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Matrix metalloproteinases in the adult brain physiology: a link between c-Fos, AP-1 and remodeling of neuronal connections?

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Matrix metalloproteinases (MMPs), together with their endogenous inhibitors (TIMPs) form an enzymatic system that plays an important role in a variety of physiological and pathological conditions. These proteins are also expressed in the brain, especially under pathological conditions, in which glia as well as invading inflammatory cells provide the major source of the MMP activity. Surprisingly little is known about the MMP function(s) in adult neuronal physiology. This review describes available data on this topic, which is presented in a context of knowledge about the MMP/TIMP system in other organs as well as in brain disorders. An analysis of the MMP and TIMP expression patterns in the brain, along with a consideration of their regulatory mechanisms and substrates, leads to the proposal of possible roles of the MMP system in the brain. This analysis suggests that MMPs may play an important role in the neuronal physiology, especially in neuronal plasticity, including their direct participation in the remodeling of synaptic connections—a mechanism pivotal for learning and memory.

Keywords: dystroglycan/extracellular matrix/hippocampus/neuronal plasticity/TIMP

Matrix metalloproteinases and their endogenous inhibitors

Matrix metalloproteinases (MMPs) constitute a family of enzymes with >20 members identified to date, which are all extracellular (predominantly pericellular, and some membrane-bound) endopeptidases requiring Zn^{2+} for their enzymatic activity (Woessner and Nagase, 2000). Their major targets are proteins of the extracellular matrix (ECM). MMPs are grouped together because of their sequence kinship and consequent structural and enzymatic similarities (Massova *et al.*, 1998). All of the MMPs are produced with an N-terminal signal peptide, which is removed after directing their synthesis into the endoplasmatic reticulum. They all contain a propeptide that has to be cleaved off to reveal enzymatic activity, and their catalytic domains, responsible also for the substrate recognition, are similar, with a conserved Zn^{2+} binding site. The vast majority of MMPs also have a hemopexin-like domain at the C-terminus that is mainly responsible for binding to certain substrates as well as other interacting proteins, including specific inhibitors (TIMPs—tissue inhibitors of metalloproteinases). A membrane-bound subclass is characterized by a single-pass transmembrane domain and a short cytoplasmic C-terminal tail or a hydrophobic region that may function as a GPI (glycophosphatidyl inositol) anchoring signal (Sternlicht and Werb, 2001). The relations among MMPs extend beyond the structure. All of them require enzymatic activation (by means of the propeptide cleavage) and this is achieved by the action of serine proteinases, such as plasmin as well as other MMPs, and involves an autocatalytic step (Yong *et al.*, 1998, 2001; Woessner and Nagase, 2000).

The TIMPs (-1, -2, -3 and -4) are small (20–22 kDa) proteins that can bind MMPs and block their activities (Woessner and Nagase, 2000). Unfortunately, only very limited knowledge is available about physiological specificity of different TIMPs towards various MMPs. In addition to their effects on the MMPs, a growth-promoting action, which is unlikely to be explained on the basis of blocking the proteolysis, has also been ascribed to some TIMPs (Woessner and Nagase, 2000).

Physiological significance of the MMP/TIMP system outside the brain

Understanding of the physiological role played by the MMPs outside the brain may greatly aid in the elucidation of their function in this organ as well. Hence, it is noteworthy that the role of MMPs has been very well documented in embryonic development and tissue morphogenesis (for reviews, see Vu and Werb, 2000; Sternlicht and Werb, 2001). The evidence for developmental significance of the MMPs and TIMPs comes from studies on their expression patterns as well as from functional experiments with inhibitors and null mutations. Paramount evidence for MMP role in physiology has been collected in the case of implantation, mammary and bone development as well as wound healing. Vu and Werb (2000) proposed that MMP activity during development might be required for: (i) degradation of the ECM in order to allow cell migration; (ii) alteration of the ECM microenvironment to modify cell behavior; and (iii) modulation of the activity of biologically important molecules by direct cleavage, release from bound stores or modifying their inhibitors.

