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Matrix Metalloproteinase-9 as a Novel Player in Synaptic Plasticity and Schizophrenia

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Recent findings implicate alterations in glutamate signaling, leading to aberrant synaptic plasticity, in schizophrenia. Matrix metalloproteinase-9 (MMP-9) has been shown to regulate glutamate receptors, be regulated by glutamate at excitatory synapses, and modulate physiological and morphological synaptic plasticity. By means of functional gene polymorphism, gene responsiveness to antipsychotics and blood plasma levels MMP-9 has recently been implicated in schizophrenia. This commentary critically reviews these findings based on the hypothesis that MMP-9 contributes to pathological synaptic plasticity in schizophrenia.

Key words: synaptic plasticity/glutamate/extracellular matrix

Matrix Metalloproteinase-9 in Animal Studies

Matrix Metalloproteinase-9 Expression and Activity in the Brain

Matrix metalloproteinase-9 (MMP-9) belongs to a family of zinc-dependent proteases, mostly secreted as inactive pro-enzymes, activated outside the cell upon proteolytic cleavage. MMPs degrade extracellular matrix constituents, other proteases, growth factors, and extracellular domains of transmembrane proteins, such as cell adhesion molecules and receptors. As a result, MMPs participate in remodeling the pericellular microenvironment and cell-signaling via either the release or processing (to reveal their binding domains) of cell-surface receptor ligands.[1]

MMP-9 is the best characterized MMP in the central nervous system. It is expressed by neurons in the adult brain and glial cells and released in response to enhanced neuronal activity under physiological and pathological conditions.[1–3] Its induction is transient, and its activity is observed within minutes following neuronal stimulation. This activity disappears within the following 10–15 minutes because of the action of endogenous inhibitors, such as tissue inhibitor of matrix metalloproteinases (TIMP-1).[2,4] At the subcellular level in neurons, MMP-9 has been found at dendritic spines that harbor the vast majority of excitatory synapses in the brain.[5,6] In addition to the protein and its enzymatic activity, MMP-9 mRNA has also been reported to be available at the same localization and is especially abundant following neuronal activation.[7,8] Interestingly, MMP-9 mRNA was shown to be locally translated at dendrites and synapses in response to neuronal stimulation by glutamate in a process that is controlled by Fragile X mental retardation protein (FMRP).[9,10] FMRP is also involved in transporting MMP-9 mRNA toward dendrites and spines.[10]

MMP-9 in Physiological and Pathological Synaptic Plasticity

MMP-9's expression pattern and specific dendritic/synaptic localization suggest a role for the enzyme in synaptic plasticity, learning, and memory. The long-term potentiation (LTP) of synaptic efficacy is regarded as a neuronal plasticity mechanism that underlies memory acquisition and storage.[11] The pivotal role of MMP-9 in the maintenance of LTP has been repeatedly demonstrated.[12] MMP-9 was also found to affect dendritic spine morphology.[12–14] Notably, a well-recognized feature of Fragile X syndrome in humans (ie, elongated dendritic spines that are reproduced in FMRP knockout mice) is accompanied by the excessive production of MMP-9 that, when inhibited, normalizes the spines and alleviates other pathological symptoms, both behavioral and peripheral.[15,16] The well-documented and mechanistically explained role of MMP-9 in driving synaptic plasticity coincides with the function of MMP-9 in phenomena that rely on plasticity, such as learning and memory, addiction, and epileptogenesis, which have been studied in various animal models.[5,7,17–19]

MMP-9 apparently plays a special role during developmental plasticity of the postnatal period. Szklarczyk and Kaczmarek[20] reported the highest levels of MMP-9, particularly in the neuropil, during a critical period of visual cortex development. Telencephalin (intercellular cell adhesion molecule-5 [ICAM-5]) regulates dendritic morphology in the developing brain. ICAM-5 downregulation is critical for the maturation of synaptic structures. Kelly et al[21] reported that ICAM-5 expression in dendritic protrusions in the mouse visual cortex decreased during this critical period to become predominantly localized to dendritic shafts. However, this phenomenon did not occur in MMP-9 knockout animals, indicating that no developmental shift in the subcellular localization of ICAM-5 occurs in the absence of MMP-9. In the rat hippocampus, Aujla et al[22] observed an increase in MMP-9 enzyme, protein, and mRNA levels at 2–10 days postnatally. Interestingly, the lack of MMP-9 resulted in larger dendritic spines only in the hippocampus in 8- to 14-day-old mice.[16] Hence, MMP-9 appears to play a particularly important role at well-defined neurodevelopmental stages in both the visual cortex and hippocampus.

