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Matrix metalloproteinases, synaptic injury, and multiple sclerosis

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Multiple sclerosis (MS) is a disease of the central nervous system in which immune mediated damage to myelin is characteristic. For an overview of this condition and its pathophysiology, please refer to one of many excellent published reviews (Sorensen and Ransohoff, 1998; Weiner, 2009). To follow, is a discussion focused on the possibility that synaptic injury occurs in at least a subset of patients, and that matrix metalloproteinases (MMPs) play a role in such.

Keywords: matrix metalloproteinase, cadherin, MMP, ICAM, synapse, multiple sclerosis, adhesion molecule

ARCHITECTURE OF THE CENTRAL SYNAPSE

Synapses are highly dynamic structures through which neurons communicate. Distal terminals of an axon make up the pre-synaptic component of the synapse, while actin rich dendritic spines constitute the post-synaptic component. The action potential is propagated along the axon to terminals, and subsequent changes in intracellular calcium lead to the release of neurotransmitter containing vesicles. Released neurotransmitter crosses the synaptic cleft and binds to specific receptors which are concentrated on dendritic spines. As synapses become stronger, the diameter of dendritic spines may concomitantly enlarge to allow for increased insertion of neurotransmitter receptors.

Synaptic structure is organized through a sequential program that involves specific protein-protein and protein-lipid interactions. While a full discussion of synapse development is beyond the scope of this review, it should be noted that synaptic cell adhesion molecules (CAMs) may contribute to this process. These molecules can also influence the structure and function of pre-formed synapses. CAMs include cadherins, neurexins, neuroligins, integrins, and immunoglobulin (Ig) superfamily molecules (IgCAMs). Of additional relevance to this review are specific pre- and post-synaptically localized proteins. Immunostaining can be used to visualize these molecules which including the pre-synaptic protein synaptophysin, and the post-synaptic density protein PSD-95.

SYNAPTIC INJURY AND MS

Cognitive impairment may occur in association with MS (Gonzalez-Rosa et al., 2006; Schulz et al., 2006). Multiple mechanisms may contribute, including axonal transection (Trapp et al., 1998) and diffuse white matter damage that impairs the connectivity of large scale networks (Audoin et al., 2006; Ranjeva et al., 2006). Gray matter damage may, however, also be important. For example, a recent MRI study showed that neocortical atrophy occurred in the earliest stages of MS and that it was significant even with minimal white matter damage (Iimuro et al., 2003).

Neocortical lesions have been linked to axonal, neuronal, and glial loss (Vercellino et al., 2005; Wegner et al., 2006). Such lesions have also been associated with *synaptic elimination*. For example, a 47% decrease in neocortical synaptophysin was noted in one study, and the authors concluded that neocortical lesions might make a major independent contribution to MS pathology (Wegner et al., 2006).

Synaptic damage also occurs in experimental allergic encephalomyelitis (EAE), an animal model of autoimmune demyelination. Analysis of synaptic protein abundance in EAE brains reveals reduced levels of the pre-synaptic proteins synaptophysin and synapsin, and reduced levels of the post-synaptic protein PSD-95. The synaptic injury was linked to infiltrating inflammatory cells (Zhu et al., 2003). The authors of this study hypothesized that disease associated changes in intracellular calcium might have activated the intracellular protease calpain, which is known to target PSD-95 (Lu et al., 2000). In related work, synaptic stripping was described in association with focal cortical inflammation initiated by the intracerebral injection of killed bacteria (BCG). In this model, axosomatic synapses were displaced by activated microglia (Trapp et al., 2007). A summary of relevant studies is shown in **Table 1**.

MATRIX METALLOPROTEASES- A FAMILY OF ZINC DEPENDENT ENDOPEPTIDASES THAT CAN TARGET VARIED SYNAPTIC SUBSTRATES

MMPs- AN OVERVIEW

MMPs are a family of zinc dependent endopeptidases, of which are found in humans. Subsets include the soluble MMPs, at least some of which may be released from vesicular stores. These forms contain a pro- domain, a catalytic domain, and typically, a hemopexin like

Table 1 | Synaptic injury in MS and relevant disease models.

