Minireview

Matrix metalloproteinases and their endogenous inhibitors in neuronal physiology of the adult brain

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Received 19 February 2004; revised 3 March 2004; accepted 7 March 2004

Available online 9 April 2004

Edited by Horst Feldmann

Abstract More than 20 matrix metalloproteinases (MMPs) and four of their endogenous tissue inhibitors (TIMPs) act together to control tightly temporally restricted, focal proteolysis of extracellular matrix. In the neurons of the adult brain several components of the TIMP/MMP system are expressed and are responsive to changes in neuronal activity. Furthermore, functional studies, especially involving blocking of MMP activities, along with the identification of MMP substrates in the brain strongly suggest that this enzymatic system plays an important physiological role in adult brain neurons, possibly being pivotal for neuronal plasticity.

Keywords: Brain; Neuron; Neuronal plasticity; Long term potentiation; Memory; Matrix metalloproteinase-9

1. Introduction

Matrix metalloproteinases (MMPs) are a family of enzymes with more than 20 members identified to date that are all extracellular (predominantly secreted pericellularly, and some membrane-bound) endopeptidases requiring Zn^{2+} for their enzymatic activity [1]. Their major targets are proteins of the extracellular matrix (ECM). MMPs are grouped together because of their sequence homology and resulting structural and enzymatic similarities [1,2]. MMPs are enzymatically activated by means of the cleavage of the propeptide [1,3,4]. Once activated, the MMPs are subject to inhibition by the tissue inhibitors of metalloproteinases (TIMPs) that bind MMPs non-covalently. There are four TIMPs identified so far: TIMP-1, -2, -3, and -4.

The regulation of MMPs' expression and activity appears to be a very complex process. In an exemplary case of MMP-9, the following steps can be delineated (Fig. 1), as indicated by collective evidence obtained in various cell types and tissues. There are a number of gene regulatory sequences driving the MMP-9 expression, with AP-1 and NF-κB being the most prominent [5]. Once produced, the MMP-9 mRNA is subjected to regulation at its stability level by nitric oxide (NO) [6]; as well it can apparently be translocated in neurons towards activated dendrites [7]. Notably, MMP-9 contains ARE-like sequences that have been suggested to be of pivotal importance for the translocation in other messages [8].

The protein is synthesized with the signal peptide responsible for a translocation to the endoplasmic reticulum, where the signal peptide is removed. Glycosylation of MMP-9 protein provides an additional level of regulation [9]. The next step is an export of MMP-9 protein, in vesicles, to the extracellular space [10]. The MMPs are produced by cells in an inactive form (pro-MMP) where the cystein residue of the propeptide region is bound to a zinc atom present in the catalytic domain. Fully active protein is produced by disruption of the cysteine–zinc interaction and enzymatic removal of the propeptide [1]. The activation of the pro-enzyme is controlled by a cascade of steps involving other MMPs and the plasmin system. For instance, another MMP, MMP-2 (activated by a MMP bound by TIMP-2) can activate pro-MMP-9 [11]. Thus, in this case TIMP-2 facilitates MMP activation. Furthermore, pro-MMP-9 can form a complex with TIMP-1 that involves interaction of the C-terminal (non-catalytic) domain of pro-MMP-9 and the C-terminal (non-inhibitory) domain of TIMP-1. This complex can interact with MMP-3 and then dissociate into free pro-MMP-9 and the TIMP-1–MMP-3 complex [1]. In addition, S-nitrosylation of MMP-9 protein can also activate pro-MMP-9 [12].

Tissue type plasminogen activator (tPA), as well as urokinase type plasminogen activator (uPA) are principal enzymes releasing active plasmin that activates MMP-1 and -3, which in

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Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; A2RE, A2 response element; BDNF, brain-derived neurotrophic factor; CA, cornu Ammoni; CDV, canine distemper virus; CNS, central nervous system; CREB, cAMP responsive element binding (protein, a transcription factor); CSPG, chondroitin sulfate proteoglycan; DG, dentate gyrus; ECM, extracellular matrix; ECS, electroconvulsive seizures; ER, endoplasmic reticulum; HSPG, heparan sulfate proteoglycan; KA, kainate; LRP, low-density lipoprotein receptor-related protein; LTP, long term potentiation; L1, outer layer of the cerebral cortex; MMP, matrix metalloproteinase; MT-MMP, membrane-type matrix metalloproteinase; NGF, nerve growth factor; NO, nitric oxide; PD, Parkinson's disease; PGs, proteoglycans; RT-PCR, reverse-transcriptase polymerase chain reaction; TIMP, tissue inhibitor of matrix metalloproteinases; tPA, tissue plasminogen activator; uPA, urokinase plasminogen activator; uPAR, uPAR receptor