MMPs in diseases of the nervous system

A great deal of data has been collected regarding the MMP/TIMP system in a variety of brain pathologies. In particular, the MMPs have been implicated in gliomas (tumors of glial origin), viral infections, inflammation,

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multiple sclerosis (MS), Alzheimer's disease, amyotrophic lateral sclerosis, brain trauma and ischemia (see Rosenberg, 1995; Rooprai and McCormick, 1997; Yong *et al.*, 1998, 2001; Lukes *et al.*, 1999; for a review, see Leppert *et al.* 2001). In the context of MS MMP-1, -2, -3 and -9 were immunolocalized to brain macrophages/ microglia and astrocytes (Yong *et al.*, 1998, 2001; Leppert *et al.*, 2001). The levels of those enzymes could be increased by various inflammatory cytokines *in vitro* as well as in animals with experimental allergic encephalomyelitis (EAE) serving as a model for MS. Furthermore, chemical inhibitors of MMP activity were shown to ameliorate the severity of the EAE (Yong *et al.*, 2001). In case of brain ischemia in rats and mice, expression and activation of the MMP-2 was observed in neurons, glia and the endothelium, whereas MMP-9 was found elevated in neurons and glia as well as myelinated fiber tracts, and MMP-3 was found in neurons (Rosenberg *et al.*, 1996; Clark *et al.*, 1997; Mun-Bryce and Rosenberg, 1998; Gasche *et al.*, 1999; Heo *et al.*, 1999; Rivera *et al.*, 2002). Inhibition of MMPs with substances displaying especially high activity against gelatinases (MMP-2 and -9), as well as injection of a neutralizing antibody against MMP-9 and a targeted disruption of the MMP-9 gene, all diminished the severity of the damaging consequences of ischemia to the brain (Romanic *et al.*, 1998; Rosenberg *et al.*, 1998; Asahi *et al.*, 2000, 2001; Jiang *et al.*, 2001).

In conclusion, the disease studies underscore the importance of the MMPs in brain dysfunctions, as well as clearly showing how important it is to investigate the cellular origins of the MMP activities within this organ, where non-neuronal cells, including the infiltrating inflammatory ones, provide the major component of pathology-related MMP overexpression. As Yong *et al.* (2001) have already pointed out, an intriguing question remains: to what extent the activation of MMPs in the response to brain-damaging treatments is detrimental to the tissue or, in contrast, represents a repair reaction.

MMP/TIMP expression patterns in the brain

Overall, the MMPs are expressed at basal conditions at very low levels in various tissues. Similarly, only a few of the MMPs were shown to be expressed in the unstimulated brain (Yong *et al.*, 2001). For instance, Pagenstecher *et al.* (1997) and Vecil *et al.* (2000) used an RNase protection assay to show that among MMP-1, -2, -3, -7, -9, -10, -11, -12, -13 and -14 only five, MMP-2, -9, -11, -12 and -14, were expressed, and mostly at rather low levels, in the mouse brain. Sekine-Aizawa *et al.* (2001) used a RT–PCR approach to show that MMP-24 (also known as MT5 MMP; see also Pei, 1999) comprises 60% of the total rat brain population of the MMPs lacking a fibronectin-like domain, followed by MMP-14 (23%), MMP-15 (13%), MMP-13 (3.3%), MMP-3 (1.3%) and MMP-8 (0.7%).

Two brain structures investigated in more detail with regard to MMP expression are the cerebellum and the hippocampus. Sekine-Aizawa *et al.* (2001) found that most of the brain MMP-24 expression originates from the cerebellum, where its mRNA is especially abundant in the granule and Purkinje neurons. A similar conclusion was obtained with regard to the protein distribution in both rat and mouse cerebellum (Hayashita-Kinoh, 2001; Sekine-Aizawa *et al.*, 2001). Using gelatinase assay, Vaillant *et al.* (1999) observed low levels of MMP-9 in the adult rat cerebellum and higher levels of the MMP-2. Abundant expression in the adult Purkinje neurons was also observed for MMP-9, -2 and -3 (Vaillant *et al.*, 1999). MMP-3 and -9 were also present in the granular neurons of the adult cerebellum (Vaillant *et al.*, 1999). It is noteworthy that the expression of MMP-3 and -9 was at high levels in the cerebellum of 15-day-old rats, i.e. at the time of intense synaptogenesis. As far as the subcellular distribution is concerned, Sekine-Aizawa *et al.* (2001) reported that MMP-24 was localized predominantly to neuronal cell soma and dendrites, whereas Vaillant *et al.* (1999) found predominant expression of MMP-2, -3 and -9 proteins only in the neuronal cell bodies.