Disease/Model	Evidence of synaptic injury	Reference(s)
Multiple sclerosis	Axonal transection	Trapp et al. (1998)
Multiple sclerosis	Reduced synaptophysin as measured by immunoautoradiography	Wegner et al. (2006)
EAE	Reduced synaptic density as assessed by Golgi staining and quantification. Exercise ameliorated this effect	Rossi et al. (2009)
EAE	Reduced synaptophysin, synapsin 1 and PSD-95 immunoreactivity that correlated with inflammatory cell infiltration	Zhu et al. (2003)
EAE	Inflammatory cell infiltration with AMPA type glutamate receptor phosphorylation and AMPA receptor-dependent synaptopathy	Centonze et al. (2009)
EAE	Alterations in excitatory transmission as determined by excitatory post-synaptic potential (EPSP) recordings	Centonze et al. (2007)
Focal cortical inflammation via intracerebral injection of killed bacteria	Synaptic stripping/microglial cell infiltration of synaptic space	Trapp et al. (2007)

domain. The latter may play a role in binding interactions. Activation of secreted soluble MMPs can occur secondary to shedding of the pro- domain, or secondary to events which influence tertiary structure such as oxidation and nitrosylation. Reductions in soluble MMP activity can be affected through binding interactions with endogenous inhibitors, or tissue inhibitors of MMPs (TIMPs). While secreted into the extracellular space, soluble MMPs can interact with specific cell surface molecules in which case their proteolytic activity may be relatively localized. In addition, select MMPs, membrane type MMPs (MT-MMPs), possess a transmembrane domain, as do the related "a disintegrin and metalloproteinase(s)" or ADAMs. Of note, is that while named for their ability to target components of the extracellular matrix such as collagen and laminin, MMPs are increasingly recognized as effectors of non-matrix proteins. MMPs process soluble molecules including chemokines and cytokines, and they also target a variety of cell surface receptors and adhesion molecules.

MMPs are expressed in the CNS by a variety of cell types. It has been shown, for example, that astrocytes can release MMP-1, -2 and -3, and that microglia can release MMP-7,-9 and -12 (Yong et al., 1998; Conant et al., 1999; Vos et al., 2000). Neurons may also release MMPs in the setting of excitotoxic injury (Szklarczyk et al., 2002; Meighan et al., 2006). MMPs are also released from activated monocytes and T cells, with monocytes releasing MMP-1,-7,-9 and -12, and T cells releasing abundant quantities of MMP-9. T cells also express MT1-MMP, which has proteolytic activity both in its membrane associated and shed extracellular domain form (Toth et al., 2005).

Of relevance to MS, MMPs have been well studied for their ability to cleave matrix proteins of the blood brain barrier and thus potentially facilitate the CNS ingress of inflammatory molecules and/or serum derived toxins (Anthony et al., 1998). MMPs have also been studied for their ability to cleave myelin basic protein (MBP) and myelin associated glycoprotein (Kieseier et al., 1999; Agrawal et al., 2008; Milward et al., 2008), and more recently, to generate immunogenic MBP peptides (Shiryaev et al., 2009). Of particular relevance to synaptic injury, however, is an emerging appreciation of MMPs as molecules that may be released proximal to the synapse (Sbai et al., 2008). A summary of relavant synaptic substrates is presented in **Table 2**.

MMPs CAN CLEAVE A VARIETY OF SYNAPTIC PROTEINS

In terms of synaptic substrates, synaptic CAMs may be of particular relevance. Given what is known about MMP substrates in extra CNS sites, MMPs may be relatively efficient in terms of their ability to process such molecules. For example, MMPs have been well studied for their role in cell migration, and it is thus intuitive that processing of CAMs would play an important role in this process. Numerous studies support this possibility. For example, metalloproteinase mediated shedding of soluble ICAM-1 has been demonstrated (Lyons and Benveniste, 1998), and soluble ICAM-1 has been shown to promote smooth muscle cell migration (Lee et al., 2008).

