Neuroscience Research 78 (2014) 50–54

Contents lists available at ScienceDirect

Neuroscience Research

journal homepage: www.elsevier.com/locate/neures

Review article

Sulfated glycans in network rewiring and plasticity after neuronal injuries

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ARTICLE INFO

Article history:
Received 28 March 2013
Received in revised form
24 September 2013
Accepted 27 September 2013
Available online 21 October 2013

Keywords:
Neuronal injury
Keratan sulfate
Condroitin sulfate

ABSTRACT

Biopolymers in the human body belong to three major classes: polynucleotides (DNA, RNA), polypeptides (proteins) and polysaccharides (glycans). Although striking progress in our understanding of neurobiology has been achieved through a focus on polypeptides as the main players, important biological functions are also expected to be attributable to glycans. Nonetheless, the significance of glycans remains largely unexplored. In this review, we focus on the roles of sulfated glycans. Axonal regeneration/sprouting after injuries does not easily occur in the adult mammalian central nervous system. This is due to the low intrinsic potential of regeneration and the emerging inhibitory molecules. The latter include the sulfated long glycans chondroitin sulfate (CS) and keratan sulfate (KS). Enzymatic ablation of CS or KS, and genetic ablation of KS promote functional recovery after spinal cord injury. Interestingly, the combination of CS and KS ablations exhibits neither additive nor synergistic effects. Thus, KS and CS work in the same pathway in inhibition of axonal regeneration/sprouting. Furthermore, CS has been implicated in neural plasticity as a functional component of the perineuronal nets surrounding inhibitory interneurons. Elucidation of the mechanisms of action for KS and CS will pave the way to treatments to promote network rewiring and plasticity after neuronal injuries.

Contents

1. Introduction

The functional neuronal circuits are formed during development as well as after injuries, depending not only on genetic information but also on plastic remodeling in response to environmental information. Gradients of extracellular cues induce second messengers, such as calcium and cyclic nucleotides, and transduce attractive and repulsive signals by steering growth cones through the creation of localized imbalances between exocytosis and endocytosis (Kolodkin and Tessier-Lavigne, 2011; Tojima et al., 2011). Since axons in the adult mammalian central nervous system (CNS) lack regenerative capacity, it is an important question whether new growth cones generated after injury use the same strategy for regeneration as embryonic neurons employ, and how the injured axons compromise the low intrinsic activity of regeneration (Bradke et al., 2012; Harel and Strittmatter, 2006). Furthermore, the emerging inhibitors after injuries are strong barriers for regeneration.

The inhibitors can be categorized into three classes: canonical axon guidance molecules, myelin-derived inhibitors, and chondroitin sulfate proteoglycans (CSPGs) (Giger et al., 2010; Harel and Strittmatter, 2006; Silver and Miller, 2004). Axon guidance molecules include semaphorins, ephrins, netrins and slit. These molecules are expressed upon injury and induce growth cone

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http://dx.doi.org/10.1016/j.neures.2013.10.005

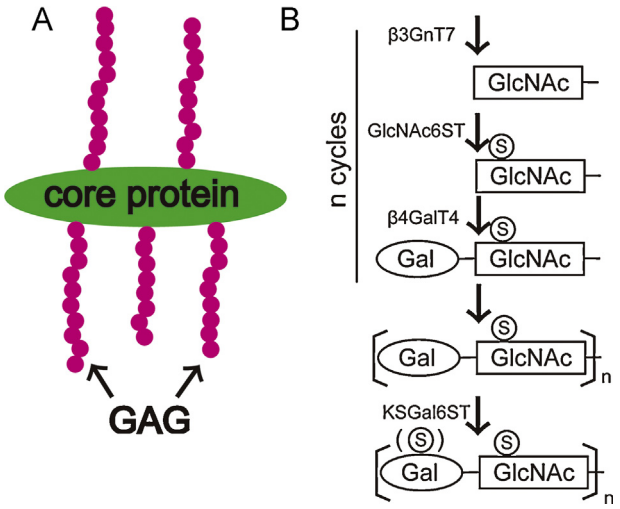

Fig. 1. Structure of proteoglycan. (A) Structure of proteoglycan. Proteoglycan consists of core protein and glycosaminoglycans (GAGs). GAG is a long sugar chain composed of repeating disaccharide units. (B) Biosynthesis of KS. KS synthesis is accomplished by a cycle of GlcNAc transfer, GlcNAc sulfation and Gal transfer that are mediated by the enzymes β3GnT7, GlcNAc6ST and β4GalT4, respectively. After elongation of the KS chain to some extents, Gal is sulfated by the enzyme KSGal6ST. This oversulfated form of KS is recognized by the antibody 5D4. GlcNAc6ST-1 is responsible for GlcNAc sulfation for the production of 5D4-resposive KS in the brain. Therefore, the deficiency of GlcNAc6ST-1 results in loss of 5D4-resposive KS in the brain.

collapse. Blocking agents against these inhibitors could be beneficial for the functional recovery after injuries, such as spinal cord injury (SCI) (Hata et al., 2006; Kaneko et al., 2006). The myelin-derived inhibitors consist of Nogo, myelin-associated glycoprotein (MAG), and oligodendrocyte myelin glycoprotein (OMgp). These glycoproteins strongly inhibit neurite outgrowth *in vitro*. However, the significance of their *in vivo* functions is still in debate. Thus, triple knockout mice of these three genes have been reported not to exhibit enhanced regeneration of axonal tracts after SCI, while another report showed that the triple knockout mice exhibited greater axonal growth and improved functional recovery (Cafferty et al., 2010; Lee et al., 2010).