0014-5793/$22.00
doi:10.1016/j.febslet.2004.03.070

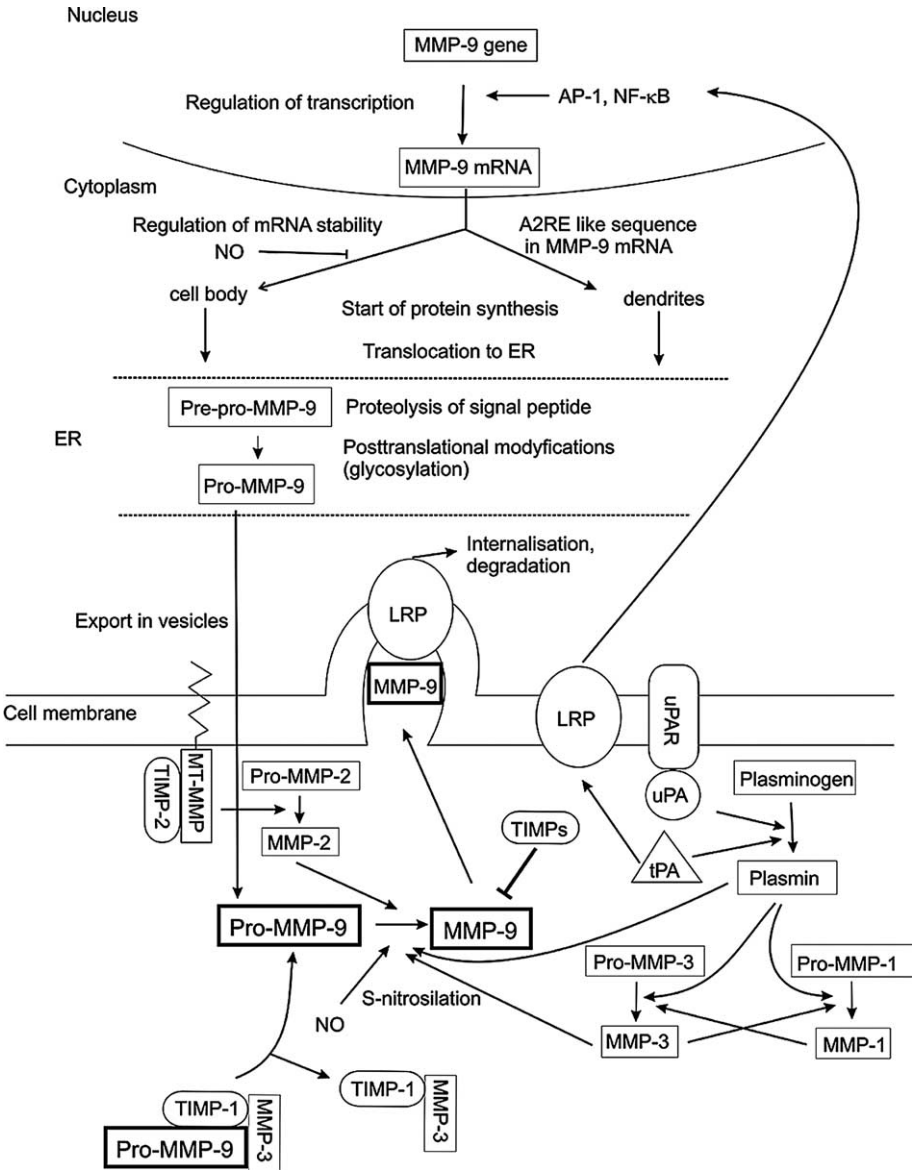

Fig. 1. Schematic representation of MMP-9 activation.

turn can cleave pro-MMP-9 [13]. Interestingly, tPA can act on MMP-9 also in a plasmin-independent manner, namely it has been shown that tPA can bind to the low-density receptor-related protein (LRP) and indirectly regulate MMP-9 gene transcription [14]. LRP can also act as a receptor for MMP-9 that mediates internalization and degradation of the enzyme [15]. Finally, MMP-9 activity can be inhibited by TIMPs [1].

