Glycosaminoglycans in Neurodegenerative Diseases

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Abstract

Glycosaminoglycans (GAGs) are linear polysaccharides that consist of alternating disaccharides sequences of uronic acids and/or galactose hexamino sugars most of which are sulfated. GAGs are ubiquitously expressed on the cell surface, in the intracellular milieu and in the extracellular matrix of all animal cells. Thus, GAGs exhibit many essential roles in a variety of physiological and pathological processes. The targets of GAGs are GAG-binding proteins and related proteins that are of significant interest to both the academic community and in the pharmaceutical industry. In this review, the structures of GAGs, their binding proteins, and analogs are presented that further the development of GAGs and their analogs for the treatment of neurodegenerative diseases agents.

Keywords

Glycosaminoglycans · Neurodegenerative diseases · Heparan sulfate · Alzheimer's disease · Parkinson's disease

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9.1 Introduction: Neurodegenerative Diseases and Glycosaminoglycans

Neurodegenerative diseases (NDDs) are a heterogeneous group of disorders that are characterized by the progressive degeneration of the structure and function of the central nervous system or the peripheral nervous system (Nature Springer 2020a). More people are living longer so that more people are of higher risk of being affected by NDDs. Research shows that genes and envi-

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ronment contribute to NDDs (Nature Springer 2020b), however, it is still generally unknown which gene or which compounds impact NDDs. There are limited medicines for the treatment of the physical or mental symptoms related with NDDs and there is an urgent need to uncover and improve our understanding of the causes and cures of NDDs.

NDDs include Alzheimer's disease (AD), Parkinson's disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), prion diseases, Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), ataxia telangiectasia, multiple sclerosis, spinocerebellar ataxia (SCA), HIV-associated neurocognitive disorders (HAND), Pick's disease, Krabbe's disease, Kennedy's disease, primary lateral sclerosis (PLS), Cockayne syndrome, spinal muscular atrophy (SMA), tabes dorsalis, progressive supranuclear palsy (PSP), and Pelizaeus-Merzbacher disease (Appel et al. 1996; Hardy 2000).

There are millions of people suffering from NDDs throughout the world. Alzheimer's disease and Parkinson's disease are the most common NDDs. The number of Americans age 65 and older with Alzheimer's dementia is expected to grow from 5.8 million to 13.8 million by mid-century (Alzheimer's Association 2020). The number of deaths associated with AD was 0.12 million in 2018 making AD as the sixth leading cause of death in the United States and the fifth leading cause of death among 65 and older Americans (Alzheimer's Association 2020). This situation has been getting worse as the number of deaths resulting from AD has increased by 146.2% between 2000 and 2018 (Alzheimer's Association 2020). The total payments in 2020 for health care, long-term care, and hospice services for people aged 65 and older with dementia in the United State is estimated as $305 billion (Alzheimer's Association 2020). The number of people living with PD in the United States is predicted to rise from 0.93 million in 2020 to 1.2 million by 2030 (Marras et al., 2018). There are more than 10 million people, who are living with PD around the world. Like AD, the incidence of PD increases with age. An estimated 4% PD people are diagnosed before 50, which is 15 years younger than AD patients are identified (Marras et al. 2018). The combined direct and indirect cost of PD is approximately $52 billion per year in the United States (Marras et al. 2018).

The extracellular matrix (ECM) plays key roles in regulating the development, function, and homeostasis of all eukaryotic cells (Mouw et al. 2014; Nita et al. 2014; Barros et al. 2011; Vieira et al. 2018; Song and Dityatev 2018). The diverse functions of tissues are reflected and facilitated through the complex chemical composition and organization of ECM, which result from a biochemical and biophysical interplay between the various cells in each tissue and the evolving microenvironment (Mouw et al. 2014; Naba et al. 2012). In the central nervous system, ECM contains basal lamina, proteoglycans (PGs), collagens, fibronectin, and elastin (Mouw et al. 2014; Cui et al. 2013; Lau et al. 2013; Hubert et al. 2009; Barros et al. 2011; Ma et al. 2020). These components are also regulated by biochemical mediators, such as interleukins, arachidonic acid and derivatives, interferons, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor (TGF), and epidermal growth factor (Carmen et al. 2019). Therefore, the dysfunction of ECM in the brain leads to neurodevelopment disorders, psychiatric dysregulation, and neurodegenerative diseases (Wang and Ding 2014; Ariga et al. 2010; Hillen et al. 2018; Fawcett et al. 2019).