MMP-9 in Human Neuropsychiatric Disorders

The importance of MMP-9 in physiological and pathological plasticity, demonstrated in animal models, is matched by its possible role in human conditions that supposedly involve aberrant plasticity. Blood or brain tissue MMP-9 levels were found to be increased in such human disorders as cocaine addiction, epilepsy, and depression.[23–26] A link to human neuropsychiatric diseases has also been suggested. For example, MMP-9 gene polymorphisms have been implicated in alcohol addiction and bipolar disorder.[27,28] One notable example of the possible role of MMP-9 in human neuropathology involves Fragile X syndrome, in which the nonspecific MMP-9 inhibitor minocycline was successfully applied in clinical trials.[29–32]

MMP-9 in Schizophrenia

Schizophrenia involves impairments in perception and cognition, as well as in avolition, culminating in a triad of positive, negative, and cognitive symptoms that are believed to reflect modifications in neuronal circuitry, the perturbation of synaptic connectivity, and alterations in dendritic spines. Although the etiology of schizophrenia remains largely unknown, it appears to involve interactions between many genes, some of which encode proteins that regulate synaptic plasticity. Notably, chromosome region 20q11-13, where the *MMP-9* gene is located,[33] has been extensively studied in terms of psychiatric disorders and linked to schizophrenia.[34] MMP-9 influences hippocampal and prefrontal cortical function[5,7,18,35,36] and is an interesting candidate molecule that is potentially involved in schizophrenia, a condition in which prefrontal cortex impairment is one of the most common pathological findings.[37,38] Furthermore, some of the candidate proteins that are implicated in schizophrenia have functional connections with either MMP-9 or MMP-9-interacting proteins, such as brain-derived neurotrophic factor (BDNF) and *N*-methyl-D-aspartate (NMDA) receptors, among others.[39,40]

Another hallmark of schizophrenia is the dysfunction of dendritic spines. Several studies reported a reduction of spine density in cortical pyramidal neurons in schizophrenia (for review, see Moyer et al[41]). Interestingly, ultrastructural studies by Roberts et al[42] demonstrated an approximately 30% reduction of striatal spine size in schizophrenia patients compared with the control population. Recently, O'Dushlaine et al[43] identified dendritic spines among the top pathways affected in schizophrenia, as revealed by the very large-scale genome-wide association study. Notably, MMP-9 has been shown to mediate morphological changes in dendritic spines after synaptic stimulation (see above), and it might be potentially involved in dendritic spine pathology in schizophrenia. Furthermore, Fragkouli et al[44] and Gkogkas et al[45] reported an increase in dendritic spine density in the hippocampus and cortex in transgenic mice that overexpress MMP-9.

MMP-9 Gene Polymorphisms and Schizophrenia

Zhang et al[46] reported that the -1562C/T polymorphic regulatory site of MMP-9 influences the rate of MMP-9 transcription by affecting the binding of a gene repressor protein. Rybakowski et al[47] genotyped this functional polymorphism in a group of 442 schizophrenia patients and 558 healthy control subjects and found that the transcriptionally less active C allele and C/C genotype were significantly, albeit slightly, more frequent in schizophrenia patients than in healthy controls. Han et al[48] studied 298 schizophrenia patients and 298 healthy controls and reported the involvement of the same gene polymorphism in schizophrenia, but they found a significant preponderance of the T allele in schizophrenia patients. This apparent discrepancy can be at least partially explained by the ethnic differences between the Asian and Polish populations in these studies. In contrast to the aforementioned investigations, in a family-based association study of the involvement of the −1562C/T polymorphism of the MMP-9 gene in schizophrenia, Groszewska et al[49] reported no significant association between this polymorphism and schizophrenia. In this study, 147 trios (patients and their healthy parents) were examined. However, the statistical analysis included only 26 informative trios,[49] which is a relatively small group for such an investigation. Interestingly, a previous study that utilized an animal model of LTP found that the fine tuning of MMP-9 levels was mandatory for physiological plasticity, and animals with either genetically increased or decreased MMP-9 levels exhibited similar LTP deficiencies.[50] Hence,

both enhanced and diminished MMP-9 levels may have pathological consequences that possibly contribute to schizophrenia.