The MMP–TIMP system has been well characterized in normal development as well as in a number of pathological conditions. In brief, MMPs are responsible for cell migration and tissue penetration and TIMPs counteract these activities. Much less is known about the enzymatic system in adult tissues and brain neurons remain especially poorly understood in this context. On the other hand, much more is known about MMPs originating from glia, especially under pathological conditions [3,4]. The purpose of this review is to present data on neuronal MMPs in the adult brain in a hope that a synopsis of the available information could help elucidate the physiological function of the system. We will focus on the MMP/TIMP expression patterns under basal conditions as well as following neuronal stimulation with a special emphasis on conditions that may reveal a beneficial rather than a detrimental role of the MMPs. The functional studies employing MMP inhibition will also be evoked in the same context. It has to be noted that the pathological involvement of MMPs has already been extensively presented and discussed in the literature [3,4,16].

2. TIMPs in the brain

All four TIMP genes have been shown to be expressed in unstimulated adult brain [17–23] (see Table 1). TIMP-1 mRNA and protein have been found to be present in the hippocampus [19] with mRNA detected in granule cells of the dentate gyrus (DG) and pyramidal cells of CA1 and CA3 subfields [20,24], whereas TIMP-1 immunoreactivity was mostly associated with the main

Table 1
Basal and induced TIMP expression in the brain

Gene	Brain structure	Expression		References
		Basal level	Upregulation/downregulation	
TIMP-1	Hippocampus	Pyramidal and granular neurons, cell bodies and dendrites	Seizures (neurons, astrocytes)[a]	[19,20,26,27]
			ECS (DG, molecular layer of DG)[a]	[24]
			Early phase of CDV infection[a]	[32]
			Transient ischemia[a]	[20]
			Experimental autoimmune encephalitis[a]	[23]
			Human T-lymphotropic virus type I infection[a]	[29,33]
			Human immunodeficiency 1-associated dementia[a]	[33]
	Cortex	Neurons, not astrocytes	KCl depolarization (neurons)[a]	[25]
			ECS (outer layer of the cerebral cortex)[a]	[24]
			Early phase of CDV infection[a]	[32]
			Cerebral contusion[a]	[25]
	Cerebellum	Neurons, Bergman glial cells	Changes during postnatal development	[17,18,21]
	Hypothalamus		Early phase of CDV infection[a]	[32]
	Substantia nigra		Parkinson's disease[a]	[31]
TIMP-2	Cortex	Predominantly neurons	Unaffected by KCl depolarization	[23,25]
	Cerebellum	Neurons	Changes during postnatal development	[17]
TIMP-3	Cortex	Predominantly neurons	Unaffected by KCl depolarization	[25]
			Early phase of CDV infection in mouse[a]	[32]
			Transient ischemia[a]	[73]
	Cerebellum	Neurons, dendrites, cell bodies	Changes during postnatal development	[17,18]
TIMP-4	Cerebellum	Purkinje cells	Changes during postnatal development	[21]

[a] Upregulation of TIMP gene expression.

neuronal layers of the hippocampus and with dentate molecular layer, stratum oriens, radiatum and lucidum [20]. TIMP-1 mRNA expression was also described in cortical neurons [24,25] and in the cerebellum [18,21], where Villant et al. [17] have found TIMP-1 protein in the cell bodies of interneurons, Purkinje cells and Bergman glia. Nedivi et al. [26] were the first to find increased levels of TIMP-1 mRNA in the hippocampal DG following seizures. Rivera et al. [19] and Jaworski et al. [27] extended this observation, by documenting elevated TIMP-1 mRNA and protein expression in all of the hippocampal subfields, thus suggesting that it is a neuronal response to the enhanced activity. Furthermore, Rivera et al. [19] found that seizures elevate TIMP-1 immunoreactivity in neuronal cell bodies and dendritic areas at early time points after seizures and in astrocytes 3 days after seizures, when the reactive gliosis is present. Gertten et al. [25] have shown that expression of TIMP-1 mRNA increases in cortical neurons after KCl-depolarization. Robust induction of TIMP-1 mRNA has been observed after acute electroconvulsive seizures (ECS) in neurons of the DG of the hippocampus and the outer layer of the cerebral cortex (L1) [24]. After chronic ECS, there is further induction in the L1 region, as well as an increase in the molecular layer of the hippocampus. In pathological conditions of brain damage evoked by ischemia [20,28] as well as viral infections [29], elevation of TIMP-1 expression has also been noted and suggested to have a neuroprotective potential. It is also of great interest that TIMP-1 gene expression in the hippocampus is regulated by AP-1 transcription factor, whose association with neuronal plasticity, including learning and memory, has been very extensively documented [27,30].