Silver and colleagues reported in 1990 that axons from the E9 chick dorsal ganglia will not cross a strip of proteoglycans coated on nitrocellulose (Snow et al., 1990a). However, digestion of chondroitin sulfate (CS) abolishes the inhibitory activity of proteoglycans. These findings triggered studies on chondroitin sulfate proteoglycans (CSPGs) as inhibitors of axonal regeneration/sprouting. Glycans consisting of repeating disaccharide units are named glycosaminoglycans (GAGs). CS is a sulfated GAG, the disaccharide units of which are composed of GlcA and GalNAc. CS chains are covalently attached to a core protein, and this whole molecule is generally called CSPG (Fig. 1). It is now accepted that CSPGs act not only as inhibitors of axonal regeneration/sprouting but also as regulators restricting synaptic plasticity and experience-dependent neural plasticity (Bradbury et al., 2002; Frischknecht et al., 2009; Gogolla et al., 2009; Moon et al., 2001; Pizzorusso et al., 2002).

We have recently found that the functions of keratan sulfate (KS) and CS merge in the same pathway in inhibition of axonal regeneration/sprouting, and that both sugar chains are essential for the inhibition (Imagama et al., 2011; Ito et al., 2010; Tauchi et al., 2012; Zhang et al., 2006). Here, we overview the currently known biological activities of CSPGs in network rewiring and plasticity after neuronal injuries. Then, we show the functions of KSPGs and discuss the relationship between KS and CS.

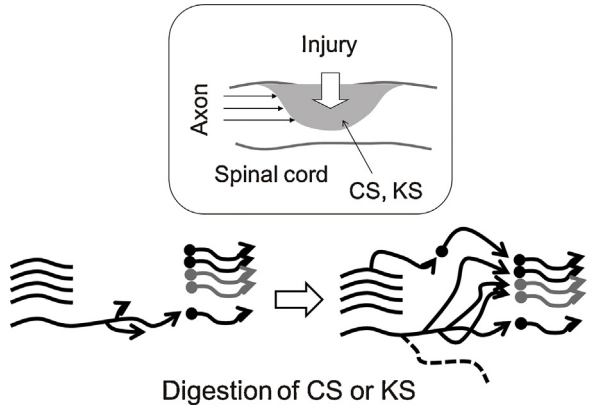

Fig. 2. Schematic presentation of CS and KS induction and the effects of their ablation. CS and KS are expressed at or around the site of injury. Axonal regeneration/sprouting hardly occur after neuronal injuries. However, if CS or KS are digested, axonal regeneration/sprouting is enhanced and functional recovery is promoted.

2. CSPGs as a major inhibitor of axonal regeneration/sprouting

Trauma to the central nervous system (CNS) leads to rupture of the blood–brain barrier, which in turn allows infiltrations of macrophage from the blood and fibroblasts from the meninges, and consequently induces glial scar formation (Silver and Miller, 2004). The glial scar consists of reactive astrocytes and other cellular components as well as extracellular molecules including CSPGs.

Round, swollen axonal ends with multiple vacuoles are often found in the glial scar, and are called dystrophic endballs. Dystrophic endballs end in the CSPG deposition in the glial scar, and persist there for at least 9.5–13 weeks after injury (Davies et al., 1999; Li and Raisman, 1995). The formation of dystrophic endballs can be recapitulated *in vitro* if axons of adult dorsal root ganglion cells are forced to grow against a gradient of CSPGs (Tom et al., 2004). Under this condition, axons cannot extend well. Neurite outgrowth on the substratum evenly coated with CSPGs is also inhibited, and this inhibition is released by the treatment with the CS-degrading enzyme chondroitinase ABC (C-ABC). Consistent with this, C-ABC promotes axonal regeneration after nigrostriatal tract transaction, sprouting of spared fibers in the cuneate nucleus after cervical spinal cord injury (SCI), and functional recovery after SCI (Bradbury et al., 2002; Massey et al., 2006; Moon et al., 2001) (Fig. 2). Therefore, the CS chains of the CSPG moiety seem to be principal actor for the CSPG-mediated inhibition of axonal regeneration/sprouting.

3. CSPGs limit experience-dependent neural plasticity and synaptic plasticity

Special extracellular matrix structures, the so-called perineuronal nets (PNNs), are found around a subset of parvalbumin-positive interneurons. PNNs consist of hyaluronan, CSPGs (aggrecan, versican, brevican, neurocan), and tenacin R. Although the precise underlying mechanisms remain elusive, PNNs have been implicated in neural plasticity. For example, ocular dominance plasticity occurs during a postnatal critical period (19–32 postnatal days in mice; 12–36 months in humans), but not in adults. CS digestion with C-ABC restores the ocular dominance plasticity in adult animals (Pizzorusso et al., 2002). Surprisingly, transgenic mice that show an infant-type sulfation pattern of CS also manifest ocular dominance plasticity in adults, suggesting the importance of sulfation modes of CS in PNNs in this plasticity (Miyata et al., 2012). These findings are of clinical importance, since ocular dominance