Experimental Neurology 274 (2015) 100–114

Contents lists available at ScienceDirect

Experimental Neurology

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

Review article

"GAG-ing with the neuron": The role of glycosaminoglycan patterning in the central nervous system

Patrice D. Smith [a,b,*,1], Vivien J. Coulson-Thomas [a,1], Simona Foscarin [a], Jessica C.F. Kwok [a], James W. Fawcett [a,*]

[a] John van Geest Centre for Brain Repair, University of Cambridge, Forvie Site, Robinson Way, Cambridge, UK
[b] Department of Neuroscience, Carleton University, Ottawa, ON, Canada

ARTICLE INFO

Article history:
Received 2 May 2015
Received in revised form 17 July 2015
Accepted 6 August 2015
Available online 12 August 2015

ABSTRACT

Proteoglycans (PGs) are a diverse family of proteins that consist of one or more glycosaminoglycan (GAG) chains, covalently linked to a core protein. PGs are major components of the extracellular matrix (ECM) and play critical roles in development, normal function and damage-response of the central nervous system (CNS). GAGs are classified based on their disaccharide subunits, into the following major groups: chondroitin sulfate (CS), heparan sulfate (HS), heparin (HEP), dermatan sulfate (DS), keratan sulfate (KS) and hyaluronic acid (HA). All except HA are modified by sulfation, giving GAG chains specific charged structures and binding properties. While significant neuroscience research has focused on the role of one PG family member, chondroitin sulfate proteoglycan (CSPG), there is ample evidence in support of a role for the other PGs in regulating CNS function in normal and pathological conditions. This review discusses the role of all the identified PG family members (CS, HS, HEP, DS, KS and HA) in normal CNS function and in the context of pathology. Understanding the pleiotropic roles of these molecules in the CNS may open the door to novel therapeutic strategies for a number of neurological conditions.

Contents

Abbreviations: AD, Alzheimer's disease; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APP, amyloid precursor protein; C4ST, chondroitin 4-O-sulfotransferase; CCL, leukocyte-derived chemotactic cytokine; ChABC, chondroitinase ABC; Chst14, carbohydrate sulfotransferase 14; CNS, central nervous system; Crtl1, cartilage link protein 1; CS, chondroitin sulfate; CSPG, chondroitin sulfate proteoglycan; D4ST, dermatan 4-O-sulfotransferase; DS, dermatan sulfate; DS-epi1 and DS-epi2, dermatan sulfate epimerase 1 and 2; DSEL, dermatan sulfate epimerase 2; DSPG, dermatan sulfate proteoglycan; EXT1 and EXT2, exostosin 1 and 2; ECM, extracellular matrix; EGF, epidermal growth factor; ER, endoplasmatic reticulum; FGF, fibroblast growth factor; GAG, glycosaminoglycan; Gal, galactose; GalNAc, N-acetylgalactosamine; GlcNAc6ST1, N-acetylgalactosamine4-sulfate 6-O-sulfotransferase; GFAP, glial fibrillary acidic protein; GlcA, glucuronic acid; GlcNAc, N-acetylglucosamine; HA, hyaluronic acid or hyaluronan; HA4, HA tetrasaccharide; HAS, hyaluronan synthase; HEP, heparin; Hh, Hedgehog; HMWHA, high molecular weight HA; HS, heparan sulfate; HSPG, heparan sulfate proteoglycan; IDD, inflammatory demyelinating diseases; IdoA, iduronic acid; IL, interleukin; KS, keratan sulfate; KSPG, keratan sulfate proteoglycan; LAR, leukocyte common antigen-related phosphatase; LMWHA, low molecular weight HA; LTP, long term potentiation; L-VDCC, L-type voltage-dependent Ca2 + channel; MAP-2, microtubule associated protein 2; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; MPS, mucopolysaccharidosis; MS, multiple sclerosis; NA, N-acetylated; NCAM, neuronal cell adhesion molecule; NG2, neuron-glia antigen 2; NgR, Nogo receptor; NMDA, N-methyl-D-aspartate; NS, N-sulfated; OPC, oligodendrocyte precursor cell; OTX2, orthodenticle homeobox 2; PG, proteoglycan; PNN, perineuronal net; PTPσ, protein tyrosine phosphatase sigma; RGC, retinal ganglion cells; RPTP, receptor protein tyrosine phosphatase; SC, spinal cord; Sema3A, semaphorin 3A; ST, sulfotransferase; tPA, tissue plasminogen activator; TIMP, tissue inhibitor of metalloproteinase; TNF, tumor necrosis factor; TGF, transforming growth factor; UST, uronyl 2-O-sulfotransferase; Wg, wingless.