As far as the possible function of TIMP-1 in the brain is concerned, very little is known. However, it should be noted that this protein delivered in an adenoviral vector was capable of inhibiting excitotoxic cell death in cultured neurons [28]. The action of TIMP-1 was anti-necrotic rather than anti-apoptotic as it was very fast (already within 1 h) and specific to glutamate-evoked neuronal loss, but not effective against chemical-induced ischemia or nerve growth factor (NGF) withdrawal. Furthermore, blocking MMP activity using synthetic MMP inhibitors as well as treatment with TIMP-3 offered no neuroprotection against excitotoxicity [28]. The possible mechanism of TIMP-1 neuroprotection involves its ability to lower intracellular calcium levels in response to glutamate [28].

TIMP-2 is the most abundantly expressed TIMP in the adult CNS [21]. In the rat cerebellum both the mRNA and protein are present in cell bodies of interneurons, Purkinje cells and granular neurons in the internal granular layer [17,18]. In the cortex expression of TIMP-2, mRNA is observed predominantly in neurons [23,25]. Notably, TIMP-2 expression appears to be neither upregulated by neuronal depolarization nor by pathological conditions that activate TIMP-1 [23,31,32]. TIMP-3 is expressed at the lowest level in the adult rat brain [21], although its mRNA has been found in the cortex [33], cerebellum [17], thalamus, olfactory bulb [22], and brain stem [18]. Immunohistochemistry has shown cerebellar TIMP-3 expression in the dendritic elongations of Purkinje cells and in the granular neurons in the internal granular layer. In contrast, TIMP-3 mRNA was only detected in the cell bodies of Purkinje cells. Pagenstecher et al. [23] have shown that TIMP-3 mRNA is expressed in choroid plexus as well as in scattered unidentified cells in the CA4 region of the hippocampus and in some gigantocellular neurons in the brain stem. During viral infections there is TIMP-3 mRNA and protein upregulation in neurons within hours [32]. TIMP-3 protein is produced by primary cultures of cortical neurons [34] and astrocytes [35]. Functionally, it has been shown that TIMP-3 may play a pro-apoptotic role in a model of neuronal cell death evoked by doxorubicin [34].

The least is known about TIMP-4 expression in the brain. TIMP-4 mRNA is present in the cerebellum, cerebrum and brain stem [18,21,36].