The most important components of the ECM are proteoglycans (PGs). PGs are a subset of heavily glycosylated glycoproteins. The "core proteins" include decorin, versican, testican, perlecan, bikunin, neurocan, aggrecan, brevican, fribromodulin, and lumican with their covalently attached carbohydrate portion being glycosaminoglycans (GAGs) (Timpl 1989; Carmen et al. 2019; Ariga et al. 2010; Wang and Ding 2014; Castillo et al. 1997; Snow et al. 1995; Smith et al. 2015; Hayes and Melrose 2018; Volpi 2006).

GAGs are a family of unbranched polysaccharides, including a repeating disaccharide unit (Fig. 9.1). The disaccharide unit usually contains an amino sugar (*N*-acetylglucosamine [GlcNAc] or *N*-acetylgalactosamine) (GalNAc) along with an uronic sugar (glucuronic acid [GlcA] or iduronic acid [IdoA]) or galactose (Gal)

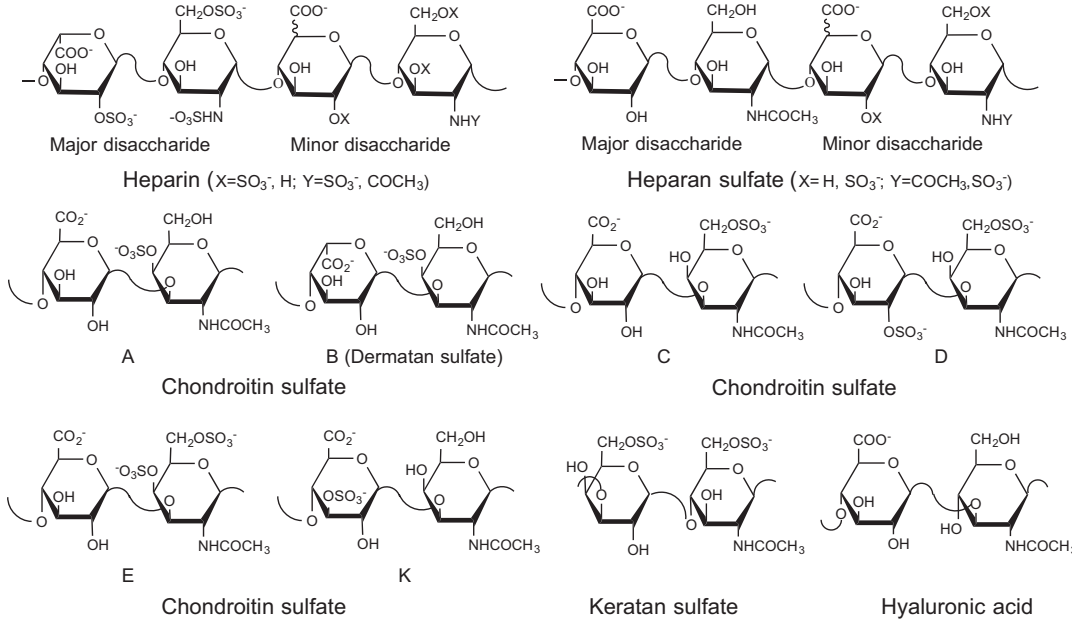

Fig. 9.1 Chemical structures of various glycosaminoglycans

(Constantopoulos and Dekaban 1975). The differences among GAGs were attributed to the type of monosaccharides, glycosidic linkage, and sulfation position and level. In this chapter, we present the importance of GAGs in the occurrence, development, and treatment of NDDs, particularly in AD.