In addition to the cerebellum, the MMP-24 mRNA and protein were also clearly detected in the rat and mouse hippocampus (in the neurons of the dentate gyrus as well as CA1, CA2 and CA3 subfields) (Jaworski, 2000; Hayashita-Kinoh, 2001; Sekine-Aizawa *et al.*, 2001). In the human hippocampus, Backstrom *et al.* (1996) detected MMP-9 mRNA and protein in the pyramidal neurons of the CA subfields, but not in the granule neurons of the dentate gyrus. Relatively low levels of the MMP-24 mRNA and protein could also be found in the pyramidal cortical neurons, and some neurons of the thalamus as well as in the olfactory bulb (Jaworski, 2000; Sekine-Aizawa *et al.*, 2001). More extensive analysis of MMP-2 and -9 expression at the level of mRNA and protein in the hippocampus indicated that whereas MMP-2 appeared to be mostly glial in origin, the MMP-9 was expressed mainly by neurons (Szklarczyk *et al.*, 2002).

In addition to MMPs, also TIMPs are found in the brain (Pagenstecher *et al.*, 1997; Vaillant *et al.*, 1999; Jaworski, 2000). In the cerebellum TIMP-4 mRNA is particularly abundant, followed by TIMP-1. On the other hand, TIMP-2 mRNA is present all over the brain, although with lower levels in the cerebellum, while TIMP-3 appears to be present predominantly in the choroid plexus (Fager and Jaworski, 2000). Within the cerebellum, the TIMP-1, -2 and -3 are expressed by the Purkinje cells, with the latter two also expressed by granule neurons (Vaillant *et al.*, 1999). TIMP-3 (protein, but not mRNA) was the only one detected in the dendrites (Vaillant *et al.*, 1999).

MMP/TIMP expression in the stimulated brain

Besides being actively produced by various non-neuronal (glial and infiltrating) cells in the brain in response to a variety of pathogenic insults (see above), MMP-9 and TIMP-1 were found to also be elevated in neurons in response to enhanced activity. Nedivi *et al.* (1993) were the first to find (by means of subtractive cloning) increased levels of TIMP-1 mRNA in the hippocampal dentate gyrus following seizures (seizures are often used as a convenient model system to investigate enhanced neuronal activity driven by the major excitatory neurotransmitter, glutamate). Rivera *et al.* (1997) and Jaworski *et al.* (1999) extended this observation, by documenting elevated TIMP-1 mRNA and protein expression in all the hippocampal subfields, thus suggesting that it is a neuronal response to the enhanced activity. Furthermore, Rivera

et al. (1997) found that seizures elevate TIMP-1 immunoreactivity in hippocampal neurons and astrocytes.

In addition, seizures activate MMP-9 at all levels—enzymatic activity, protein and mRNA expression (Zhang *et al.*, 1998; Szklarczyk *et al.*, 2002). Enzymatic activity (as well as the abundance of the protein contained within a membrane-bound fraction) is elevated already at 6 h after the seizures, whereas mRNA expression peaks at 24–72 h, suggesting that elevated gene expression might be a response to, rather than cause for, the active protein release. Most interestingly, the enhanced mRNA expression was observed both in the neuronal cell bodies as well as in the dendritic layer, suggesting an activity-driven translocation of the MMP-9 mRNA (Szklarczyk *et al.*, 2002). Such a phenomenon could have important consequences for neuronal plasticity, including learning and memory, as it has already been observed for mRNAs that are apparently locally translated at the activated, selected synapses (for a review, see Job and Eberwine, 2001; Steward and Schuman, 2001). It is believed that such local mRNA translation could provide a mechanism for synapse-specific control of protein synthesis, which may underlie delineation of synaptic specificity in long-term memory formation (see Frey and Morris, 1998; Martin *et al.*, 2000).

Direct connection between MMP-9 expression and learning has recently been suggested by Wright *et al.* (2002) reporting that MMP-9 enzymatic activity is enhanced in the rat hippocampus in the course of spatial learning. Possible involvement of MMP-9 in brain physiology is also supported by the results of Taishi *et al.* (2001), who reported that manipulation with sleep and ambient temperature may affect the MMP-9 mRNA levels in the cerebral cortex and hippocampus. Parallel analysis of brain-derived neurotrophic factor (BDNF), tissue-type plasminogen activator (tPA) and immediate early gene—*arc* mRNA expression—all implicated previously in neuronal plasticity, and all responsive in various ways to the modulation of sleep and temperature conditions as shown by Taishi *et al.* (2001), led the authors to suggest that the aforementioned genes, sleep and synaptic plasticity are somehow linked.

