



HAL
open science

ADAMTS proteoglycanases in the physiological and pathological central nervous system.

Sighild Lemarchant, Mathilde Pruvost, Joan Montaner, Evelyne Emery, Denis Vivien, Katja Kanninen, Jari Koistinaho

► To cite this version:

Sighild Lemarchant, Mathilde Pruvost, Joan Montaner, Evelyne Emery, Denis Vivien, et al.. ADAMTS proteoglycanases in the physiological and pathological central nervous system.. *Journal of Neuroinflammation*, 2013, 10 (1), pp.133. 10.1186/1742-2094-10-133 . inserm-00903345

HAL Id: inserm-00903345

<https://inserm.hal.science/inserm-00903345>

Submitted on 12 Nov 2013

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

REVIEW

Open Access

ADAMTS proteoglycanases in the physiological and pathological central nervous system

Sighild Lemarchant^{1*}, Mathilde Pruvost², Joan Montaner³, Evelyne Emery^{2,4}, Denis Vivien², Katja Kanninen¹ and Jari Koistinaho^{1,5}

Abstract

ADAMTS-1, -4, -5 and -9 belong to 'a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)' family and more precisely to the proteoglycanases subgroup based on their common ability to degrade chondroitin sulfate proteoglycans. They have been extensively investigated for their involvement in inflammation-induced osteoarthritis, and a growing body of evidence indicates that they may be of key importance in the physiological and pathological central nervous system (CNS). In this review, we discuss the deregulated expression of ADAMTS proteoglycanases during acute CNS injuries, such as stroke and spinal cord injury. Then, we provide new insights on ADAMTS proteoglycanases mediating synaptic plasticity, neurorepair, angiogenesis and inflammation mechanisms. Altogether, this review allows us to propose that ADAMTS proteoglycanases may be original therapeutic targets for CNS injuries.

Keywords: A disintegrin and metalloproteinase with thrombospondin motifs, Proteoglycanases, Stroke, Spinal cord injury, Chondroitin sulfate proteoglycan, Synaptic plasticity, Inflammation, Angiogenesis, Neurorepair

Introduction

The ADAMTS proteases belong to 'a disintegrin and metalloproteinase with thrombospondin motifs' family, composed of 19 members. They are multi-domain proteins synthesized as pre-pro-enzymes containing from the N- to the C-terminal end: a peptide signal, a pro-domain, a zinc binding metalloproteinase domain, a disintegrin-like domain, a thrombospondin domain, a cysteine-rich domain, a spacer domain and finally a variable number of thrombospondin motifs in the C-terminal end [1,2]. Pre-pro-ADAMTS proteases can be cleaved by furin or furin-like proteases at the N- and C-terminal positions triggering, respectively, their activity and their future location within the extracellular matrix (ECM) via the removal of the pro-domain, and their substrate specificity [3-11]. When secreted, ADAMTS proteases are capable of binding ECM components via their thrombospondin motifs [3], which can be then cleaved by the metalloproteinase domain. ADAMTS proteases are classified in three subfamilies

based on their preference to cleave specific ECM macromolecules as follows [12-14]: proteoglycans (ADAMTS-1, -4, -5, -8, -9, -15 and -20), pro-collagens (ADAMTS-2, -3 and -14) or the von Willebrand factor (ADAMTS-13). This review will focus on the ADAMTS proteoglycanases present in the central nervous system (CNS), with special emphasis on ADAMTS-1, -4, -5 and -9, which are key enzymes in the degradation of the aggregating chondroitin sulfate proteoglycans (CSPGs) [14].

CSPGs are a family of ECM macromolecules characterized by a core protein and a variable number of glycosaminoglycan chains. The major CSPGs found in the CNS are lecticans (for example, aggrecan, brevican, neurocan and versican), phosphocan and type 2 neuroglycan. They are concentrated into perineuronal nets (PNNs) that enwrap a subset of neurons and control the path finding and guidance of axons during CNS development. After CNS injury, CSPGs are rapidly upregulated within the glial scar and exert both beneficial and deleterious effects. For instance, their contribution to the establishment of a dense glial scar initially constitutes a protective barrier to limit the propagation of damage, but also represents a harmful barrier to subsequent neurorepair and neuroplasticity [15].

* Correspondence: sighild.lemarchant@uef.fi

¹Department of Neurobiology, A. I. Virtanen Institute for Molecular Sciences, Biocenter Kuopio, University of Eastern Finland, P.O. Box 1627, 70211 Kuopio, Finland

Full list of author information is available at the end of the article

While ADAMTS proteoglycanases have been extensively described for their deleterious effect in osteoarthritis, rheumatoid arthritis and vertebral disc degeneration, it is only recently that their role in the CNS has been discussed. Therefore, in this review we will provide up-to-date information about the increasing evidence for the involvement of ADAMTS proteoglycanases in physiological conditions and CNS pathological disease states including ischemic stroke and spinal cord injury (SCI).

ADAMTS proteoglycanases in the physiological central nervous system

ADAMTS proteoglycanases are present in several CNS structures, including the cortex, the hippocampus, the striatum and the spinal cord [16-21]. While it is clear that astrocytes express ADAMTS proteoglycanases *in vitro* and *in vivo* [22-25], their presence in neurons under physiological conditions is controversial. ADAMTS-4 was identified in dentate granule neurons and pyramidal cells by *in situ* hybridization in rat brains [16]. Similarly, the expression of ADAMTS-4 was described in cortical neurons *in vitro* [25], but a more recent investigation failed to detect ADAMTS-4 in cerebellar granule neurons *in vitro* [24]. The presence of ADAMTS-4 has also been reported in cortical microglia *in vitro* [24,25] (Table 1).