* Corresponding authors at: John van Geest Centre for Brain Repair, University of Cambridge, Forvie Site, Robinson Way, Cambridge, UK.
E-mail addresses: Patrice.Smith@carleton.ca (P.D. Smith), jf108@cam.ac.uk (J.W. Fawcett).

[1] Denotes equal contribution.

http://dx.doi.org/10.1016/j.expneurol.2015.08.004
0014-4886/

1. Introduction

The extracellular matrix (ECM) is composed of a wide variety of glycoproteins and proteoglycans which act together to produce a complex and dynamic environment. The ECM plays a critical role in maintaining the structural integrity of the nervous system through its many effects on neurons, glia, inflammatory cells and other cell types. Proteoglycans (PGs) form an integral component of the ECM and are essential for the biology of the nervous system. PGs are a group of glycoconjugates consisting of glycosaminoglycan (GAG) side chains covalently linked to a core protein. GAGs are a heterogeneous family of linear polysaccharides composed of a repeating disaccharide unit. The identity of the disaccharide unit results in a classification of GAGs into five major groups: chondroitin sulfate (CS), heparin (HEP) and heparan sulfate (HS), dermatan sulfate (DS), keratan sulfate (KS) and hyaluronic acid (HA). HS chains are made up of repeating disaccharides of N-acetylglucosamine (GlcNAc) and glucuronic acid (GlcA), while CS contains N-acetylgalactosamine (GalNAc) and GlcA, DS contains GalNAc and iduronic acid (IdoA) and KS contains galactose and GalNAc residues. HA is composed of GlcNAc and GlcA disaccharides. For HS, CS, and DS, the GAG chains are attached to protein cores via a tetrasaccharide linkage region bound to a serine residue, while HA chains are not attached to a protein core. The structural heterogeneity and complexity of HS, CS, DS, and KS are controlled by enzymatic modifications, including sulfation and epimerization, which dictate their distinct biological functions. Different sulfation patterns result in variable charged modules along the GAG chains producing specific binding sites for a wide variety of molecules and receptors (Fig. 1). In addition, the protein cores can affect the function of PGs by localizing the GAGs to particular regions. Sulfated GAGs are ubiquitous to the animal kingdom in both vertebrate and invertebrate phylogenetic tree, whereas in the bacterial kingdom only non-sulfated chains of GAGs are found (Yamada et al., 2011). The appearance of CS and HS, in the animal kingdom, coincides with the emergence of eumetazoa, which are animals that display true tissues organized into germ layers that produce neurons (Yamada et al., 2011). In this review we attempt to present a global overview of the literature surrounding the role of PGs in the nervous system, with a particular focus on the role of GAG patterning in the normal and pathological CNS. Topics to be covered include the general biological function of PGs in the CNS including, the role of these molecules in neurodevelopment, neuroplasticity and neuropathology.