Table 2
Basal and induced MMP expression in the brain

Gene	Brain structure	Expression		References
		Basal level	Upregulation/downregulation	
MMP-2	Hippocampus	Uniformly distributed, gray matter, astrocytes	Unaffected by spatial learning	[7,38]
			Seizures (3–7 days)[a]	[39,40]
			Sprouting[a]	[37]
			Traumatic brain injury[a]	[37]
			Transient ischemia[a]	[20]
			Early phase of CDV infection[a]	[32]
	Cortex	Astroglia, some neurons	Seizures (3–7 days)[a]	[39,40]
			Transient ischemia[a]	[42]
			ALS[b]	[57]
	Cerebellum	Purkinje cells	Changes during postnatal development	[17]
	Striatum			[40,74]
	Substantia nigra		Parkinson's disease[b]	[31]
	Pons		Spinocerebellar ataxia type 3[a]	[75]
MMP-3	Cortex		Transient ischemia[a]	[43]
			Traumatic brain injury[a]	[46]
	Cerebellum	Neurons, cell bodies, Bergman glia fibers	Changes during postnatal development	[17]
MMP-7	Brain	More than three orders of magnitude less than MMP-9		[76]
MMP-8	Brain	Two orders of magnitude less than MMP-9		[61,76]
MMP-9	Hippocampus	Pyramidal and granular neurons, cell bodies and dendrites	Seizures (neurons, dendrites, astrocytes)[a]	[7,20,39–41]
			Spatial learning[a]	[38]
			Sleep deprivation[b]	[52]
			Alzheimer's disease[a]	[77]
			Early phase of CDV infection[a]	[32]
			Transient ischemia[a]	[20]
	Cortex	Cortical neurons (cytoplasm and apical dendrites), white matter KCl	Seizures[a]	[39,40,42]
			Spatial learning[a]	[38]
			Depolarization (neurons)[a]	[25]
			Modulated by sleep	[52]
			Cerebral contusion[a]	[25]
			ALS[b]	[57]
			Transient ischemia[a]	[12,42,43]
	Striatum			[20,42,74]
	Cerebellum	Neurons, granule cell precursors, cell bodies, Bergman glial processes	Changes during postnatal development	[17,38–40,53]
MMP-10	Brain	Two orders of magnitude less than MMP-9		[76]
MMP-11	Brain	Similar amount as MMP-9		[76]
MMP-12	Cortex		Traumatic brain injury[a]	[46]
MMP-13	Brain	Two orders of magnitude less than MMP-9		[61,76]
MMP-14	Cortex		Early phase of CDV infection[a]	[32]
	Hypothalamus		Early phase of CDV infection[a]	[32]
MMP-15	Brain	Similar amount to MMP-9		[61,76]
MMP-16	Brain	Similar amount to MMP-9		[61,76]
	Nucleus accumbens		Inducible by CREB transgene	[78]
MMP-24	Hippocampus	Pyramidal and granular neurons	Changes during postnatal development	[61–63]
	Cortex	Neurons	Changes during postnatal development	[61]
	Cerebellum	Neurons, cell bodies and dendrites	Changes during postnatal development	[61–63]

[a] Upregulation of MMP gene expression.
[b] Downregulation of MMP gene expression.

3. MMPs in the brain

Thus far, gelatinases (MMP-2 and MMP-9) have been the most frequently investigated MMPs in the brain (see Table 2). This situation has probably been driven mostly by the fact that they are relatively easily detectable and measurable by zymography, both gel-based and in situ, in which the ability to digest denatured collagen IV (gelatin) is employed.

MMP-2 mRNA, protein, and enzymatic activity have been detected in various brain structures and reported to be preferably astroglial in origin [7,20,37–41]. In addition, Planas et al. [42] found MMP-2 also in some cortical neurons, and neuronal MMP-2 has also been described in the cerebellum, including the Purkinje neurons [17,38–40]. In vitro studies have shown that MMP-2 activity is produced by astrocytes and microglia [43], oligodendrocytes [44,45] and even neurons [46]. However, it shall be noted that neuronal cultures consist of very immature populations of cells. It is thus interesting that MMP-2 is expressed at a much higher level during postnatal cortical development than in the adult neocortex (Dzwonek et al., unpublished). Inducible expression of MMP-2 in glia has also been noted following brain ischemia [20,42], kainate (KA) treatment as well as traumatic and viral brain injury [32,37,40,47–49]. Interestingly, Asahi et al. [50] showed that MMP-2 gene knockout in mice has no effect on brain injury after permanent and transient focal ischemia. On the other hand, stereotactical implantation of conditioned medium including pro-MMP-2 to the mouse basal ganglia results in neuronal death and neuroinflammation with ensuing behavioral deficits [48]. This pathological chain is abrogated by the MMP activity inhibitory drug Prinomastat or by implantation of an inactive MMP-2 Glu375Ala mutant. A potentially functional role of MMP-2 in post-lesion axonal sprouting and neuronal plasticity has been suggested by Reeves and colleagues, who reported that deafferentation and subsequent functional plastic recovery of the entorhinal cortex projections to the hippocampal DG correlate with increased MMP-2 activity, and the MMP inhibitor FN-439 prevents recovery [37,51]. However, it shall be noted that the inhibitor is not MMP-2 specific.

In contrast to MMP-2, MMP-9 mRNA and protein expression [7,20,52] as well as its activity [7,20,38–40,53] have been detected in the hippocampus, cerebellum and cortex, predominantly in neurons. MMP-9 (at the protein and enzymatic activity levels) has been found mainly in cell bodies and dendrites [7,42]. Furthermore, in vitro studies showed MMP-9 protein expression in the neuronal processes of cultured hippocampal neurons [7]. A more limited level of MMP-9 expression has also been observed in glia, in particular in astrocytes and microglia, both in vivo and in vitro [17,43–45].