Regulation of neuronal MMP expression and activity

As limited data are available on MMPs and TIMPs in neuronal physiology of the adult brain, important clues may come from extensive knowledge collected on regulation of this enzymatic system in other cells. MMPs are very elaborately controlled, especially at the levels of gene expression and enzymatic activation to produce a functional form, as well as through the inhibition by TIMPs (Sternlicht and Werb, 2001). In certain cases, there are also mechanisms affecting specifically the mRNA stability, protein secretion as well as specific degradation and clearance (Sternlicht and Werb, 2001). Particularly revealing are results on regulation of the MMPs and TIMPs by factors that have already been shown to play pivotal roles in the brain.

There are many instances when neuronal cell surface receptors, bound by specific ligands, affect function of the AP-1 transcription factor (Herdegen and Leah, 1998). AP-1 is a dimer made of Jun (c-Jun, JunB and JunD) or Jun and Fos (c-Fos, FosB, ΔFosB, Fra-1 and Fra-2) proteins. In the brain, a transient activation of AP-1 is intimately linked to neuronal plasticity (for example, see Kaczmarek, 1993; Kaczmarek and Chaudhuri, 1997; Kaczmarek, 2002). However, despite multiple efforts, our understanding of AP-1 in the brain is very limited. Thus, it is very interesting to note that in other organs AP-1 has been shown to play a major role in regulating the expression of a number of MMP genes. For MMP-9, the evidence for control exerted by AP-1 is paramount, although a number of other transcription factors/regulatory elements appear to play a role too. However, it has to be stressed that the MMP (including MMP-9) gene regulation may occur in a cell-specific manner (Sato and Seiki, 1993; Benbow and Brinckerhoff, 1997). Unfortunately, apparently no extensive analyses of the neuronal regulation of the MMP gene expression have been reported.

On the other hand, the most advanced example for AP-1 control of gene expression in the adult brain has been provided for TIMP-1. It has been known that the TIMP-1 gene promoter contains a non-canonical AP-1 responsive element, playing a role in gene regulation in non-neuronal cells (Alitalo *et al.*, 1990; Campbell *et al.*, 1991; Edwards *et al.*, 1992; Bugno *et al.*, 1995; Logan *et al.*, 1996; Botelho *et al.*, 1998). Jaworski *et al.* (1999) combined a variety of approaches to show that the gene encoding TIMP-1 may be an AP-1 target in the rodent hippocampus in response to seizures. The evidence was based on the following findings: (i) the AP-1 transcription factor that accumulated in seizure-stimulated hippocampi (Kaminska *et al.*, 1994) was capable of binding the TIMP-1 AP-1 responsive DNA regulatory element in a sequence-dependent manner, and this AP-1 DNA binding activity contained such proteins as c-Fos, c-Jun, JunB and JunD; (ii) increase in TIMP-1 mRNA levels following *c-fos* mRNA accumulation was dependent on prior protein synthesis, and was spatially correlated with c-Fos protein expression; (iii) TIMP-1 promoter was seizure-responsive in the hippocampi of transgenic TIMP-1-LacZ mice; (iv) glutamate was able to activate expression of a reporter gene, driven by TIMP-1 promoter containing an intact AP-1 site, in cultured neurons of the dentate gyrus, and mutation of this promoter element abolished the expression (Jaworski *et al.*, 1999).

Once the MMP proteins are released, their activation occurs via cleavage of the propeptide. Plasmin, a serine proteinase plays a major role in this reaction (Sternlicht and Werb, 2001). Plasmin, in turn, is produced from plasminogen due to activity of tPA or urokinase plasminogen activator (uPA). It is conspicuous that all three—plasmin, tPA and uPA—have repeatedly been implicated in neuronal plasticity, including learning and memory, by virtues of their expression patterns as well as by functional studies involving specific inhibitors, transgenic mice and null mutants (Qian *et al.*, 1993; Meiri *et al.*, 1994; Seeds *et al.*, 1995; Baranes *et al.*, 1998; Madani *et al.*, 1999; Yoshida and Shiosaka, 1999).

