Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2025.63.009903

Matrix Metalloproteinases as Therapeutic Targets of Neuroinflammation in Alzheimer's Disease

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ARTICLE INFO

Received: September 23, 2025

Published: October 09, 2025

Citation: Sarah Li. Matrix Metalloproteinases as Therapeutic Targets of Neuroinflammation in Alzheimer's Disease. Biomed J Sci & Tech Res 63(3)-2025. BJSTR. MS.ID.009903.

ABSTRACT

Matrix metalloproteinases (MMPs) are zinc-dependent proteases that regulate extracellular matrix remodeling, neuronal plasticity, and blood-brain barrier (BBB) integrity. Dysregulation of their activity contributes to neuroinflammation and neurodegeneration in Alzheimer's Disease (AD). Among the family, MMP-2, MMP-3 and MMP-9 are strongly implicated in AD pathology. Overexpression of these enzymes correlate with amyloid-β disposition, tau hyperphosphorylation and BBB disruption, leading to amplified neuronal injury and cognitive decline. While endogenous tissue inhibitors of metalloproteinases (TIMPs) maintain physiological balance, their short half-life limits therapeutic application. This has driven interest in small molecule inhibitors to modulate MMP activity. Broad spectrum agents such as doxycycline reduce neuronal injury by suppressing MMP-2 and MMP-9 activity, yet are associated with off-target toxicity due to lack of selectivity. More recent efforts focus on selective inhibitors targeting selective MMP isoforms. Natural compounds, including flavonoids and polyphenols also demonstrate inhibitory effects on MMP-2 and MMP-9 along with antioxidant and anti-inflammatory effects. Targeted inhibition of MMPs present promising potential therapeutic options for reducing neuroinflammation in AD.

Keywords: Neurodegeneration; Alzheimer's Disease; Neuroinflammation; Matrix Metalloproteinase

Abbreviations: AD: Alzheimer's Disease; BBB: Blood-Brain Barrier; CNS: Central Nervous System; ECM: Extracellular Matrix; MMP: Matrix Metalloproteinase; PNS: Peripheral Nervous System; RT-PCR: Reverse Transcription-Polymerase Chain Reaction; TIMP: Tissue Inhibitors of Metalloproteinases

Introduction

Microglia mediate inflammatory response which negatively impacts the brain and contributes to Alzheimer's Disease. While microglia are activated in response to cell damage where it phagocytose neuron debris, forming the first line of defense in the central nervous system (CNS), they also contribute to the release of proteinases (MMP) and pro-inflammatory cytokines (TNFa, IL-6, IL-1β) which can exacerbate neuron damage [1]. In particular, overexpression of MMP-2, MMP-3, MMP-9 has been linked to β-amyloid deposition and tauopathy in vascular dementia of AD [2]. Identifying selective small molecule inhibitors of these MMPs presents a promising therapeutic potential to reduce neuroinflammation and slow AD progression.

MMPs in the Brain

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases with diverse biological and pathophysiological roles, ranging from tissue remodelling and wound healing to tumor invasion and metastasis [3,4]. In the CNS, MMPs regulate blood-brain barrier integrity, neuronal plasticity and extracellular matrix remodeling. To date, 26 human MMPs have been identified and are separated into six functional subgroups: collagenases (MMP-1, MMP-8, MMP-13), gelatinases (MMP-2, MMP-9), stromelysins (MMP-3, MMP-10, MMP-11), matrilysins (MMP-7, MMP-26), membrane-type MMPs (MT-1—6 MMPs) and undefined archetype MMPs (MMP-12, MMP-19, MMP-20, MMP-21, MMP-22, MMP-23, MMP-27, MMP-28) [5]. Under normal conditions, most MMP levels are tightly regulated and expression induced under pathological conditions, with the exception of MMP-2 and MMP-9 which are constitutively expressed in the brain [6]. MMPs are secreted as inactive zymogens in the pre-proenzyme form, requiring proteolytic cleavage of the pro-peptide domain to become active. The majority of MMPs are activated by other MMPs or proteases. Structurally, all members of the MMP family share a similar self-inhibitory pro-domain, catalytic domain and zinc-binding domain.

The primary biological function of MMP is to catalyze matrix and non-matrix proteins, especially the extracellular matrix (ECM) [3]. Since the ECM is a dynamic structure that constantly undergoes remodeling, the degradation of its components by MMPs alters cell-matrix and cell-cell interactions which is essential for maintaining tissue homeostasis, releasing bioactive molecules and regulating ECM composition [7]. Partial degradation of ECM by MMPs aid in side branching of epithelial cell morphogenesis while also producing ECM fragments to supply building blocks of cell proliferation. Of note, different MMPs preferentially target substrates, such that MMP-3 and MMP-10 degrade proteoglycan and laminin while MMP-2 and MMP-9 target denatured collagen [8]. Besides remodeling the ECM, MMPs disrupts the blood-brain barrier (BBB) integrity by digesting tight junctions and basement membrane proteins, leading to development of diseases [9]. In addition, MMPs also activate molecules such as cytokines, cell surface receptors and apoptotic ligands through cleavage, thereby amplifying neuroinflammatory cascades [7].