In the physiological CNS, evidence exists for a role of ADAMTS proteoglycanases in neural plasticity *in vitro* and *in vivo*. Yuan and collaborators were the first to discover evidence of the presence of ADAMTS-1, -4 and ADAMTS-cleaved brevican fragments in the physiological CNS in rats, particularly in plastic regions such as the hippocampus, suggesting the involvement of the ADAMTS proteoglycanases in the malleability of PNNs-containing brevican [16]. Hamel and collaborators (2008) discovered that a recombinant active ADAMTS-4 promoted neurite growth of cortical neurons *in vitro* i) by degrading CSPGs via its proteolytic activity, and ii) by activating the MAP/ERK (mitogen activated protein/extracellular signal-regulated kinase) signaling pathway, presumably due to the activation of tyrosin kinase receptors by the thrombospondin domain of ADAMTS-4 [26]. However, the concept of CSPGs/ADAMTS proteoglycanases working in concert to regulate plasticity has been explored only recently *in vivo* [19]. Interestingly, the expression of synaptic proteins, such as synaptosomal-associated protein 25 (SNAP-25), postsynaptic density protein 95 (PSD-95) and synaptophysin, was decreased in the developing frontal cortex of ADAMTS-1 deficient female mice, but not in male mice, suggesting a gender-specific involvement of ADAMTS-1 in synaptic plasticity. However, the decline in expression of synaptic proteins was not accompanied by any modifications of CSPGs present in PNNs, or by deficits of learning and memory [19]. Recently, Krstic and collaborators (2012) proposed

ADAMTS-4 and ADAMTS-5 as proteases capable of cleaving Reelin, an extracellular molecule also involved in neurodevelopment and in synaptic plasticity induced learning and memory processes [20]. Interestingly, ADAMTS-induced cleavage of Reelin is thought to partly promote its aggregation during aging, and to participate in the well-known synaptic plasticity defects in elderly CNS tissues [20].

To summarize, ADAMTS proteoglycanases in the physiological CNS are synthesized mainly by astrocytes and expressed in several CNS structures. Interestingly, increasing evidence suggests that they may play critical roles in the control of synaptic plasticity during development and aging via both proteolytic-dependent and -independent mechanisms.

ADAMTS proteoglycanases in the pathological central nervous system

Proteolysis of the ECM can be both beneficial and harmful in several pathological states of the CNS, including ischemic stroke and SCI [27]. A tight control of the local environment is crucial to ensure a moderate remodeling of the ECM in order to promote neuronal plasticity and survival, or vascular remodeling, after acute CNS injuries. While the expression and associated beneficial or deleterious effects of matrix metalloproteinases (MMPs) have been extensively reported in several CNS diseases, recent publications strongly suggest that the ADAMTS proteoglycanases may also be important in ECM proteolysis in CNS injuries.

ADAMTS proteoglycanases: cytokine- and cell-specific inducible proteases

Several cytokines, including IL-1 β (interleukin-1 β), IL-6, IFN- γ (γ -interferon), TGF- β (transforming growth factor- β) and TNF- α (tumor necrosis factor- α), have previously been described to regulate the expression of ADAMTS proteoglycanases in non-CNS cell types [28-31]. The cytokine-rich environment following CNS injuries is therefore likely to induce the expression of a complex pattern of ADAMTS proteoglycanases in a cell- and cytokine-dependent manner. An increased synthesis of ADAMTS-4, -5 and -9 by astrocytes was reported after transient middle cerebral artery occlusion (tMCAO) [32,33]. Similarly, injured neurons were described to synthesize ADAMTS-9 after tMCAO [32], but not after contusion-induced SCI [34]. Interestingly, ADAMTS-1 was also specifically up-regulated in cerebral motor neurons after peripheral nerve injury [35]. Few cytokines have been already proposed to regulate ADAMTS proteoglycanases expression in the CNS (Table 1). IL-1 α in combination with IL-1 receptor type 1 promotes ADAMTS-1 transcription in a N1E-115 neuroblast cell line *in vitro* and in motoneurons after nerve injury *in vivo* [35]. ADAMTS-4 mRNA and protein

Table 1 Cellular expression of ADAMTS proteoglycanases in the physiological and pathological central nervous system

Cell type		ADAMTS-1	ADAMTS-4	ADAMTS-5	ADAMTS-9
Astrocytes	<i>In vitro</i> : Primary cerebral cultures (mouse) [34] Primary cortical cultures (rat) [24,25] Primary cerebral cultures (human) [23]: - TNF- α treatment - IL1- β treatment	Yes (mRNA)	Yes (mRNA)	Yes (mRNA)	Yes (mRNA)
			Yes (mRNA/WB)		
		Yes (mRNA/WB/ICC)	Yes (mRNA/WB/ICC)	Yes (mRNA/WB/ICC)	
		\uparrow mRNA stable protein	\uparrow mRNA \uparrow protein	stable mRNA stable protein	
		stable mRNA	stable mRNA	stable mRNA	
	<i>In vivo</i> : Brain white matter (human) [22] Spinal cord white matter (rat) [21] Injured brain, tMCAO (mouse) [33] Injured cerebral cortex, tMCAO (rat) [32] Injured spinal cord, SCI by contusion (mouse) [34]	Yes (IHC)	Yes (IHC)	Yes (IHC)	
		Yes (IHC)	Yes (IHC)	Yes (IHC)	
			Yes (mRNA)	Yes (mRNA)	
		Yes (IHC)		Yes (IHC)	Yes (mRNA) Yes (IHC)
	Neurons	<i>In vitro</i> : Primary cortical cultures (rat) [25] Primary cerebellar granule neurons cultures (rat) [24]		Yes (WB)	
			No (mRNA)		
<i>In vivo</i> : Hippocampus, dentate granule neurons and pyramidal neurons (rat) [16]: - Physiological conditions - Kainate-induced CNS excitotoxicity Injured cerebral cortex, tMCAO (rat) [32] Injured spinal cord, SCI by contusion (mouse) [34]		No (mRNA)	Yes (mRNA)		
		Yes (mRNA)	Yes (mRNA)		
					Yes (mRNA) No (IHC)
Microglia		<i>In vitro</i> : Primary cerebral/cortical cultures (rat) [24,25]		Yes (mRNA/WB)	
Monocytes / Macrophages	<i>In vitro</i> : THP-1 monocyte cell line (human) [36,37] THP-1-derived macrophages (human) [36,37]: - TGF- β treatment [36,38] - IFN- γ treatment [36,37] - TNF- α treatment [37] - IL1- β treatment [37]	Yes (mRNA) Yes (mRNA) \uparrow mRNA \downarrow mRNA slight \uparrow mRNA	Yes (mRNA/WB) Yes (mRNA/WB) \uparrow mRNA/ \downarrow mRNA stable/ \uparrow mRNA \uparrow mRNA stable mRNA	Yes (mRNA) Yes (mRNA) \uparrow mRNA stable mRNA slight \uparrow mRNA slight \uparrow mRNA	Yes (mRNA) Yes (mRNA) \uparrow mRNA \uparrow mRNA slight \uparrow mRNA slight \uparrow mRNA