9.2 Heparan Sulfate in Neurodegenerative Diseases

Cell surface heparan sulfate proteoglycans (HSPGs) act as coreceptors for an extensive and structurally diverse range of extrinsic effector proteins and many of these regulatory signals in the microenvironment of cells converge on HSPGs (Gallagher 2015; Celesia 1991; Cui et al. 2013; Fukuchi et al. 1998; Leonova and Galzitskaia 2015; Mahley 1996; O'Callaghan et al. 2018; van Horssen et al. 2003; Zhang et al. 2014). Heparan sulfate (HS) is the carbohydrate or GAG component of HSPGs. HS is synthesized in the Golgi. HS is comprised of an uronic acid (GlcA or IdoA) and a glucosamine (GlcN) residue (Fig. 9.1). Sulfate substitution is found on the amine group and at different hydroxyl groups, providing a variety of different disaccharide units in HS. The structural variation in HS is attributed to a variety of sulfotransferases and C5 epimerase (Li and Kusche-Gullberg 2016; Xu et al. 2011; Peterson et al. 2009; Presto et al. 2008; Kero et al. 2018; Li et al. 2003; Bullock et al. 1998). Glycosyl transferases (or polysaccharide syntheses) control the length of an HS chain and sulfotransferases control the sulfate patterns of saccharide residues and C5 epimerase converts GlcA into IdoA.

Each particular cell type or tissue shows the specific expression of HS metabolic machinery, leading to different sulfate signatures that can vary as a consequence of aging, tissue injury, or disease (Maiza et al. 2018). These changes in composition and sequence impact the interaction between HS and numerous proteins or peptides that are known as heparan sulfate binding proteins (HSBP) (Li and Kusche-Gullberg 2016; Xu and Esko 2014). In addition, HS can protect HSBP from proteolytic degradation, increasing the bioavailability of amyloidogenic proteins, and also in prompting their aggregation (Maiza et al. 2018; Ancsin 2003; Zhang and Li 2010; Kisilevsky et al. 2007; van Horssen et al. 2003).

Protein aggregation is a process in which misfolded proteins interact together to form well-structured fibrils, leading to the formation of filaments, known as amyloids (Maiza et al. 2018). Accumulation of amyloids in the brain tissue is related to many neurodegenerative diseases, including AD, PD, and HD (Som Chaudhury and Das Mukhopadhyay 2018; Ross and Poirier 2004; Collinge 2016; Peng et al. 2020).

AD is characterized by two major types of brain lesions and involves two main proteins, Aβ and Tau. Aβ forms amyloid plaques by extracellular accumulation while Tau makes neurofibrillary tangles through intraneuronal accumulation (Scheltens et al. 2016).

Snow et al. (1990) first described HS implication in amyloid plaque formation in the brains of AD patients. Many studies have subsequently demonstrated that HS plays a vital role in the aggregation of Aβ peptides (Castillo et al. 1997; Snow et al. 1994; Bame et al. 1997; Cotman et al. 2000; van Horssen et al. 2003; Patey 2006; O'Callaghan et al. 2008; Geneste et al. 2014; Fu et al. 2016; Liu et al. 2016; Nguyen and Rabenstein 2016; Vera et al. 2017; Maiza et al. 2018; Wesen et al. 2018). For example, the overexpression of HS degrading heparanase, decrease the number of Aβ amyloid plaques without altering the production and proportion of Aβ40 and Aβ42 peptides, which are derived from the sequential cleavage of amyloid precursor protein by β- and γ-secretases (Jendresen et al. 2015; Nagai et al. 2007; Schworer et al. 2013; Cheng et al. 2014). Additionally, HS interacts with residues 12–18 (VHHQKLV) in Aβ40 and Aβ42 and also breaks the anionic bridge of Aβ42 between lysine 28 and alanine 42, leading to the acceleration of the aggregation process (Zhang et al. 2014). Moreover, sulfation content and pattern of HS also influence Aβ peptide aggregation. Highly sulfated HS deposits in both Aβ40 and Aβ42 amyloids while under sulfated HS only deposits in Aβ40 amyloid, suggesting that high sulfation content will prompt the aggregation of the Aβ42 peptide in the AD's brains (Maiza et al. 2018). On the aspects of sulfation pattern, it was found that different isoforms of amyloids require an HS with different sulfation patterns to promote the interaction between HS and Aβ. For example, Aβ amyloid fibrils require *N*- and 2-*O*-sulfation while Aβ monomer requires 6-*O*-sulfation (Lindahl et al. 1999). The secondary structure of Aβ peptides is impacted by the degree of polymerization (DP), disaccharide sequences, sulfate content, and sulfation pattern suggesting that HS is involved in the Aβ aggregation process in the AD brain (Maiza et al. 2018).