Role of Individual MMPs

MMPs are expressed throughout the body, however, their RNA and protein expression patterns vary between cell types (Tables 1 & 2). In the brain, distinct MMP isoforms are expressed in specific regions and cell types, where they regulate neuronal activity and the blood-brain barrier (BBB) function (Table 3). MMP-2, a gelatinase, plays a key role in injury and repair by degrading capillary basal lamina components and promoting angiogenesis and neurogenesis [10]. In addition, MMP-2 plays an important role in glial cell activation and blood brain barrier disruption. In chronic cerebral hypoperfusion, BBB disruption induces MMP-2 activity, which in turn activates glial cells and results in white matter lesions [10]. This process promotes astrogliosis, where activated astrocytes and microglia express elevated levels of MMP-2 and MMP-3 in vascular dementia, contributing to demyelination [10]. Although MMP-2 and MMP-9 share similar substrate specificity, MMP-2 more efficiently digests myelin than MMP-9, making it particularly important in white matter pathology [10].

Table 1: RNA expression of selected MMPs in human cell types.

RNA Expression of MMP							
Cell Types	**MMP-2**	**MMP-3**	**MMP-7**	**MMP-9**	**MMP-12**	**MMP-14**	**MMP-24**
Neuron	✓ medium	✓ high	—	✓ low	—	✓ low	✓ high
Glial Cells	✓ low	✓ high	—	✓ medium	—	—	—
Endothelia	✓ low	✓ high	—	—	—	✓ medium	—
Purkinje	—	—	—	—	—	—	✓ high

Note: Data from The Human Protein Atlas.

Table 2: Protein expression of selected MMPs in human cell types.

Protein Expression of MMP							
Cell Type	**MMP-2**	**MMP-3**	**MMP-7**	**MMP-9**	**MMP-12**	**MMP-14**	**MMP-24**
Neuron	✓	✓		✓	✓		✓
Microglia		✓	✓	✓	✓	✓	
Astrocyte	✓					✓	
Endothelia	✓				✓		
Purkinje		✓					
Oligodendrocyte		✓					

Note: Data from Beroun, et al. [8,15].

Table 3: RNA expression of MMP in different brain regions measured in pTMP.

RNA Expression of MMP (pTMP)							
Brain Region	**MMP-2**	**MMP-3**	**MMP-7**	**MMP-9**	**MMP-12 Undetected in Brain**	**MMP-14**	**MMP-24**
Amygdala	✓ 2.2			✓ 0.4		✓ 3.2	✓ 3.8
Basal Ganglia	✓ 2.7			✓ 0.6		✓ 5.1	✓ 6.0
Cerebellum	✓ 1.7					✓ 5.0	✓ 106.4
Cerebral Cortex	✓ 1.9			✓ 0.6		✓ 3.5	✓ 9.0
Hippocampal Formation	✓ 2.4			✓ 0.3		✓ 4.4	✓ 3.9
Hypothalamus	✓ 3	✓ 0.6		✓ 0.5		✓ 4.8	✓ 5.6
Midbrain	✓ 2.5			✓ 0.5		✓ 4.6	✓ 2.7
Pituitary Gland	✓ 21.4	✓ 1.9	✓ 0.5	✓ 1.4		✓ 21.4	✓ 5.7
Spinal Cord	✓ 6.7			✓ 0.4		✓ 8.7	✓ 1.8

Note: Data from GTEx Human Brain RNA-Seq dataset, The Human Protein Atlas.

MMP-3 is primarily expressed in brain endothelial cells and is involved in the remodelling of ECM basal lamina of the BBB [11]. Under normal conditions in the human adult brain, MMP-3 expression is low in the CNS while its expression is found to be increased in neurodegenerative disorders, ischemia or trauma [11]. In the case of temporal lobe epilepsy with hippocampal sclerosis, a neurodegenerative disorder in the hippocampus with chronic neuroinflammation and gliosis, reactive astrocytes and microglia secrete interleukin-1β (IL-1β), which induces astrocytic MMP-3 expression [12]. Elevated MMP-3 may compromise vascular integrity, disrupt the BBB and exacerbate neuronal injury [13]. MMP-9 is essential for CNS development and plasticity [14]. It is expressed by numerous cell types including neurons, glial cells, endothelial cells, microglia, astrocytes and oligodendrocytes in both the CNS and peripheral nervous system (PNS) (Figure 1) [15]. In the brain, its expression is commonly detected in the cerebellum, brainstem, hippocampus and neocortex. Through its ability to cleave cell surface receptors leading to synaptic and circuit reorganization, MMP-9 regulates synaptogenesis, myelination and axon pathfinding [14].

