitment in most tissues. One major exception is the liver which does not use these molecules. Neutrophils will adhere in both sinusoids and post-sinusoidal venules but blocking integrins and selectins only blocks neutrophil adhesion in the post-sinusoidal vessels. Using a adhesion molecule screen, we discovered that hyaluronan is expressed most in liver and mainly in the sinusoids. Removal of hyaluronan or inhibition of its receptor CD44 prevented this recruitment. CD44 and hyaluronan were not sufficient alone to induce adhesion in sinusoids. We ultimately indentified a hyaluronan structure modifying protein as key to allowing for cell adhesion in sinusoids. Hyaluronan functions as a key molecule in neutrophil recruitment.