This table depicts the various cell types expressing the major ADAMTS proteoglycanases (ADAMTS-1, -4, -5 and -9) *in vitro* and/or *in vivo* under physiological and/or pathological CNS conditions. It also indicates if ADAMTS proteoglycanases were detected at the mRNA level or at the protein level (WB, ICC, IHC). Numbers indicate the concerned references. ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; CNS, central nervous system; ICC/IHC, Immunocyto/histochemistry; IFN- γ , γ -interferon; IL-1 β , interleukin-1 β ; SCI, spinal cord injury; TGF- β , transforming growth factor- β ; tMCAO, transient middle cerebral artery occlusion; TNF- α , tumor necrosis factor- α ; WB, western blot.

expressions were increased by TNF- α in human astrocyte cultures after 24 hours of treatment, while only upregulation of ADAMTS-1 mRNA or ADAMTS-5 protein levels were reported. Under similar conditions, IL-1 β did not regulate the transcription of ADAMTS proteoglycanases, although it seems that there is a trend for an increased mRNA expression of ADAMTS-4 [23]. Beyond astrocytes, microglia and neurons, macrophages that infiltrate brain or spinal cord after injury may also be an important source of ADAMTS-1, -4 and -5 [36,37]. Interestingly, while TNF- α and IFN- γ increase the expression of ADAMTS-4 in macrophages induced by differentiation of human monocytic cell line THP1 [37], TGF- β negatively

regulates ADAMTS-4 expression through the MAPK and the Smad-2 and -3 signaling pathways [36]. In similar conditions, it was also described that TGF- β can increase the synthesis of ADAMTS-4 [38].

Accordingly, modification of ADAMTS proteoglycanases expression has been reported after CNS injuries including stroke and SCI (Table 2). Yuan and collaborators were first to discover evidence of the increase of ADAMTS-1, -4 and ADAMTS-cleaved brevican fragments after intraperitoneal injection of kainate-induced CNS excitotoxicity, in the cortex and in the hippocampus, by pyramidal neurons and dentate granule neurons [16]. After tMCAO, the expression of ADAMTS-1, -4, and -9

Table 2 Deregulated expression of ADAMTS proteoglycanases after central nervous system injuries

	STROKE		SCI	
	tMCAO model		Contusion model	
	Early stage ^a	Late stage ^b	Early stage ^c	Late stage ^d
ADAMTS-1				
<i>mRNA level</i>	↑ (rat) [23]	stable (rat) [23]	↑ (mouse) [34]	
<i>Protein level</i>	stable (rat) [23]	↑ (rat) [23]		
ADAMTS-4				
<i>mRNA level</i>	↑ (rat/mouse) [23,33]	stable (rat) [23]	stable (mouse) [34]	
<i>Protein level</i>	stable (rat) [23]	↑ (rat) [23]		slight ↑ (rat) [24]
<i>Activity</i>				↑ (rat) [24]
ADAMTS-5				
<i>mRNA level</i>	↑ (mouse) [33]	slight ↑ (rat) [23]	↑ (mouse) [34]	
<i>Protein level</i>				
ADAMTS-9				
<i>mRNA level</i>	↑ (rat) [32]		↑ (mouse) [34]	
<i>Protein level</i>	↑ (rat) [32]	not detected (rat) [32]		

This table depicts the expression and/or activity of the major ADAMTS proteoglycanases (ADAMTS-1, -4, -5 and -9) in the time course of CNS injuries, including ischemic stroke (tMCAO model) and spinal cord injury (contusion model). ^a6 to 24 h, ^b5 to 7d after stroke onset; ^c3 to 24 h, ^d7d after SCI onset. Numbers indicate the concerned references. ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; CNS, central nervous system; SCI, spinal cord injury; tMCAO, transient middle cerebral artery occlusion.

is upregulated [23,32]. Surprisingly, whereas mRNA changes were observed in the ipsilateral hemisphere acutely at 6 and 24 hours after stroke onset, the upregulation of the protein levels of ADAMTS-1 and -4 was only observed 5 days after injury. Because TNF- α was shown to promote ADAMTS-1 and -4 mRNA levels as well as ADAMTS-4 and -5 protein levels in human astrocyte cultures, it was hypothesized that the increase of TNF- α expression in the acute phase of stroke may be responsible for the upregulation of ADAMTS-1 and -4 by astrocytes [23]. Surprisingly, it is only recently that the upregulation of ADAMTS-4 and -5 mRNA levels were detected in astrocytes after tMCAO in mice 24 hours after stroke onset [33]. The expression of ADAMTS-9 was increased in the acute phase of stroke within 24 hours post occlusion at both the mRNA and protein levels, but rather than astrocytes, neurons were predominantly affected in both contralateral and ipsilateral hemispheres [32]. Similarly, upregulation of ADAMTS-1, -5 and -9 mRNA levels were reported in the acute phase of contusion-induced SCI in mice, whereas no changes to ADAMTS-4 expression were observed [34]. Tauchi and colleagues (2012) detected a slight increase of ADAMTS-4 protein levels associated with a significant increase in ADAMTS-4 enzymatic activity in spinal cord lysates from the lesion site one week after contusion-induced SCI in rats [24]. Demircan and colleagues (2013) also described the astrocytes as being a main source of ADAMTS-1, -5 and -9 in the spinal cord after SCI.