Unlike Aβ, Tau is a soluble protein, which does not aggregate *in vitro* without the incorporation of polyanionic molecules. An abnormally phosphorylated Tau protein (P-Tau) is found in AD brain. P-Tau deposits inside neurons along with HS forming paired helical filaments and grow into neurofibrillary tangles (NFTs). This suggests that HS is part of the Tau aggregation process and also regulates the P-Tau aggregation process (Snow et al. 1990; Konno et al. 2004; Iqbal et al. 2010). In addition, HSPGs also participate in the spreading of Tau-related proteins (Holmes et al. 2013; Goedert and Spillantini 2017). HS plays a vital role in the process of Tau misfolding, phosphorylation, aggregation, and spreading in the AD brain. This has been a hot research topic in elucidating the role of HS structure on Tau pathology. For example, the 3-*O*-sulfated HS might act as a molecular chaperone for abnormal Tau phosphorylation (Sepulveda-Diaz et al. 2015; Alavi Naini and Soussi-Yanicostas 2018; Thacker et al. 2014; Zhao et al. 2019). In addition, 6-*O*-sulfated heparan sulfate is required for interaction with Tau and also for Tau internalization (Zhao et al. 2017; Rauch et al. 2018). Moreover, it was reported that knockouts of HS extension enzymes (polysaccharide synthases) exostosin 1 (*EXT1*), exostosin 2 (*EXT2*), exostosin 3 (*EXT3*), *N*-deacetylase, *N*-sulfotransferase (*NDST1*), and 6-*O*-sulfotransferase (*HS6ST2*) significantly reduce Tau uptake, suggesting that Tau aggregates display specific interactions with HSPGs that depend on chain length and the position of sulfate groups (Stopschinski et al. 2018; Garcia et al. 2017). HS accumulates with protein deposits not only in AD, but also in other neurodegenerative diseases, which is summarized in Table 9.1.

Table 9.1 Neurodegenerative disease-related GAG-binding proteins

Types	Related proteins	Neurodegenerative diseases	References
GAGs	Aβ	Alzheimer's disease	Dawkins and Small (2014), Castillo et al. (1999), Madine et al. (2009), Genedani et al. (2010), Huynh et al. (2012), Stewart et al. (2016, 2017), Stopschinski et al. (2018), Takase et al. (2016), Timmer et al. (2010), van Horssen et al. (2003)
GAGs	Amyloid protein precursor (APP)	Alzheimer's disease	Small et al. (1994), Hamazaki (1987), Heegaard (1998), Coria et al. (1988), Kalaria et al. (1991), Danielsen et al. (1997), Lazarov and Demars (2012), Nalivaeva and Turner (2013), Castillo et al. (1999)
GAGs	Androgen receptor protein	Kennedy's disease	Rusmini et al. (2016), Hashimura et al. (2005)
–	Ataxin-1	Spinocerebellar Ataxia	Sullivan et al. (2019), Trott and Houenou (2012)
GAGs/ analogues	β, γ-secretase	Neurodegenerative diseases	Sun et al. (2017), Yang et al. (2019), Zhou et al. (2019), Leveugle et al. (1997), Patey et al. (2006, 2008)
GAGs/ analogues	Enzyme: Heparanase, glucuronate transferase	Neurodegenerative diseases	Ariga et al. (2010), Li et al. (2005), Lauri et al. (1999), Kisilevsky et al. (2007)
HS/HP/ CS/DS	Extracellular matrix proteins	Neurodegenerative diseases	Gallagher (2015), Alberts et al. (2015), Gundersen (1987), Rivas et al. (1992), Cescon et al. (2016), Streit et al. (1993), Snow et al. (1996)
HS/HP	Fibroblast growth factor, fibroblast growth factor-2	Neurodegenerative diseases	Woodbury and Ikezu (2014), Zhang et al. (2019), Bellucci et al. (2007)
HS/HP/ CS/DS	Glial cell line-derived neurotrophic factor (GDNF)	Parkinson's disease	Grondin et al. (2019), Gallagher (2015), Djerbal et al. (2017), Sugahara and Kitagawa (2000)
GAGs	Growth factors	Alzheimer's disease	Huynh et al. (2019)
–	Huntingtin protein	Huntington's disease	Koyuncu et al. (2017)
GAGs/ analogues	Lipoproteins: ApoE, ApoB, lipoprotein lipase	Alzheimer's disease	Dong et al. (2001), Arai et al. (1999), Lam et al. (2011), Mahley and Ji (1999), Gonzales et al. (2013), Gordts et al. (2014), Stanford et al. (2009, 2010), Li et al. (2005), Eisenberg et al. (1992), Strittmatter et al. (1993), Corder et al. (1994), Shuvaev and Siest (2000)
CS/DS	Midkine/ pleiotrophin	Neurodegenerative diseases	Deepa et al. (2002), Nandini et al. (2004), Matsumoto et al. (1994), Kadomatsu (2005), Kadomatsu and Muramatsu (2004), Ueoka et al. (2000), Mizumoto et al. (2013), Yasuhara et al. (1993), Solera et al. (2016)
HP	Nardilysin	Alzheimer's disease	Bernstein et al. (2013)
HS/HP	PrP^{Sc}	Prion disease	Ben-Zaken et al. (2003), Warner et al. (2002), Horonchik et al. (2005)
HS/HP	Selenoprotein P	Alzheimer's disease	Solovyev et al. (2018)
KS	Sulfotransferase "GlcNAc6ST1"	Alzheimer's disease	Zhang et al. (2017)
HP	Superoxide dismutase	Amyotrophic lateral sclerosis	Sangwan and Eisenberg (2016), Mizuguchi et al. (2010), Zhao et al. (2014)