Szklarczyk et al. [7] and Zhang et al. [40] have shown that KA treatment results in upregulation of MMP-9 mRNA, protein and enzymatic activity in hippocampal DG and neocortex early after seizures (6–24 h). The exclusive hippocampal localization of MMP-9 upregulation within the DG suggests MMP-9 involvement in synaptic plasticity [54]. Most interestingly, the enhanced mRNA expression was observed both in the neuronal cell bodies as well as in dendritic layer, implying an activity-driven translocation of the MMP-9 mRNA. Jourquin et al. [41] have shown that MMP-9, but not MMP-2, activity is induced by KA in organotypic cultures of the hippocampus. Furthermore, MMP-9 mRNA levels were increased after KCl-depolarization in the cortex [25] and enzymatic activity of MMP-9, but not MMP-2, was found to be elevated in the rat hippocampus and prefrontal cortex in the course of spatial learning [38]. On the other hand, MMP-9 mRNA level decreases in the cerebral cortex after sleep deprivation whereas after enhanced ambient temperature, a condition that promotes sleep, increases [52]. During postnatal cerebellar development, MMP-9 is expressed by granule and Purkinje neurons of the cerebellum [53]. MMP-9 promotes cerebellar granule cell migration and axonal growth during early postnatal life [53]. In this period cerebellar granule cell apoptosis coincides with the initial period of synaptogenesis between parallel fibers and Purkinje cells. In MMP-9 deficient mice, a decreased physiological, granule cell apoptosis during the period is observed [53], suggesting a potential connection(s) between neuronal survival, synaptogenesis and MMP-9. These results show a close association of MMP-9 expression with neuronal physiology. Apparently, no functional data have been reported specifically on MMP-9 and neuronal plasticity, despite the availability of MMP-9 knockout mice. Those animals were, however, used for brain damage studies, and it has been found that lack of MMP-9 reduces the neurodegeneration evoked by either ischemia or brain trauma [55,56]. This notion appears surprising in the context of the previously described data implicating MMP-9 in neuronal plasticity. However, although under the variety of neurodegenerative conditions (ischemia, brain trauma, viral infections, amyotrophic lateral sclerosis, ALS, Parkinson's disease, PD, Alzheimer's disease, AD) MMP-9 still remains mainly neuronal in origin, it is not clear whether it is expressed by the neurons prone to death and/or those attempting to recover from the damage [12,20,31, 32,43,57–59]. As it has recently been pointed out that both possibilities should be equally considered [60].

MMP-24 (MT5-MMP) is the next member of the family, whose expression was investigated in the brain by various researchers. Sekine-Aizawa et al. [61] used an reverse-transcriptase polymerase chain reaction (RT-PCR) approach to show that MMP-24 comprises 60% of the total rat brain population of the non-gelatinase MMPs. In the adult mouse brain strong MMP-24 mRNA signals were detected in the DG of the hippocampus, the granular layer of the cerebellum [61–63], the olfactory bulb and the thalamus [61,63]. The presence of MMP-24 protein was also detected by immunostaining at the hippocampal pyramidal and granular neurons as well as in cell bodies and dendrites of granule cells in the cerebellum [61,62]. In vitro studies have shown that MMP-24 is expressed at the growth cone of neurons [62].

Among the other MMPs, less frequently studied in the brain is MMP-3. Villant et al. [17] investigated MMP-3 protein expression in rat cerebellum. They found that MMP-3 is present in cell bodies of interneurons, Purkinje cells, granular neurons in the internal granular layer and in Bergman glia fibers. MMP-3 protein has also been found in cortical neurons [34] and astrocytes [35] in culture, however, Rosenberg et al. [43] could not find MMP-3 immunostaining in cerebral cortex of spontaneously hypertensive rats. Nevertheless, MMP-3 appeared in neurons and activated microglia/macrophages of ischemic cerebral cortex [43]. Non-ischemic neurons showed scattered and punctuated MMP-3 immunopatterns, whereas ischemic ones diffuse staining co-localized with cell bodies. MMP-3 induction in brain pathology can be related to its anti-apoptotic action exerted by shedding of the death receptors from neuronal cell surface, thus abrogating apoptotic signaling [34].