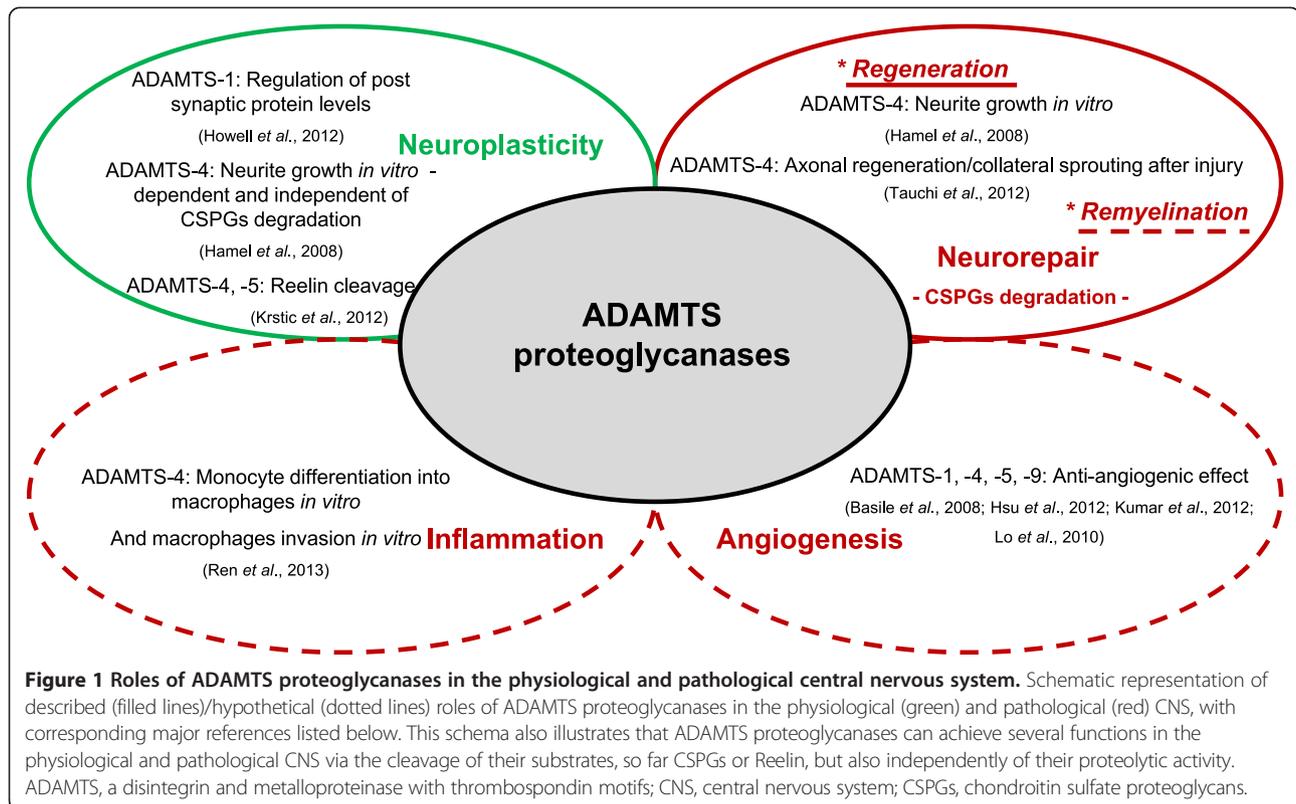
However, they did not observe the presence of ADAMTS-9 in neurons after SCI [34].

To summarize, CNS injuries including ischemic stroke or SCI lead to the upregulation of different combinations of ADAMTS proteoglycanases, respectively ADAMTS-1, -4, -9 and ADAMTS-1, -5, -9 (Table 2). A cytokine regulation and/or cell-specific expression of ADAMTS proteoglycanases expression strongly suggest that each of them may be associated to a specific local turnover of CSPGs, assuming that they have non-redundant and cooperative functions in the CNS. Several clues indicate that ADAMTS proteoglycanases may have both beneficial and deleterious effects after CNS injuries as described hereafter and summarized in Figure 1.

ADAMTS proteoglycanases: inflammatory and anti-angiogenic proteases in the central nervous system? ADAMTS proteoglycanases and macrophage infiltration

A growing body of evidence suggests that ADAMTS proteoglycanases may be involved in the neuroinflammatory response after CNS injury by promoting the infiltration of macrophages into the CNS:

1. ADAMTS-4 is increased during the differentiation of human monocytes into macrophages *in vitro* [37] and is required for macrophages invasion *in vitro* [38].
2. Versican is the primary CSPG present in the vasculature and is a potent substrate for ADAMTS proteoglycanases [39], which begs the question of



whether upregulation of the ADAMTS proteoglycanases at the neurovascular unit may participate in the leakage of the blood brain/spinal cord barrier after ischemic stroke or SCI. It would be consistent with local degradation of versican by ADAMTS proteoglycanases synthesized by endothelial cells [40-42] and/or monocytes/macrophages [36].

Altogether, it can be hypothesized that ADAMTS proteoglycanases, particularly ADAMTS-4, may be a key player of the macrophage infiltration into the CNS after injury either directly or indirectly by promoting the leakage of the blood brain/spinal cord barrier.

ADAMTS proteoglycanases and angiogenesis

The involvement of ADAMTS proteases has been largely investigated in angiogenesis mechanisms occurring in cancer, yet similar mechanisms may also occur in the CNS. Both proteinase-dependent and independent anti-angiogenic functions for most of the ADAMTS proteases, including proteoglycanases, have been described [42-45]. For instance, it has been proposed that ADAMTS proteoglycanases can negatively regulate angiogenesis via the sequestration of the most potent pro-angiogenic factor, VEGF (vascular endothelial growth factor) or via the release of anti-angiogenic fragments derived from thrombospondin type 1 and 2 motifs. Besides its pro-angiogenic

effect, VEGF has also been shown to promote vascular permeability, neuroinflammation, neuritic growth and neuroprotection particularly after ischemic stroke or SCI [46]. Therefore, it is possible to hypothesize that the sequestration of VEGF by endogenous ADAMTS proteoglycanases may have both protective and harmful effects in the CNS. To conclude, the effect of ADAMTS proteoglycanases in angiogenesis processes after acute CNS injuries remains largely unknown and deserves further investigation.