(continued)

Table 9.1 (continued)

Types	Related proteins	Neurodegenerative diseases	References
HS/HP	Syndecan-1 and 3	Neurodegenerative diseases	van Horssen et al. (2003), Stanford et al. (2009), Kaksonen et al. (2002)
GAGs/ analogues	α-Synuclein protein	Alzheimer's disease, Parkinson's disease	Cohlberg et al. (2002), Lehri-Boufala et al. (2015), Mehra et al. (2018), Stopschinski et al. (2018), van Horssen et al. (2004), Holmes et al. (2013)
GAGs	Tau protein	Alzheimer's disease, Pick's disease, progressive supranuclear palsy	Alavi Naini and Soussi-Yanicostas (2018), Goedert et al. (1996), Snow et al. (1990), Huynh et al. (2019), Holmes et al. (2013)

9.3 Heparin in Neurodegenerative Diseases

Heparin (HP) (Fig. 9.1) has a high negative charge density (about 3.3 negative charges per disaccharide), especially compared to the related HS (about 0.8 sulfate groups per disaccharide in typical HS) (Weiss et al., 2017). HP is composed of 90% L-IdoA and 10% D-GlcA while HS consists of primarily GlcA (Capila and Linhardt 2002). Moreover, HP has an average molecular weight of about 15 kDa, ranging from 5 to 40 kDa while HS has a 30 kDa average molecular weight, ranging from 5 to 50 kDa. HP has a lower molecular weight, a higher sulfate content, and a higher IdoA content than HS. HS is ubiquitously expressed in all animal cells while HP is produced and stored selectively in the secretory granules of connective-tissue mast cells (Weiss et al. 2017; Guyton and Hall 2006).

HP, an anticoagulant drug, is used as a surrogate for HS in most research (Xu and Esko 2014) because HP is commercially available in ton quantities while HS is only available in gram quantities. Moreover, the higher sulfation level in HP results in its tight binding to HSBPs. Currently, HP has been reported to bind to more than 300 secreted and membrane associated human proteins and, in most cases, the natural ligand is HS (Xu and Esko 2014; Ori et al. 2011). These HSBPs can be divided into several major categories, chemokines and cytokines (~60), growth factors and morphogens in development and tissue repair (~50), blood coagulation factors (~25), extracellular structural proteins (~25), complement proteins (~20), single-transmembrane signaling receptor (~15), cell adhesion proteins (~10), and other proteins (5–10), such as proteins in intracellular granules, lipid-binding proteins, and "helper proteins" (Xu and Esko 2014). These HSBPs play key roles in NDDs (summarized in Table 9.1). There are many excellent reviews (Alavi Naini and Soussi-Yanicostas 2018; Muramatsu 1993; Stutzmann et al. 2002; Ma et al. 2007; Dudas et al. 2008; Bergamaschini et al. 2009; Ariga et al. 2010; Dudas and Semeniken 2012; Szczubialka et al. 2012; Wang and Ding 2014; Woodbury and Ikezu 2014; Lima et al. 2017) on HP or HS and NDDs.