Another important reason to focus on the potential for MMPs to mediate CAM cleavage in the setting of a disease that includes synaptic injury, however, lies in an abundance of evidence suggesting that CAMs are critical to synaptic structure and function (Sakurai et al., 1998). And though unrelated to synaptic injury *per se*, it is worth mentioning that CAM family members such as SynCAM4 might also mediate axon-glial interactions critical to processes including remyelination (Spiegel et al., 2007).

Synaptic CAMs have been shown to influence neuronal cell migration (Takeuchi and O'Leary, 2006), dendrite morphology (Tian et al., 2007), and the genesis/formation of the excitatory/inhibitory pre-synaptic complex (Biederer et al., 2002). Varied studies have also shown CAM integrity influences long term potentiation (LTP), a potential measure of learning and memory (Benson et al., 2000). It is therefore likely that metalloproteinase dependent processing of CAMs will likely have effects on both the formation and function of the synapse. In support of this possibility is a recent study which showed that ICAM-5 cleavage was linked to changes in dendrite morphology (Tian et al., 2007). This study was focused on MMP-2 and -9, MMPs which are elevated in MS as will be discussed in a section to follow. We also observed that varied MMPs could cleave ICAM-5 from hippocampal neurons, and that this could occur within 5 min of cell stimulation with NMDA (Conant et al., 2010). Rapid cleavage suggests that MMPs might be released from preformed neuronal stores to rapidly modulate synaptic protein integrity.

Table 2 | Synaptic proteins that are processed by MMPs.

Substrate	Protease	Relevance to synaptic structure/function	Reference(s)
N-cadherin	MT5-MMP MMP-7 ADAM-10	Synapse formation and plasticity	Williams et al. (2010), Monea et al. (2006), Kohutek et al. (2009)
Telencephalin/ ICAM-5	MMP-2, -3, -7, -9	Shedding is associated with changes in dendritic spine morphology and may play a role in select forms of plasticity	Conant et al. (2010), Tian et al. (2007)
NR1	MMP-3 MMP-7	Obligate subunit of the NMDA type glutamate receptor	Pauly et al. (2008), Szklarczyk et al. (2008)
NR2A	MMP-7	Subunit of the NMDA type glutamate receptor	Szklarczyk et al. (2008)
Neuronal pentraxin receptor (NPR)	ADAM-17	Ectodomain shedding allows an N terminal fragment to surround and internalize AMPA type glutamate receptors, thus contributing to synaptic plasticity/long term depression	Cho et al. (2008)
SNAP-25	MMP-7	Synaptic vesicle/neurotransmitter release	Szklarczyk et al. (2007b)
Pro-BDNF	MMP-3 MMP-7	Effector of neuronal survival and synaptic plasticity	Lee et al. (2001)
IGFBP-6	MMP-9 MMP-12	IGFBP-6 may sequester IGF, a potent effector of neuronal survival and a potential contributor to synapse formation	Larsen et al. (2006)
Brevican	MMP-9	Structural stability of the synapse. Proteolytic cleavage has been associated with synaptic loss	Yuan et al. (2002)
Laminin-γ2	MT1-MMP	Structural stability of the synapse	Koshikawa et al. (2005)

ICAM-5 is but one of several synaptic CAMs that may be targeted by MMPs. For example, work from the laboratory of Patricia Maness has shown that MMPs can cleave NCAM (Hinkle et al., 2006), a molecule that may play a role in synapse formation (Muller et al., 2010). Others have shown that MMPs can process cadherins including N-cadherin and E-cadherin (Monea et al., 2006). N-cadherin has been linked to varied effects on the synapse. It can influence synaptic vesicle clustering (Stan et al., 2010), LTP (Tang et al., 1998; Bozdagi et al., 2000), and dendritic spine morphogenesis (Togashi et al., 2002). MMPs have also been shown to target synaptic dystroglycan (Michaluk et al., 2007), and though of less relevance to the CNS, agrin (VanSaun and Werle, 2000).