ADAMTS proteoglycanases and neurorepair

Neurorepair including neuroregeneration and remyelination is compromised in the chronic phase of stroke or SCI partly because of an overexpression of CSPGs [47,48]. In parallel with the upregulation of CSPGs within the glial scar, ischemic stroke is also associated with degradation of PNNs containing CSPGs at the lesion site, but also in the peri-ischemic area and the contralateral hemisphere after permanent MCAO. Although the degradation of the PNNs occurred predominantly in the lesion core and was associated with the invasion of monocytes/macrophages, the transient reduction of neurons containing PNNs in the peri-ischemic area or the contralateral hemisphere is more likely associated with an attempt at neurorepair [49]. It is tempting to hypothesize that after CNS injuries, the loss of PNNs may be caused by increased local secretion

of neuronal ADAMTS proteoglycanases (as described for ADAMTS-1 and ADAMTS-9) triggering adverse effects: neuroinflammation in the lesion core and an attempt at neuroplasticity in surrounding tissues. However, these attempts at axonal regeneration/collateral sprouting are too transient and/or unsuccessful to efficiently penetrate the repellent CSPGs-rich glial scar and to improve long term functional recovery.

The inhibition of CSPGs can be relieved by the bacterial enzyme chondroitinase ABC which removes the chondroitin sulfate chains from the core proteins, thus promoting axonal regeneration/collateral sprouting of a wide variety of neuron tracts and functional recovery after stroke or SCI [49-57]. However, the core proteins remain intact and can still inhibit neuroregeneration/remyelination. ADAMTS proteoglycanases are physiological enzymes capable of achieving the complete degradation of CSPGs [1,2]. Surprisingly, evidence that ADAMTS proteoglycanases may improve neurite growth and axonal regeneration/collateral sprouting has recently emerged:

1. Hamel and collaborators (2008) reported that a recombinant active ADAMTS-4 can promote neurite growth of cortical neurons *in vitro* dependently or independently of its proteolytic activity as described above [26].
2. Cua and collaborators (2013) reported that ADAMTS-4 was more efficient at degrading CSPGs and inducing subsequent neurite growth *in vitro* than chondroitinase ABC or MMPs [58].
3. The treatment of mice submitted to contusion-induced SCI with recombinant ADAMTS-4 improves axonal regeneration/collateral sprouting of serotonergic fibers and subsequent functional recovery via the degradation of neurocan [24].

In addition to the inhibition of axonal regeneration/collateral sprouting in CNS injuries, CSPGs are also strongly upregulated within the white matter where they contribute to the inhibition of remyelination of injured axons. Interestingly, chondroitinase ABC can prevent CSPGs-inhibition of remyelination *in vitro* and *in vivo* after contusion-induced SCI in rats and in a lysolecithin-induced demyelination model in mice [47,48,59]. Moreover, olfactory ensheathing cell-based therapies promote remyelination after acute injuries [60] and these cells were recently reported to express ADAMTS-4 [61,62]. This raises the question of whether ADAMTS-4 or any ADAMTS proteoglycanases could improve remyelination of injured axons more efficiently than chondroitinase ABC does.

To conclude, the overexpression of ADAMTS proteoglycanases induced by acute CNS injuries such as stroke or SCI seems harmful in the acute phase through enhancing neuroinflammation, and beneficial (or at least safe)

in later phases to initiate neurorepair (Figure 1). A combination approach may represent an attractive therapeutic opportunity: first, the administration of an inhibitor of ADAMTS proteoglycanases activity, such as TIMP-3 (tissue inhibitor of metalloproteinases-3) [63], or an inhibitor of their synthesis, such as the anti-inflammatory compound WIN-34B [29], in the acute phase of CNS injuries to overcome ADAMTS-induced macrophage infiltration; then, the administration of active ADAMTS proteoglycanases in the chronic phase of CNS injuries to enhance neuroregeneration/neuroplasticity/remyelination, by using already commercially available recombinant proteins, or by using lentiviral gene therapy approach in cell transplantation-based therapies. However, the administration of any therapeutic molecule to treat CNS disorders is challenging; in addition to finding the most appropriate timing, their passage across the blood brain/spinal cord barrier can also be problematic [64]. However, nasal delivery of therapeutic molecules to the brain allows them to bypass the barrier and represents a safe and convenient system for pre-clinical and clinical studies [65].

Conclusions

Exciting evidence for the involvement of ADAMTS proteoglycanases in the CNS in mechanisms governing synaptic plasticity during development and aging has been proposed quite recently and has emphasized the proteolytic-dependent and -independent actions of these ADAMTS proteoglycanases. However, more research is required to determine whether ADAMTS proteoglycanases have redundant spatiotemporal expressions and functions in the physiological and also pathological CNS. After CNS injuries such as stroke and SCI, it seems obvious that ADAMTS proteoglycanases may be detrimental in the acute phase of injury while they may have a beneficial role later on as summarized in Figure 1. Even though their roles in angiogenesis and macrophage infiltration within the injured CNS have not been addressed yet, the early inhibition of ADAMTS proteoglycanases synthesis/activity after brain or spinal cord injuries may represent a rational therapeutic approach to limit the invasion of macrophages and/or to promote angiogenesis. This review clearly supports the postulate that the ADAMTS proteoglycanases, in particular ADAMTS-4, should be considered as key proteases to promote neurorepair after CNS injuries.

Abbreviations

ADAMTS: A disintegrin and metalloproteinase with thrombospondin motifs; CNS: Central nervous system; CSPG: Chondroitin sulfate proteoglycan; ECM: Extracellular matrix; ERK: Extracellular signal-regulated kinase; IFN- γ : γ -Interferon; IL-1: Interleukin-1; MAP: Mitogen activated protein; MAPK: Mitogen activated protein kinase; MMP: Matrix metalloproteinase; NF- κ B: Nuclear factor kappa-light-chain-enhancer of activated B cells; PNN: Perineuronal net; PSD-95: Postsynaptic density protein 95; SCI: Spinal

cord injury; SNAP-25: Synaptosomal-associated protein 25; TGF- β : Transforming growth factor- β ; TIMP-3: Tissue inhibitor of metalloproteinases-3; tMCAO: Transient middle cerebral artery occlusion; TNF- α : Tumor necrosis factor- α ; VEGF: Vascular endothelial growth factor.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SL planned and wrote the review. All authors gave critical comments on the draft of the manuscript based on their expertise on pre-clinical (SL, MP, DV, KK, JK) and/or clinical studies (JM, EE) on stroke and/or spinal cord injuries. SL and MP prepared the tables/figures. KK helped in editing the manuscript. All authors read and approved the final version of the manuscript.