MMP-9 in the Blood and Schizophrenia

A link between MMP-9 and schizophrenia was also revealed by Domenici et al[24] who focused on protein profiling in a large population of psychiatric patients using an unbiased approach. A total of 79 proteins were analyzed, including several proteins that belong to pathways or mechanisms that have been previously suspected to be involved in the etiology of schizophrenia. Plasma biomarker profiling revealed that the levels of TIMP-1 (which is known to block MMP-9 activity) and MMP-9 were among those that were the most elevated in schizophrenia patients.[24] Similar results regarding blood MMP-9 levels in schizophrenia patients were reported by Yamamori et al.[51] MMP-9 plays a role in the conversion of proBDNF to its mature form, and the potential contribution of BDNF to the pathophysiology of schizophrenia has been reported.[52] Yamamori et al[51] also examined the plasma levels of mature BDNF and the correlation between the abundance of mature BDNF and MMP-9. A significant association was found between the levels of mature BDNF and MMP-9 in schizophrenia patients but not in healthy controls. However, no difference in mature BDNF blood levels was found between these two groups. Moreover, Yamamori et al[51] assessed the correlation between the blood levels of MMP-9 and positive and negative symptom scores on the Positive and Negative Symptom Scale and found no significant association. Similarly, no correlation was found between MMP-9 levels and the duration of the illness. Findings that contrasted with the results reported by Domenici et al[24] and Yamamori et al[51] were reported by Niitsu et al[53] They examined 63 patients with chronic schizophrenia and 52 age- and sex-matched healthy subjects and found no differences in the serum levels of MMP-9 in these two groups.

One possible explanation for the discrepancy between the results of these studies could be the proportion of active smokers in the examined groups. The cohort investigated by Domenici et al[24] included a higher percentage of active smokers among the schizophrenia patients compared with controls. In the study performed by Niitsu et al,[53] the number of smokers was lower for male patients compared with male controls. Interestingly, Niitsu et al[53] reported an increase in MMP-9 levels in smoking males compared with non-smoking males in the schizophrenia group. No such correlation was found in the male control group or in females. As a result, the authors speculated that the blood levels of MMP-9 in schizophrenia patients may be affected by smoking, and the differences in the proportions of smokers and non-smokers between groups may have biased the results. Within this context, the possible connection between MMP-9 and nicotine addiction[48,54] should be evaluated.

Based on suggested links between schizophrenia and immunological disorders, Chang et al[54] examined the involvement of a number of candidate proteins, including MMP-9, in schizophrenia and autoimmune disorders. A significantly higher frequency of positive MMP-9 activity in blood was found in schizophrenia patients compared with healthy controls. Another unbiased study demonstrated the possible involvement of MMP-9 in schizophrenia[55] and compared gene expression profiles in peripheral blood mononuclear cells between healthy individuals and treatment-naive schizophrenia patients before and 6 weeks after initiating pharmacological treatment. Notably, among the selected genes, MMP-9 mRNA was the most markedly upregulated in peripheral blood mononuclear cells in treatment-naive schizophrenia patients compared with controls, with a marked downregulation following treatment.

Concluding Remarks

This minireview points to an intriguing crossroads between schizophrenia, synaptic plasticity, and MMP-9. Interestingly, alterations in glutamate signaling lead to aberrant plasticity, which has been implicated in schizophrenia. MMP-9 has been recently shown to regulate and be regulated by glutamate at excitatory synapses. MMP-9 activity has also been reported to be an important factor that shapes synaptic plasticity at the physiological and morphological levels.[1,3,56] Numerous unbiased high-throughput approaches indicated the possible involvement of synaptic proteins, including neuroligins and neurexins, and their genes in schizophrenia.[43,57–59] A trans-synaptic link that involves neurexins and extends from the presynaptic side to neuroligin-1 or dystroglycan at the postsynaptic side can be broken after MMP-9-driven cleavage of each of these proteins, and such MMP-9 activity may affect synaptic efficacy.[2,35,60]

MMP-9 also appears to be greatly important neurodevelopmentally (see above). Well-known factors that purportedly promote schizophrenia (eg, chronic stress[61] and neurotrauma[62]) enhance MMP-9 levels in the brain, which may have functional consequences.[63,64]

The potential clinical relevance of MMP-9 in schizophrenia might also be supported by findings regarding minocycline. This tetracycline antibiotic is known for its pleiotropic effects, including microglia-dependent neuroinflammation. Interestingly, minocycline has strong direct inhibitory activity against MMP-9. Furthermore, it was shown to diminish MMP-9 activity both *in vitro* and *in vivo* and in human subjects who suffer from Fragile X syndrome, in which enhanced MMP-9 activity was implicated as a pathogenic factor.[10,15,16,32] In schizophrenia, minocycline has been tested as a potential therapeutic. A recent meta-analysis of clinical trials suggested that minocycline may be effective in ameliorating the negative symptoms of schizophrenia.[65] Several animal and human studies have suggested that minocycline