2. Synthesis of proteoglycans

The biosynthesis of GAGs does not follow the classical DNA–RNA–protein paradigm in which there is a template; rather, it is a dynamic enzymatically-regulated process that enables the structural heterogeneity of these molecules (Prydz and Dalen, 2000). The function of the sulfation patterning in the CNS will be discussed in more detail later in this review. GAG biosynthesis commences in the late endoplasmic reticulum and/or the cis-Golgi compartment, with the addition of a xylose to specific amino acid residues on core proteins by xylosyltransferase

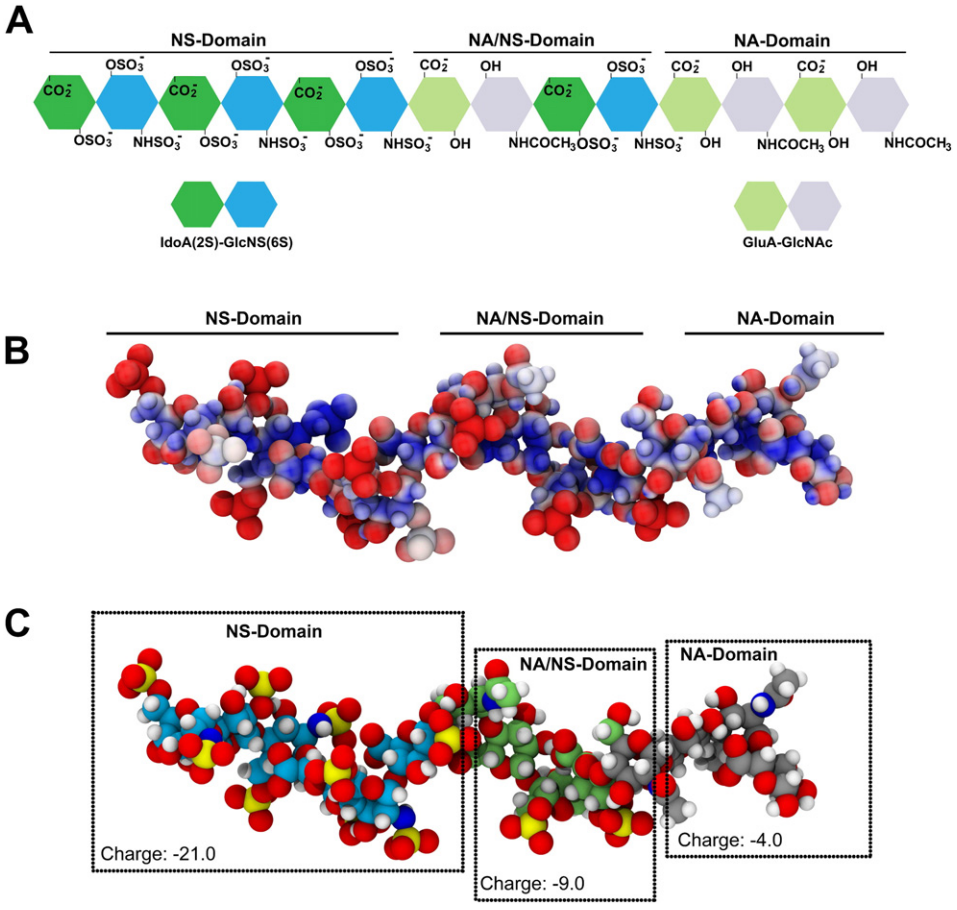

Fig. 1. Structure of HS domains. A: Structural features of HS. HS is comprised repeating disaccharide units (GlcA or IdoA and GlcN) and may carry patches of sulfation interspersed with unsulfated regions creating specific domains, namely NS (N-sulfated)-, NA (N-acetylated) and NA/NS-domains. B: Structure of HS demonstrating a dense negative electrostatic potential for NS-domain and less negative electrostatic potential for the NA-domain (red: negative; blue: positive and white: neutral). C: Van der Walls Radii representation of the NS-domain (carbon atoms in cyan), NA/NS-domain (carbon atoms in green) and NA-domain (carbon atoms in gray). Isosurfaces of the potential were visualized in VMD (Humphrey et al., 1996). The VMD PMEPOT plugin was used to compute the electrostatic potentials (Aksimentiev and Schulten, 2005).