Acknowledgements

This work was supported by the University of Eastern Finland and the ERANET-Neuron research program 'ProteA: Proteases before, during and after stroke', 2012–2015.

Author details

¹Department of Neurobiology, A. I. Virtanen Institute for Molecular Sciences, Biocenter Kuopio, University of Eastern Finland, P.O. Box 1627, 70211 Kuopio, Finland. ²INSERM, INSERM UMR-S 919, "Serine Proteases and Pathophysiology of the neurovascular Unit", University of Caen Basse-Normandie, GIP Cyceron, Bd H. Becquerel, BP 5229, 14074 Caen Cedex, France. ³Neurovascular Research Laboratory, Vall d'Hebron Research Institute, Universitat Autònoma de Barcelona, Barcelona, Spain. ⁴Department of Neurosurgery, Caen University Hospital, Avenue de la Côte de Nacre, 14000 Caen, France. ⁵Department of Oncology, Kuopio University Hospital, P.O. Box 1777, 70211 Kuopio, Finland.

Received: 13 September 2013 Accepted: 17 October 2013

Published: 31 October 2013

References

1. Tang BL: ADAMTS: a novel family of extracellular matrix proteases. *Int J Biochem Cell Biol* 2001, **33**:33–44.
2. Apte SS: A disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motifs: the ADAMTS family. *Int J Biochem Cell Biol* 2004, **36**:981–985.
3. Flannery CR, Zeng W, Corcoran C, Collins-Racie LA, Chockalingam PS, Hebert T, Mackie SA, McDonagh T, Crawford TK, Tomkinson KN, LaVallie ER, Morris EA: Autocatalytic cleavage of ADAMTS-4 (Aggrecanase-1) reveals multiple glycosaminoglycan-binding sites. *J Biol Chem* 2002, **277**:42775–42780.
4. Lin EA, Liu CJ: The role of ADAMTSs in arthritis. *Protein Cell* 2010, **1**:33–47.
5. Wang P, Tortorella M, England K, Malfait AM, Thomas G, Arner EC, Pei D: Proprotein convertase furin interacts with and cleaves pro-ADAMTS4 (Aggrecanase-1) in the trans-Golgi network. *J Biol Chem* 2004, **279**:15434–15440.
6. Tortorella M, Pratta M, Liu RQ, Abbaszade I, Ross H, Burn T, Arner E: The thrombospondin motif of aggrecanase-1 (ADAMTS-4) is critical for aggrecan substrate recognition and cleavage. *J Biol Chem* 2000, **275**:25791–25797.
7. Rodriguez-Manzaneque JC, Milchanowski AB, Dufour EK, Leduc R, Iruela-Arispe ML: Characterization of METH-1/ADAMTS1 processing reveals two distinct active forms. *J Biol Chem* 2000, **275**:33471–33479.
8. Gao G, Westling J, Thompson VP, Howell TD, Gottschall PE, Sandy JD: Activation of the proteolytic activity of ADAMTS4 (aggrecanase-1) by C-terminal truncation. *J Biol Chem* 2002, **277**:11034–11041.
9. Majerus EM, Zheng X, Tuley EA, Sadler JE: Cleavage of the ADAMTS13 propeptide is not required for protease activity. *J Biol Chem* 2003, **278**:46643–46648.
10. Gao G, Plaas A, Thompson VP, Jin S, Zuo F, Sandy JD: ADAMTS4 (aggrecanase-1) activation on the cell surface involves C-terminal cleavage by glycosylphosphatidylinositol-anchored membrane type 4-matrix metalloproteinase and binding of the activated proteinase to chondroitin sulfate and heparan sulfate on syndecan-1. *J Biol Chem* 2004, **279**:10042–10051.
11. Porter S, Clark IM, Kevorkian L, Edwards DR: The ADAMTS metalloproteinases. *Biochem J* 2005, **386**:15–27.
12. Llamazares M, Cal S, Quesada V, López-Otín C: Identification and characterization of ADAMTS-20 defines a novel subfamily of metalloproteinases-disintegrins with multiple thrombospondin-1 repeats and a unique GON domain. *J Biol Chem* 2003, **278**:13382–13389.
13. Nicholson AC, Malik SB, Logsdon JM, Van Meir EG: Functional evolution of ADAMTS genes: evidence from analyses of phylogeny and gene organization. *BMC Evol Biol* 2005, **5**:11.
14. Stanton H, Melrose J, Little CB, Fosang AJ: Proteoglycan degradation by the ADAMTS family of proteinases. *Biochim Biophys Acta* 2011, **1812**:1616–1629.
15. Rolls A, Shechter R, Schwartz M: The bright side of the glial scar in CNS repair. *Nat Rev Neurosci* 2009, **10**:235–241.