Table 1. MMP-9 and Schizophrenia in Human Studies

Type of Study	Results	Number of Patients/ Controls	Gender: Patients/ Controls	Age (mean ± SD): Patients/ Controls	Origin of Subjects	Treatment Status	Remarks	Reference
-1562C/T MMP-9 gene polymorphism	C allele more frequent in SZ	442/558	M: 233/223 F: 199/335	M: 29.4 ± 10.7/ 40.2 ± 12.7 F: 32.6 ± 11.9/ 40.8 ± 12.0	Poland	ND	No psychiatric assessment of the control subjects	Rybakowski et al[47]
-1562C/T MMP-9 gene polymorphism	T allele more frequent in SZ	298/298	M: 247/236 F: 51/62	41.1 ± 12.9/ 42.3 ± 11.0	China	ND	—	Han et al[48]
-1562C/T MMP-9 gene polymorphism	No association	147 trios[a]	M: 73 F: 74	25.03 ± 6.67	Poland	ND	In the statistical analysis only 26 informative trios were included	Groszewska et al[49]
Plasma bio-marker analysis	Increased levels of MMP-9 in SZ	229/254	M: 115/81 F: 114/173	37.8 ± 10.7/ 48.9 ± 14.2	Caucasian	Mixed	Higher percentage of active smokers among the SZ	Domenici et al[24]
Plasma levels of MMP-9	Increased levels of MMP-9 in SZ	22/22	M: 12/12 F: 10/10	38.1 ± 13.2/ 38.1 ± 12.9	Japan	On treatment	Only treatment-resistant SZ included	Yamamori et al[51]
Plasma levels of MMP-9	No association	63/52	M: 26/25 F: 37/27	35.9 ± 8.2/ 34.9 ± 7.3	Japan	On treatment	In M a significant interaction effect for diagnosis and smoking status was observed in MMP-9 levels	Niitsu et al[53]
Plasma MMP-9 activity levels	Increased MMP-9 activity in SZ	46/22	All males	40 ± 10.42/ 33 ± 5.88	Taiwan	On treatment	Broad range of different drugs used for medication	Chang et al[54]
Gene expression profiling in lymphocytes	MMP-9 mRNA up-regulation in SZ	10/11	M: 8/5 F: 2/6	Age range 19–65; mean age not stated	Sri Lanka	Naive	Small sample size	Kumarasinghe et al[55]

Notes: F, Females; M, males; ND, no data; SZ, schizophrenic patients.
[a]Patient and his/her both healthy parents.

might also have a potential therapeutic effect on cognitive dysfunction in schizophrenia.[66–68]

In summary, multiple studies, notably those that used unbiased approaches, support a link between MMP-9 and schizophrenia. Unknown, however, is whether increased or decreased MMP-9 levels contribute to the disease. This is not entirely surprising, and possibly very fine tuning of the enzymatic activity of MMP-9 is required to maintain proper synaptic plasticity, which has been demonstrated in an animal study.[50] Notably, several human studies (see table 1) did not show an association between MMP-9 and schizophrenia or between the -1562C/T gene polymorphism and blood MMP-9 levels. Another controversial issue is whether the effects of MMP-9 on synaptic plasticity are indeed pivotal for schizophrenia or whether other phenomena that involve MMP-9 are important because the disease includes a large variety of aspects that involve MMP-9, such as tissue remodeling, angiogenesis, blood-brain barrier integrity, neuroinflammation, and myelination (for review, see Chopra et al[69]). It should be noted that MMP-9 seems to play a role in various other neurological and psychiatric diseases such as, eg, epilepsy, Fragile X syndrome, alcohol and cocaine addiction, multiple sclerosis, Alzheimer's disease, and bipolar disorder. This of course raises the question of whether MMP-9 dysfunction is specific and possibly causative for schizophrenia. The data available certainly suggest that MMP-9 is not specific to schizophrenia, though, nevertheless, may still play a causative role. It is intriguing that aberrant synaptic plasticity has in fact been associated with several of the aforementioned disorders. Hence a possible functional role of MMP-9 in synaptic plasticity may implicate the enzyme in the pathogeneses of, eg, epileptogenesis, addiction, or schizophrenia. On the other hand, extrasynaptic activities of MMP-9 may help to understand its role in multiple sclerosis (immune functions) or Alzheimer's disease (clearing of neurotoxic beta-amyloid deposits).

Finally, the precise causes of disturbances in MMP-9 in schizophrenia have not been identified, and this enzyme might be produced in the brain by neurons, astrocytes, microglia, and oligodendroglia. Nevertheless, compelling, albeit circumstantial, evidence suggests connections between schizophrenia, synaptic plasticity, and MMP-9. Future studies should further test the hypothesis that MMP-9 is functionally involved in the pathogenesis of schizophrenia. Additionally, although the role of altered serum MMP-9 levels in schizophrenia remains unclear, one may propose to further investigate this association as a candidate biological marker for schizophrenia.

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