Though future studies will determine the extent to which MMPs target synaptic CAMs in MS and EAE, at least one study has shown that CAM levels may be reduced in the latter. This study showed that levels of NCAM-1 were reduced in CA1 and CA3 regions of the hippocampus, while levels of MMPs -2 and -9 were increased in the same (Jovanova-Nesic and Shoenfeld, 2006).

While a variety of synaptic CAMs may be susceptible to MMP mediated proteolysis, additional synaptic proteins might be processed as well. For example, two studies have shown that MMPs can process the NR1 subunit of the *N*-methyl-D-aspartate (NMDA) type glutamate receptor (Pauly et al., 2008; Szklarczyk et al., 2008). These studies were focused on MMP-3 and -7, MMPs that have a relatively broad spectrum of substrates and that may be released by activated glia in the context of CNS inflammation. It was also shown that MMP-7 mediated cleavage of NR1 was associated with a reduction in NMDA stimulated calcium flux (Szklarczyk et al., 2008). In another study, it was shown that a transmembrane MMP could cleave neuronal pentraxin to affect an internalization of α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor subunits (Cho et al., 2008). Thus, from these studies, MMPs might dampen glutamate transmission, something that could be protective in the setting of acute inflammation.

Additional synaptic modulators that may be processed by MMPs include G protein coupled receptors of the proteinase activated receptor family (Boire et al., 2005). Activation of these receptors follows from cleavage of the N terminus and the subsequent exposure of a tethered peptide ligand. These receptors are abundantly expressed on neurons (D'Andrea et al., 1998; Wang and Reiser, 2003) and their activation could potentially modulate synaptic structure and function.

MMP-DEPENDENT PROCESSING OF SYNAPTIC SUBSTRATES PLAYS AN IMPORTANT ROLE IN NORMAL SYNAPTIC PHYSIOLOGY

While a relatively new area of investigation, published studies suggest that MMPs may play a critical role in learning and memory. For example, a broad spectrum MMP inhibitor has been shown to reduce multiple forms of hippocampal CA1 plasticity (Meighan et al., 2007), and MMP-9 activity has been implicated in the maintenance of late LTP (Nagy et al., 2006). In addition, antisense to MMPs has been shown to prevent acquisition in the Morris water maze test (Meighan et al., 2006), and methamphetamine-induced behavioral sensitization is reduced in mice lacking MMP-2 or MMP-9 (Mizoguchi et al., 2007). Similarly, proteases have been shown to contribute to cocaine associated conditioned place preference (Brown et al., 2007, 2008; Maiya et al., 2009). In a more recent study, it was shown that a broad spectrum MMP inhibitor could prevent reconsolidation of a fear association memory that was not dependent on contextual cues (Brown et al., 2009). The mechanisms by which MMPs are important to learning and memory are as yet unclear, though we and others have suggested

that the regulated processing of synaptic CAMs with subsequent effects on synaptic structure, likely plays a role (Tian et al., 2007; Conant et al., 2010).