16. Yuan W, Matthews RT, Sandy JD, Gottschall PE: Association between protease-specific proteolytic cleavage of brevicin and synaptic loss in the dentate gyrus of kainate-treated rats. *Neuroscience* 2002, **114**:1091–1101.
17. Miguel RF, Pollak A, Lubec G: Metalloproteinase ADAMTS-1 but not ADAMTS-5 is manifold overexpressed in neurodegenerative disorders as Down syndrome, Alzheimer's and Pick's disease. *Brain Res Mol Brain Res* 2005, **133**:1–5.
18. Jungers KA, Le Goff C, Somerville RP, Apte SS: Adamts9 is widely expressed during mouse embryo development. *Gene Expr Patterns* 2005, **5**:609–617.
19. Howell MD, Torres-Collado AX, Iruela-Arispe ML, Gottschall PE: Selective decline of synaptic protein levels in the frontal cortex of female mice deficient in the extracellular metalloproteinase ADAMTS1. *PLoS One* 2012, **7**:e47226.
20. Krstic D, Rodriguez M, Knuesel I: Regulated proteolytic processing of Reelin through interplay of tissue plasminogen activator (tPA), ADAMTS-4, ADAMTS-5, and their modulators. *PLoS One* 2012, **7**:e47793.
21. Cross AK, Haddock G, Surr J, Plumb J, Bunning RA, Buttler DJ, Woodroffe MN: Differential expression of ADAMTS-1, -4, -5 and TIMP-3 in rat spinal cord at different stages of acute experimental autoimmune encephalomyelitis. *J Autoimmun* 2006, **26**:16–23.
22. Haddock G, Cross AK, Plumb J, Surr J, Buttler DJ, Bunning RA, Woodroffe MN: Expression of ADAMTS-1, -4, -5 and TIMP-3 in normal and multiple sclerosis CNS white matter. *Mult Scler* 2006, **12**:386–396.
23. Cross AK, Haddock G, Stock CJ, Allan S, Surr J, Bunning RA, Buttler DJ, Woodroffe MN: ADAMTS-1 and -4 are up-regulated following transient middle cerebral artery occlusion in the rat and their expression is modulated by TNF in cultured astrocytes. *Brain Res* 2006, **1088**:19–30.
24. Tauchi R, Imagama S, Natori T, Ohgomori T, Muramoto A, Shinjo R, Matsuyama Y, Ishiguro N, Kadomatsu K: The endogenous proteoglycan-degrading enzyme ADAMTS-4 promotes functional recovery after spinal cord injury. *J Neuroinflammation* 2012, **9**:53.
25. Hamel MG, Mayer J, Gottschall PE: Altered production and proteolytic processing of brevicin by transforming growth factor beta in cultured astrocytes. *J Neurochem* 2005, **93**:1533–1541.
26. Hamel MG, Ajmo JM, Leonardo CC, Zuo F, Sandy JD, Gottschall PE: Multimodal signaling by the ADAMTSs (a disintegrin and metalloproteinase with thrombospondin motifs) promotes neurite extension. *Exp Neurol* 2008, **210**:428–440.
27. Bonneh-Barkay D, Wiley CA: Brain extracellular matrix in neurodegeneration. *Brain Pathol* 2009, **19**:573–585.
28. Tian Y, Yuan W, Fujita N, Wang J, Wang H, Shapiro IM, Risbud MV: Inflammatory cytokines associated with degenerative disc disease control aggrecanase-1 (ADAMTS-4) expression in nucleus pulposus cells through MAPK and NF- κ B. *Am J Pathol* 2013, **182**:2310–2321.
29. Huh JE, Seo BK, Park YC, Kim JI, Lee JD, Choi DY, Baek YH, Park DS: WIN-34B, a new herbal medicine, inhibits the inflammatory response by inactivating I κ B- α phosphorylation and mitogen activated protein kinase pathways in fibroblast-like synoviocytes. *J Ethnopharmacol* 2012, **143**:779–786.
30. Mimata Y, Kamataki A, Oikawa S, Murakami K, Uzuki IM, Shimamura T, Sawai T: Interleukin-6 upregulates expression of ADAMTS-4 in fibroblast-like synoviocytes from patients with rheumatoid arthritis. *Int J Rheum Dis* 2012, **15**:36–44.
31. Séguin CA, Bojarski M, Pilliar RM, Roughley PJ, Kandel RA: Differential regulation of matrix degrading enzymes in a TNF α -induced model of nucleus pulposus tissue degeneration. *Matrix Biol* 2006, **25**:409–418.
32. Reid MJ, Cross AK, Haddock G, Allan SM, Stock CJ, Woodroffe MN, Buttler DJ, Bunning RA: ADAMTS-9 expression is up-regulated following transient middle cerebral artery occlusion (tMCAo) in the rat. *Neurosci Lett* 2009, **452**:252–257.