MMP substrates in the brain

The list of MMP substrates is long (for example, see Liu et al, 2000; Woessner and Nagase, 2000; Kridel *et al.*, 2001; Yamada *et al.*, 2001). However, very little is known

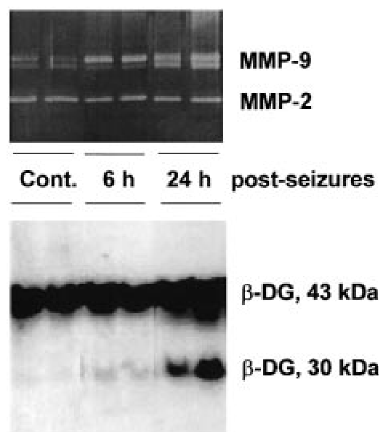

Fig. 1. Neuronal activity-driven limited proteolysis of β-dystroglycan. The adult Wistar rats were treated with 10 mg/kg sodium kainate (see Kaminska *et al*., 1994) and the animals displaying robust seizues were killed at either 6 or 24 h afterwards, along with the control ones (Cont.). The hippocampi were then dissected and the proteins extracted either for zymographic assay of MMP activity with gelatin as a substrate (see Szklarczyk *et al*., 2002) or for immunoblotting detection of β-dystroglycan (with the antibody kindly provided by Dr T.Petrucci; Rosa *et al*., 1996).

about which of them could comprise the *in vivo* targets for MMPs. The situation gets even more complicated for the brain, as composition of the ECM differs markedly from the one typical to other organs. The extracellular space between neurons in adult brain lacks a basal lamina and apparently does not contain such classical MMP-susceptible ECM proteins as laminins and collagens (Sugita *et al.*, 2001). Nevertheless, there are MMP targets that are available in the brain and could be involved in neuronal plasticity. Integrins appear to be especially appealing in this context, as several lines of evidence suggest that integrins play important roles in neuronal plasticity, including learning and memory (see Rohrbough, 2000; Chun *et al.*, 2001). In addition, recently, Lee *et al.* (2001) have identified pro-NGF and pro-BDNF as MMP (MMP-3 and MMP-7) substrates. The role of the neurotrophins, including NGF and BDNF, in neuronal plasticity has been well documented.

The most fascinating hypothesis may, however, be proposed after considering recent observations that dystroglycan may be a physiological target for MMP activity (most probably MMP-2 or -9; see Yamada *et al.*, 2001). Although this phenomenon was not pronounced in the brain, our recent results show that similar proteolytic breakdown of the β-dystroglycan also occurs in the rat hippocampus in response to kainate in a temporal pattern parallel to increased levels of the MMP enzymatic activity (Figure 1). Furthermore, recent evidence based on a brain-limited knockout of dystroglycan, shows that this protein plays an important role in LTP (long-term potentiation of synaptic efficacy), serving as a model of neuronal plasticity (Moore *et al.*, 2002).

Dystroglycan is a molecule that extends from the postsynaptic side into the ECM. Inside the cell, dystroglycan binds dystrophin, which is involved in linking various proteins with the cytoskeleton. It has also been shown that dystroglycan comprises the major target for neurexins (Sugita *et al.*, 2001). Neurexins (I, II, III: α and β) are