ELEVATED LEVELS OF MMPs MAY INTERFERE WITH MMP-DEPENDENT LEARNING, AND WHEN SUSTAINED, MAY CONTRIBUTE TO SYNAPTIC INJURY

While physiological release of MMPs may enhance synaptic transmission, substantially elevated levels of these enzymes, as may occur with MS, might have different effects. Elevated levels might cause processes to which MMPs contribute, such as LTP, to go awry. In addition, high levels of MMPs might be neurotoxic. This latter possibility is supported by a variety of studies. For example, we have shown that high levels of MMP-1 were toxic to neurons in organotypic and dissociated cultures (Vos et al., 2000). Moreover, several investigators have shown that MMP-9 may be neurotoxic (Gu et al., 2002; Jourquin et al., 2003; Thornton et al., 2008). In one study, recombinant MMP-9 caused pyramidal cell toxicity in hippocampal cultures (Jourquin et al., 2003). Published studies also suggest that the synapse may be vulnerable to MMP mediated toxicity. We noted that long term treatment of hippocampal neurons with MMP-7 led to a reduction in synaptic stability as determined by reductions in post-synaptic density length and terminal area (Szklarczyk et al., 2007a). And in a recent study of traumatic brain injury, it was noted that synapse loss, measured by reductions in synaptophysin, was prevented by an MMP inhibitor (Ding et al., 2009).

VARIED MMPs MAY BE ELEVATED IN ASSOCIATION WITH MS AND EAE

Elevated levels of select MMPs, including MMP-2, 7, -9, and -12, have been detected in association with MS (Maeda and Sobel, 1996; Cossins et al., 1997; Lindberg et al., 2001; Vos et al., 2003; Diaz-Sanchez et al., 2006), and elevated MMP levels have been correlated with disease severity and disability (Benesova et al., 2009). Elevated levels of MMPs including MMP-7 and MMP-9 have also been detected in EAE. In one study of adoptive transfer EAE, mRNA for MMP-7 was increased with maximum levels at peak disease. Levels of mRNA for MMP-9 were also elevated, while those of MMP-2 or -3 were not (Kieseier et al., 1998). The transcriptional expression of MMPs has also been examined in MS. In one study of post-mortem MS brain tissue by real-time polymerase chain reaction, it was noted that the mRNA expression of MMP-7 and -9 was upregulated throughout all stages of lesion formation with active inflammation (Lindberg et al., 2001). In this study, mRNA levels of while MMP-2,-3, and tumor necrosis factor (TNF)-alpha-converting-enzyme were not elevated. In a more recent study of mRNA in peripheral blood leukocytes from MS patients, MMP-7 and MT1-MMP were upregulated in relapsing remitting or chronic progressive patients as compared to controls. In this study, MMP-9 levels were not increased.

In work related to the question of whether MMPs are increased with MS, the possibility that polymorphisms influencing MMP expression may alter disease risk and/or severity has been examined. Fernandes and colleagues looked at the $C^{-1562}T$ polymorphism, which leads to increased MMP-9 expression, in a large cohort of patients (165 MS, 191 controls) and found that the polymorphism was associated with increased disease severity as assessed by the Expanded Disability Status Scale (Kurtzke, 1983; Fernandes et al., 2009). Increased $C^{-1562}T$ risk for MS was also noted in a recent Polish population study (Mirowska-Guzel et al., 2009).

MMP INHIBITORS HAVE SHOWN PROMISE TOWARD MS TREATMENT

Evidence from previously published studies suggests that overall, MMPs may play a detrimental role in MS. For example, TIMP-1 overexpression has been linked to a reduction in the infiltration of leukocytes as well as a reduced disease score on day 18 (Althoff et al., 2010). In related work, C57/Bl6 mice deficient in tissue inhibitor of metalloproteinases-1 (TIMP-1) show increased myelin pathology as compared to their wild type counterparts following MOG induced EAE (Crocker et al., 2006). Whether synaptic changes occurred and were also limited is unknown. Of interest, while TIMP-1 expression may typically increase in EAE and play a myelin protective role, TIMP-1 levels do not generally increase in MS (Crocker et al., 2006).