33. Zamanian JL, Xu L, Foo LC, Nouri N, Zhou L, Giffard RG, Barres BA: **Genomic analysis of reactive astrogliosis.** *J Neurosci* 2012, **32**:6391–6410.
34. Demircan K, Yonezawa T, Takigawa T, Topcu V, Erdogan S, Ucar F, Armutcu F, Yigitoglu MR, Ninomiya Y, Hirohata S: **ADAMTS1, ADAMTS5, ADAMTS9 and aggrecanase-generated proteoglycan fragments are induced following spinal cord injury in mouse.** *Neurosci Lett* 2013, **544**:25–30.
35. Sasaki M, Seo-Kiryu S, Kato R, Kita S, Kiyama H: **A disintegrin and metalloprotease with thrombospondin type1 motifs (ADAMTS-1) and IL-1 receptor type 1 mRNAs are simultaneously induced in nerve injured motor neurons.** *Brain Res Mol Brain Res* 2001, **89**:158–163.
36. Ashlin TG, Kwan AP, Ramji DP: **Regulation of ADAMTS-1, -4 and -5 expression in human macrophages: differential regulation by key cytokines implicated in atherosclerosis and novel synergism between TL1A and IL-17.** *Cytokine* 2013, **64**:234–242.
37. Wågsäter D, Björk H, Zhu C, Björkregren J, Valen G, Hamsten A, Eriksson P: **ADAMTS-4 and -8 are inflammatory regulated enzymes expressed in macrophage-rich areas of human atherosclerotic plaques.** *Atherosclerosis* 2008, **196**:514–522.
38. Ren P, Zhang L, Xu G, Palmero LC, Albini PT, Coselli JS, Shen YH, LeMaire SA: **ADAMTS-1 and ADAMTS-4 levels are elevated in thoracic aortic aneurysms and dissections.** *Ann Thorac Surg* 2013, **95**:570–577.
39. Westling J, Gottschall PE, Thompson VP, Cockburn A, Perides G, Zimmermann DR, Sandy JD: **ADAMTS4 (aggrecanase-1) cleaves human brain versican V2 at Glu405-Gln406 to generate glial hyaluronate binding protein.** *Biochem J* 2004, **377**:787–795.
40. Didangelos A, Mayr U, Monaco C, Mayr M: **Novel role of ADAMTS-5 protein in proteoglycan turnover and lipoprotein retention in atherosclerosis.** *J Biol Chem* 2012, **287**:19341–19345.
41. Diamantis I, Lüthi M, Hösl M, Reichen J: **Cloning of the rat ADAMTS-1 gene and its down regulation in endothelial cells in cirrhotic rats.** *Liver* 2000, **20**:165–172.
42. Hsu YP, Staton CA, Cross N, Buttle DJ: **Anti-angiogenic properties of ADAMTS-4 in vitro.** *Int J Exp Pathol* 2012, **93**:70–77.
43. Basile DP, Fredrich K, Chelladurai B, Leonard EC, Parrish AR: **Renal ischemia reperfusion inhibits VEGF expression and induces ADAMTS-1, a novel VEGF inhibitor.** *Am J Physiol Renal Physiol* 2008, **294**:F928–F936.
44. Lo PH, Lung HL, Cheung AK, Apte SS, Chan KW, Kwong FM, Ko JM, Cheng Y, Law S, Srivastava G, Zabarovsky ER, Tsao SW, Tang JC, Stanbridge EJ, Lung ML: **Extracellular protease ADAMTS9 suppresses esophageal and nasopharyngeal carcinoma tumor formation by inhibiting angiogenesis.** *Cancer Res* 2010, **70**:5567–5576.
45. Kumar S, Sharghi-Namini S, Rao N, Ge R: **ADAMTS5 functions as an anti-angiogenic and anti-tumorigenic protein independent of its proteoglycanase activity.** *Am J Pathol* 2012, **181**:1056–1068.
46. Lafuente JV, Ortuzar N, Bengoetxea H, Bulnes S, Argandoña EG: **Vascular endothelial growth factor and other angiogenic factors: key molecules in brain development and restoration.** *Int Rev Neurobiol* 2012, **102**:317–346.
47. Lau LW, Keough MB, Haylock-Jacobs S, Cua R, Döring A, Sloka S, Stirling DP, Rivest S, Yong VW: **Chondroitin sulfate proteoglycans in demyelinated lesions impair remyelination.** *Ann Neurol* 2012, **72**:419–432.
48. Siebert JR, Stelzner DJ, Osterhout DJ: **Chondroitinase treatment following spinal contusion injury increases migration of oligodendrocyte progenitor cells.** *Exp Neurol* 2011, **231**:19–29.
49. Hobohm C, Günther A, Grosche J, Rossner S, Schneider D, Brückner G: **Decomposition and long-lasting downregulation of extracellular matrix in perineuronal nets induced by focal cerebral ischemia in rats.** *J Neurosci Res* 2005, **80**:539–548.
50. Gherardini L, Gennaro M, Pizzorusso T: **Perilesional treatment with chondroitinase ABC and motor training promote functional recovery after stroke in rats.** *Cereb Cortex* 2013. epub ahead of print.
51. Hill JJ, Jin K, Mao XO, Xie L, Greenberg DA: **Intracerebral chondroitinase ABC and heparan sulfate proteoglycan glypican improve outcome from chronic stroke in rats.** *Proc Natl Acad Sci U S A* 2012, **109**:9155–9160.
52. Soleman S, Yip PK, Duricki DA, Moon LD: **Delayed treatment with chondroitinase ABC promotes sensorimotor recovery and plasticity after stroke in aged rats.** *Brain* 2012, **135**:1210–1223.
53. Zuo J, Neubauer D, Dyess K, Ferguson TA, Muir D: **Degradation of chondroitin sulfate proteoglycan enhances the neurite-promoting potential of spinal cord tissue.** *Exp Neurol* 1998, **154**:654–662.
54. Zuo J, Neubauer D, Graham J, Krekoski CA, Ferguson TA, Muir D: **Regeneration of axons after nerve transection repair is enhanced by degradation of chondroitin sulfate proteoglycan.** *Exp Neurol* 2002, **176**:221–228.
55. Bradbury EJ, Carter LM: **Manipulating the glial scar: chondroitinase ABC as a therapy for spinal cord injury.** *Brain Res Bull* 2011, **84**:306–316.
56. Bradbury EJ, Moon LD, Popat RJ, King VR, Bennett GS, Patel PN, Fawcett JW, McMahon SB: **Chondroitinase ABC promotes functional recovery after spinal cord injury.** *Nature* 2002, **416**:636–640.
57. Tom VJ, Sandrow-Feinberg HR, Miller K, Santi L, Connors T, Lemay MA, Houlié JD: **Combining peripheral nerve grafts and chondroitinase promotes functional axonal regeneration in the chronically injured spinal cord.** *J Neurosci* 2009, **29**:14881–14890.
58. Cua RC, Lau LW, Keough MB, Midha R, Apte SS, Yong VW: **Overcoming neurite-inhibitory chondroitin sulfate proteoglycans in the astrocyte matrix.** *Glia* 2013, **61**:972–984.
59. Siebert JR, Osterhout DJ: **The inhibitory effects of chondroitin sulfate proteoglycans on oligodendrocytes.** *J Neurochem* 2011, **119**:176–188.
60. Sasaki M, Lankford KL, Radtke C, Honmou O, Kocsis JD: **Remyelination after olfactory ensheathing cell transplantation into diverse demyelinating environments.** *Exp Neurol* 2011, **229**:88–98.
61. Mayeur A, Duclos C, Honoré A, Gauberti M, Drouot L, Do Rego JC, Bon-Mardion N, Jean L, Vérin E, Emery E, et al: **Potential of olfactory ensheathing cells from different sources for spinal cord repair.** *PLoS One* 2013, **8**:e62860.
62. Guéroult N, Derambure C, Drouot L, Bon-Mardion N, Duclos C, Boyer O, Marie JP: **Comparative gene expression profiling of olfactory ensheathing cells from olfactory bulb and olfactory mucosa.** *Glia* 2010, **58**:1570–1580.
63. Lim NH, Kashiwagi M, Visse R, Jones J, Enghild JJ, Brew K, Nagase H: **Reactive-site mutants of N-TIMP-3 that selectively inhibit ADAMTS-4 and ADAMTS-5: biological and structural implications.** *Biochem J* 2010, **431**:113–122.
64. Daneman R: **The blood–brain barrier in health and disease.** *Ann Neurol* 2012, **72**:648–672.
65. Pardeshi CV, Belgamwar VS: **Direct nose to brain drug delivery via integrated nerve pathways bypassing the blood–brain barrier: an excellent platform for brain targeting.** *Expert Opin Drug Deliv* 2013, **10**:957–972.

doi:10.1186/1742-2094-10-133

Cite this article as: Lemarchant et al.: ADAMTS proteoglycanases in the physiological and pathological central nervous system. *Journal of Neuroinflammation* 2013 **10**:133.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