9.4 Chondroitin Sulfate and Dermatan Sulfate in Neurodegenerative Diseases

Chondroitin sulfate (CS) was first found from cartilage by Fisher and Boedecker in 1861, isolated in purer form by Krukenburg in 1884, elucidated the full structure of CS by Levene and Forge until 1915 (Djerbal et al. 2017). The different forms are attributed to sulfation pattern and epimerization pattern, which divided CS into six forms (Fig. 9.1), namely chondroitin-4-sulfate (CS-A), chondroitin-6-sulfate (CS-C), chondroitin-2,6-sulfate (CS-D), chondroitin-4,6-sulfate (CS-E), chondroitin-3-sulfate (CS-K), and chondroitin sulfate B (CS-B), which is the product of uronic acid epimerization and also named dermatan sulfate (DS).

CS is found in the ECM, at the cell surface, associated with the plasma membrane in most

animal tissues, and also, in the case of CS-E, in the intracellular granules of certain cells like mast cells (Yamada et al. 2011; Stevens et al. 1988; Thompson et al. 1988; Farrugia et al. 2016). The expression of CS is different in different tissues and the highest level is found in the ECM in cartilage and in the central nervous system (Djerbal et al. 2017). CS is synthesized in the Golgi. Like HS, CS is also linked to the "core proteins" to form chondroitin sulfate proteoglycans (CSPGs) in the ECM and at the cell surface, and are involved in the formation, development, and maintenance of brain morphology and function (Djerbal et al. 2017; Egea et al. 2010; Kastana et al., 2019; Khan et al. 2020; Kwok et al., 2008; Maeda et al. 2010; Malavaki et al. 2008; Malmstrom et al. 2012; Mikami and Kitagawa 2013, 2015; Purushothaman et al. 2012; Rani et al. 2018; Rauvala et al. 2017; Avram et al. 2014; Carulli et al. 2005; Maeda 2010; Oohira et al. 2004; Sugahara and Mikami 2007). The ratio of CS to HS in the central nervous system (CNS) is 9:1 while it is 7:3 in the perineuronal net (PNN) matrix. There are many proteins that interact with various forms of CS (depending on the different sulfate content, pattern, and uronic acid epimerization) to accomplish their functions in promoting growth, differentiation, guidance, and plasticity. These proteins can be divided into several categories (Djerbal et al. 2017), growth factors (neurotrophic factors, FGF, and Midkine and pleiotrophin), receptors (receptor protein tyrosine phosphatases and Nogo receptors NgR1 and NgR3), cell adhesion molecules, guidance proteins (semaphoring), extracellular matrix proteins (collagen VI, laminin and fibronectin), and pathological protein (amyloid precursor protein). These CS binding proteins and their functions in the NDDs are summarized in Table 9.1.

9.5 Hyaluronic Acid in Neurodegenerative Diseases

Hyaluronic acid (HA) was firstly discovered by Meyer and John Palmer in 1934 from vitreous body in cow's eye. As the simplest structure among GAGs, HA is composed of GlcA and GlcNAc (Fig. 9.1) with a molecular weight range from 5000 to 20 million Da (Carmen et al. 2019; Toole 2004). HA is synthesized on the cell membrane without any modification by a class of integral membrane proteins, named hyaluronan synthases (HAS1, HAS2, and HAS3) (Toole 2004). More than half of HA is localized in the skin, about 25% is in the skeleton and supporting structures and less than 10% is in the skeletal muscle (Reed et al. 1988).

The sulfate moiety is necessary for the formation of amyloid fibrils, as confirmed the lack of fibril formation in the presence of HA (Ariga et al. 2010) and it is suggested that HA might inhibit the fibril formation and be useful for treating AD. There is a positive correlation between HA accumulation and AD neuropathology, suggesting that HA synthesis and metabolism play a role in AD (Reed et al. 2019). More specifically, HA reduces Aβ42 oligomer uptake and supports neuron cell survival (Bejoy et al. 2018). During the progression of AD, the abolishing of axonal-localization of HAS1 and an increased expression of HAS3 results in the upregulation of short-chain HA production and the reorganization of the ECM, providing biochemical and physical support to aggrecan-based perineuronal nets and regulation of neuronal plasticity (Li et al. 2017).