Studies using MMP inhibitors also suggest that these enzymes may contribute to disease pathology. For example, minocycline, an inhibitor that penetrates the brain and spinal cord, has been shown to suppress ongoing disease activity and to limit disease progression in a study that examined MOG immunized rats (Popovic et al., 2002). While minocycline has effects additional to the inhibition of MMP activity and expression, the authors noted that MMP-2 expression was increased in areas of inflammation in sham treated animals and that such expression was indeed reduced in minocycline treated animals (Popovic et al., 2002). They also pointed out that models of rheumatoid arthritis support the view that inhibition of MMP expression is at least in part responsible for the clinical efficacy of minocycline. Other animal studies also support a role for minocycline as a therapeutic agent. For example, when given in combination with glatiramer acetate or interferon-γ, minocycline therapy was associated with decreased inflammation, demyelination and axonal injury in MOG induced murine EAE (Giuliani et al., 2005a,b). In animal studies focused on *particular* MMPs, however, the situation is more complex. Studies suggest that while inhibition of family members including MMP-7 and -9 might benefit disease severity (Yong et al., 2007; Buhler et al., 2009), inhibition of MMP-12 might actually be detrimental (Weaver et al., 2005; Goncalves DaSilva and Yong, 2009). Thus, in the future it might be beneficial to design inhibitors that are somewhat selective (Yong et al., 2007).

Work from human studies also suggests that general inhibition of MMP activity might hold promise. A recent pilot study has demonstrated that minocycline could reduce gadolinium enhancing MRI lesions in MS within 2 weeks of treatment (Metz et al., 2004). Moreover, after 24 months of therapy, patients remained stable. In related work, estriol has been shown to reduce gadolinium enhancing lesions and to reduce levels of MMP-9 (Sicotte et al., 2002; Gold et al., 2009). In other work consistent with a role for MMPs in MS, interferon-β (IFN-β was shown to reduce MMP secretion and T cell migration (Leppert et al., 1996; Stuve et al., 1996). IFN therapy has also been linked to reduced peripheral blood mRNA for MMP-8, -9 and -19 (Bernal et al., 2009), and with decreased mRNA for MMP-7 in relapsing remitting, but not chronic progressive, patients (Galboiz et al., 2001). In a related study, IFN-β was associated with an early and sustained (24 month)

increase in TIMP-1 in MS patients classified as responders based on clinical criteria. Non-responders did not demonstrate this increase (Comabella et al., 2009).

In studies of inflammation related not to MS, but to spinal cord injury in mice, inhibition of MMP activity may also be of benefit. Of interest are findings suggesting that inhibition of MMP activity in the first 3 days following injury has benefit (Noble et al., 2002), while inhibition after this early period may actually hinder long term recovery (Trivedi, et al., 2005; Yong et al., 2007). One possibility is that injurious MMPs are particularly elevated at early time points while reparative MMPs are elevated at later time points (Hsu et al., 2006). Another non-mutually exclusive possibility is that particularly high levels of MMPs may be injurious while lower levels may be reparative. And finally, dynamics of the system as a whole may vary as a function of time after injury, and MMPs may in turn have a differential overall role that is dependent on these changes.

Whether the potential to inhibit cleavage of synaptic CAMs is involved in the protective effects of MMP inhibitors in MS and other inflammatory conditions of the CNS remains to be determined. Questions of timing and specificity with respect to particular MMPs will also need to be addressed. It is tempting to speculate, however, that MMP inhibitors would generally act to diminish synaptic changes that occur with inflammation.

CONCLUSIONS AND FUTURE DIRECTIONS

MMPs levels may be substantially increased in association with MS. While these enzymes have been well studied for their ability to process proteins that contribute to blood brain barrier and myelin integrity, their potential to process synaptic proteins warrants additional investigation. MMP mediated cleavage of synaptic proteins may be adaptive or even protective in the setting of acute non-sustained inflammation, in that reduced synaptic function may limit neurotoxicity. Long-lived reductions in synaptic integrity might instead lead to irreparable synaptic damage. Alternatively, acute injury may be associated with particularly high and toxic levels of MMPs, while sustained but more moderate increases in MMP activity may instead promote neuronal process outgrowth and synaptic repair. If we are to design rational treatment strategies that would target MMP-dependent events including synaptic proteolysis, we will need to know more regarding the question of whether, and when, these events are protective as opposed to injurious. We will also need to know more about the role of specific MMPs in these processes.

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