4. Proteins targeted by MMPs in brain neurons

Search for the MMPs' target molecules can help discover and explain MMPs' role(s) in brain physiology. Two major reasons make this task very challenging. First, the MMPs

appear to be quite promiscuous in recognizing their substrates, and their *hic et nunc* activity, temporally and spatially very restricted, determines what is to be digested. Furthermore, intraneuronal ECM of the adult brain does not contain the classical ECM proteins like agrin, collagen, laminin or perlecan reported to be susceptible to MMP activities in other tissues [64]. Thus, there are virtually no well documented physiological MMP target proteins, and just a handful of pathological ones. According to the leading concept of this review, we limit the description of the targets to those which are expressed by brain neurons.

A very promising MMP physiological brain target molecule is β-dystroglycan [65,66]. Dystroglycan is a cell surface protein protruding from postsynaptic membrane and bound (probably throughout the synaptic cleft) to presynaptic neurexins, implicated in neurotransmitter release [64,67]. Genetic evidence implicated dystroglycan in long term potentiation (LTP), a model of neuronal plasticity [68]. These results and considerations have prompted us to propose that MMP-9 can be involved in synaptic plasticity by modifying the local environment and even serve as a retrograde messenger at activated synapses [66].

Amyloid peptide, a hallmark of AD could be another target of MMP-9 in the brain. In the human AD hippocampus there is an accumulation of MMP-9 zymogen in both the neurons as well as senile plaques and neurofibrillary tangles [58]. Furthermore, upon incubation in vitro, activated MMP-9 cleaves a synthetic β-amyloid peptide Aβ 1–4 at several sites, especially within the membrane spanning domain at Leu34–Met35, generating a non-neurotoxic form of amyloid peptide [58].

Several substrates of potential physiological significance have been proposed for MMP-24. In vitro, this enzyme cleaves proteoglycans (PGs), including chondroitin sulfate proteoglycan (CSPG) [69]. In the mouse brain similar cleavage also occurs and CSPG together with heparan sulfate proteoglycan (HSPG) could comprise the MMP-24 targets [62]. PGs, abundant brain ECM molecules, regulate synaptogenesis inhibiting neurite extension and, therefore, can also be involved in synaptic plasticity. In a neurite extension assay, MMP-24 eliminates the inhibitory effect of HSPG or CSPG on the neurite outgrowth without hindering the neurite-promoting potential of laminin. The action of MMP-24 is blocked by its activity inhibitor BB-94. It should not remain overlooked that MMP-24 can activate other MMP zymogens, e.g., MMP-2 [69]. Thus it is possible that MMP-24 may exert the aforementioned effects indirectly. Interestingly, neuronal MMP-2 degrades CSPG in vitro in regenerating chicken embryonic root ganglionic neurons playing an important role in the regeneration of peripheral nerves [70].

It is well established that neurotrophins such as NGF and brain-derived neurotrophic factor (BDNF) participate in neuronal survival and synaptic plasticity. Their precursors contain consensus sites for cleavage by MMP-3 and MMP-7 [71]. Indeed, the proteases can extracellularly cleave secreted pro-neurotrophins [72].

5. Concluding remarks

TIMPs and MMPs display distinct expression patterns in adult brain neurons, and their levels are regulated by neuronal activity, clearly implicating specific components of the TIMP/MMP system in neuronal physiology. Results from subcellular localization as well as functional studies point to possible role(s) of TIMPs and MMPs in axonal, dendritic and synaptic functions. Altogether these data suggest that, besides playing well documented roles in neuronal pathologies, selective members of TIMP and MMP families are important for neuronal plasticity. Recent rapid development of the tools allowing to approach the TIMP/MMP system functionally should greatly facilitate further studies aiming at the elucidation of their physiological functions. It remains especially intriguing whether activated MMPs play detrimental and/or beneficial roles in response to neuronal damage. Other major questions to be addressed in future studies are those about regulation of MMPs' and TIMPs' expression and function, as well as defining their physiological partners and targets. Clearly, we are just witnessing an opening of studies on this important enzymatic system in brain physiology.

Acknowledgements: The work on MMPs in Kaczmarek's laboratory has been supported by KBN (State Committee for Scientific Research, Poland Grant PBZ-MIN-005/P04/2003), the International Centre for Genetic Engineering and Biotechnology, ICGEB, Trieste, Italy, and the Wellcome Trust.

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