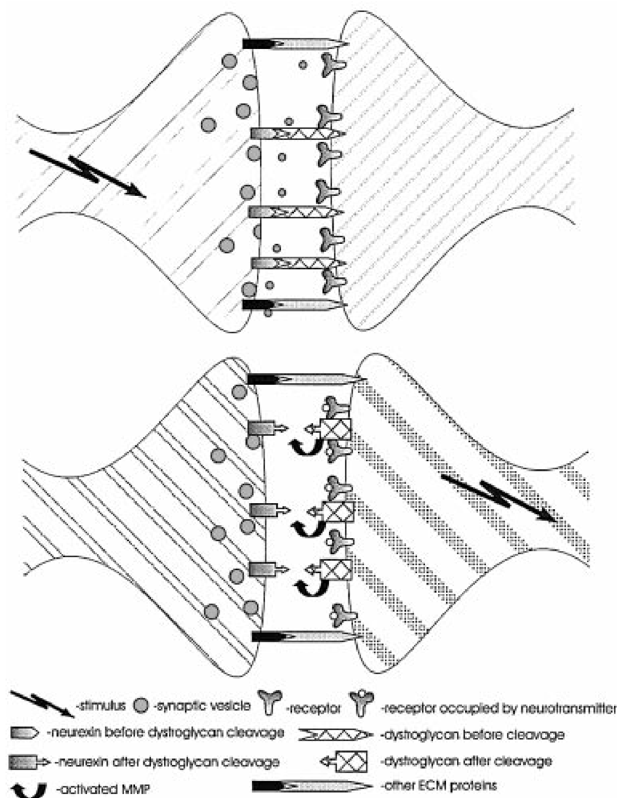

Fig. 2. Schematic representation of putative retrograde messenger function exerted by the MMPs at the activated synapse. At the steady state, the presynaptic and postsynaptic sides are directly linked through transmembrane/ECM molecules, such as neurexin and dystroglycan (top panel); activity-driven release of the neurotransmitter results is stimulation of the postsynaptic side, which in turn releases active MMPs (bottom panel). The MMPs perform limited proteolysis of dystroglycan that results in allosteric modulation of both the neurexins and the remaining part of dystroglycan, which in turn produces specific structure/function changes in both the pre- and postsynaptic cytoplasmic environment (as shown in the figure by changes in the background pattern).

apparent recognition molecules that extend from the presynaptic side into the ECM. Interestingly, Górecki *et al.* (1999) found that Neurexin IIα mRNA accumulated in the dentate gyrus of the hippocampus in response to enhanced neuronal activity, whereas mRNA for dystrophin (Dp71 isoform) disappeared from the same region after such treatment (Gorecki *et al.*, 1998). These observations, combined with the fact that the dentate gyrus is selectively engaged in neuronal plasticity after kainate treatment, suggest a possible role for both proteins in plasticity phenomena. It is thus tempting to suggest that presynaptic membrane-bound neurexins interact directly with postsynaptic dystroglycan molecules, which in turn communicate through dystrophin with postsynaptic cytoskeleton and other proteins. Cleavage of dystroglycan by MMP (such as neuronal MMP-9) could produce conformation changes that affect both pre- (neurexin) and postsynaptic (dystroglycan–dystrophin) elements. The major question remains whether such structural changes affect cytoorganization and/or any signal transduction pathways on both sides of the synapse. If this is the case, this phenomenon could play the most important role in neuronal plasticity, serving a function of a retrograde messenger to be activated at the postsynaptic side in response to enhanced neuronal activity, and acting on the

presynaptic side (Figure 2). Such signals have been intensely searched for, because of the conceptual framework provided by Hebb (1949) to explain learning. Hebb's proposal demanded that both neurons, whose connection is to be strengthened, had to be simultaneously active.

Concluding remarks: functions of the neuronal MMPs in the brain physiology

Despite their marked presence in the brain, especially in response to enhanced neuronal activity, as well as given important functional roles of MMPs in brain dysfunctions, very little is still known about physiological functions of these enzymes in the nerve tissue. Two enzymes that appear to be most interesting to study are MMP-24 in the cerebellum and MMP-9 in the hippocampus, along with all the TIMPs. The expression patterns and the regulatory mechanisms offer clues as far as the possible roles of these proteins are concerned. The massive activation and an increase in the mRNA as well as protein levels in the stimulated hippocampus appear to be a good indication for possible involvement of the MMP-9 in neuronal plasticity, i.e. experience-dependent reorganization of synaptic connections. In this context, it would be of great interest to analyze subcellular, including possible synaptic, distribution of this enzyme. The fact that TIMP-1 is controlled by AP-1 transcription factor in the hippocampus, along with an expected role for AP-1 in regulation of the neuronal MMP-9 gene (as already proven for non-neuronal cells) further supports the notion of a relation of this enzyme system with plasticity. Similarly, involvement of plasmin, which is controlled by tPA and uPA in MMP activation, is also suggestive as far as the role of the MMP/TIMP system in neuronal plasticity is concerned. Another clue for the MMP functions in the brain comes from identification of their substrates and interacting proteins with integrins, and dystroglycan appearing to be especially interesting for neuronal plasticity. Notably, those substrates perform either structural or signaling roles in neuronal functioning and thus, an involvement of the selected MMPs in control of ECM architecture as well as information transfer can be envisaged. In aggregate, it is safe to conclude that MMPs together with their endogenous inhibitors are expected to play a significant role in neuronal functions, including synaptic reorganization. It is up to forthcoming studies to verify this hypothesis.

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