9.6 Keratan Sulfate in Neurodegenerative Diseases

Keratan sulfate (KS) was first isolated from the cornea and is found in brain, skeletal, and nervous tissues (Meyer et al. 1953; Funderburgh 2000; Kleene and Schachner 2004; Lindahl et al. 1996). KS consists of disaccharide unit [Gal and GlcNAc], sulfated at C6 of both Gal and GlcNAc residues (Fig. 9.1). KS is covalently attached to a "core protein" through its reducing end in both an *O*-linkage to *N*-acetylated galactosamine (GalNAc) or *N*-linkage Fuc-Man-GlcNAc-linked oligosaccharides and can be terminated with a sialic acid residue or a Gal or GalNAc at the non-

reducing end of KS (Funderburgh 2000). KS is synthesized by Golgi-resident enzymes, such as galactosyltransferase, *N*-acetylglucosaminyl transferase, and Gal/GlcNAc/GalNAc sulfotransferases (Uchimura and Rosen 2006; Christner et al. 1979; Funderburgh 2000). KS plays an indispensable, suppressive role in ALS pathology progression by microglial activation and proliferation, suggesting that KS might be a new target for the treatment of ALS (Foyez et al. 2015; Hirano et al. 2013). Deficiency of a sulfotransferase "GlcNAc6ST1" synthesizing sialylated KS can modulate AD pathology, suggesting that GlcNAc6ST1 also might be a good target (Zhang et al. 2017).

9.7 Glycosaminoglycans and Their Analogues in Neurodegenerative Diseases

Aβ is an important target for treating AD. Although Aβ self-aggregates to form amyloid fibrils in vitro, amyloid aggregation and fibril formation can be enhanced in the presence of PGs or GAGs (Castillo et al. 1998, 1999). Their binding sites in Aβ at the 13–16 amino acid region (His-His-Gln-Lys), particular of His 13, are important for the interaction between GAGs with Aβ (Ariga et al., 2010). The sequence of the effectiveness of GAGs on prompting fibril formation is HP > HS > CS = DS. In HP the sequence of the effectiveness based on sulfate content and position is HP > *N*-desulfated *N*-acetylated HP > completely desulfated *N*-desulfated HP > completely desulfated *N*-acetylated HP (Castillo et al. 1998, 1999). Fibril formation can be inhibited by low molecular weight heparin (LMWH, MW 4000–6000), suggesting that GAG analogs might be used in inhibiting fibril formation. Research on NDDs have examined "neuroparin," a low molecular weight GAG (Ma et al. 2003; Dudas et al. 2008), a specific disaccharide (CSPG-DS) (Rolls et al. 2004), and HP oligosaccharides (Ariga et al. 2010). There are also some Aβ related targets, including ApoE and β-secretase (Shuvaev and Siest 2000; Leveugle et al. 1997; Patey et al. 2006, 2008). There are also some GAG analogs, such pentosan polysulfate, that have been used to target Aβ (Ariga et al. 2010).

Tau is also an important target for treating AD. Unlike Aβ, Tau needs polyanionic molecules to aggregate. In addition, Tau phosphorylation plays an important role in AD progression. Therefore, Tau is an important target for curing AD. In terms of GAGs and their analogs that influence Tau phosphorylation by the proline-directed protein kinases NCLK, GSK3β and MAP kinase, HP, dextran sulfate, pentosan polysulfate, and HS show efficacy, while KS, HA, and dextran and poly-L-glutamic acid are ineffective. It is interesting to note that CS and DS had intermediate effects when Tau was phosphorylated by NCLK and GSK3β, but no effect when Tau was modified by MAP kinase (Hasegawa et al. 1997). There are a number of reviews on the GAGs analogs and their biological activities (Mende et al. 2016; Morla 2019; Zhang et al. 2020; Fraser et al. 2001; Arlov and Skjak-Braek 2017; Coombe and Kett 2012).

9.8 Conclusion

This chapter described the importance of GAGs in NDDs. The data presented probably underrepresents the significance of GAGs, as GAGs interact with many proteins. In addition, there are many GAGs attached to a variety of core proteins. These core proteins can also exhibit important roles in the progression of NDDs. There is still much to uncover about the role of GAGs in NDDs. The development of effective compounds to target the interactions of GAGs for the treatment of NDDs still represents a formidable challenge.

Compliance with Ethical Standards

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