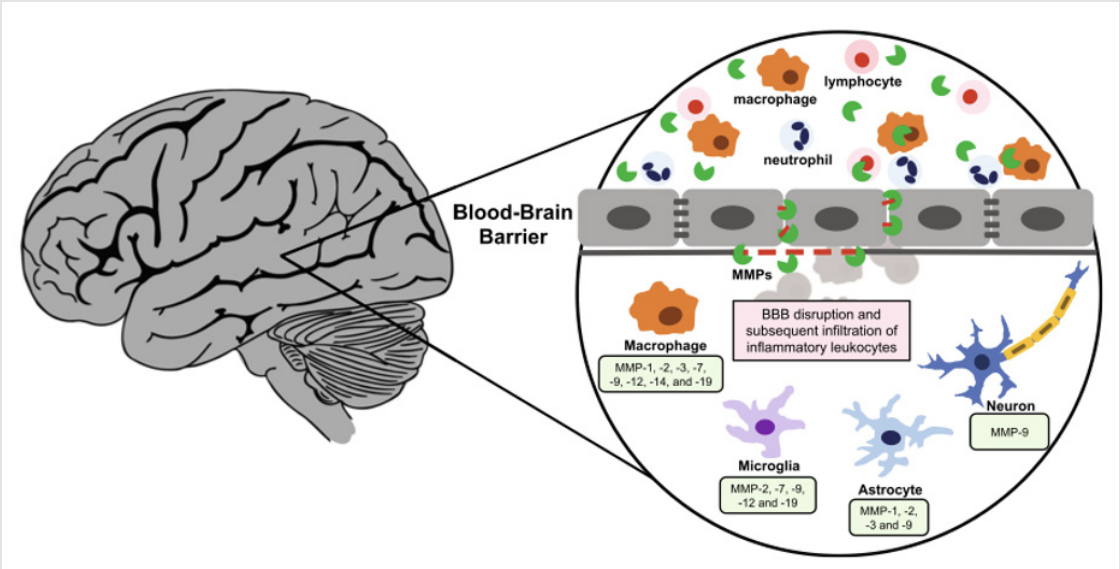

Figure 1: Secretion of MMPs by immune cells for blood-brain-barrier breakdown (Chopra, et al. [21]).

It has been suggested that MMP-9 is important not only in developing synaptic networks during CNS development in early postnatal periods, but also in restructuring synaptic connections in the adult brain [14]. Therefore, MMP-9 levels are highest during the critical period of early development, and are drastically reduced in adulthood. However, in response to synaptic activity, MMP-9 activity increases in the adult brain [16,17]. In the adult brain, excessive MMP-9 release, particularly by infiltrating neurophils, can disrupt the BBB by cleaving the ECM, tight junction proteins and adherence junction proteins [14]. MMP-12 contributes to neuroinflammation. Liu, et al. [18] found that MMP-12 deficiency in mice reduces neuroinflammation via modulation of adult brain-derived microglia while unaffecting cultured microglia [18]. In addition, increased expression of MMP-12 due to aging can promote the recruitment of bone marrow-derived microglia to the brain in order to exhibit neuroinflammatory effects [15]. Furthermore, MMP-12 is often upregulated during cerebral ischemia and acts not only to damage the BBB integrity, but also induce the expression of MMP-9 and other factors involved in BBB damage [19]. It is found that suppression of MMP-12 activity can reduce cerebral infarct size and maintain the BBB by blocking the disruption of tight junction proteins [19].

Pathophysiology of MMP in Vascular Dementia and Alzheimer's Disease

Unregulated MMP activity is linked to stroke, cardiovascular and neurodegenerative disease. Under conditions of hypoxia, MMPs are induced and disrupt the basal lamina as well as tight junction proteins of cerebral blood vessels. It has been identified that MMP-2, MMP-3, and MMP-9 are found in brains with white matter lesions due to stroke or vascular dementia [20]. Increased MMP-9 expression in the CSF from the blood was especially noted, which may be due to blood extravasation, infiltrating leukocyte release or production by brain cells [10]. In AD, excessive MMP expression parallels disease progression. Post-mortem analysis in AD patients show a higher than normal amount of MMP in the white matter and senile plaques of the brain [4]. Specifically, MMP-2, MMP-3 and MMP-9 are highly expressed in AD brain tissues, and have thus been used as biomarkers for early AD diagnosis [21]. MMP-2,3,9 cleave amyloid β monomers and oligomers while MMP-9 cleave fibrils and clear amyloid plaques in the brain [3]. Reductions in MMP-2 and MMP-3 levels may lead to accumulation of insoluble amyloid β and formation of plaques, consequently causing the development of AD [3]. Furthermore, overexpression of MMP-2, MMP-3, and MMP-9 have been commonly found in a variety of pathologies including neuroinflammation, blood brain barrier disruption and demyelination.

During neuroinflammation, expression of MMPs are upregulated through activation of neural and immune cells including microglia, endothelial cells, astrocytes, neutrophils and others. Through post-mortem analysis, upregulation of these MMPs are often found in the brain of AD patients. Deb and Gottschalk studying the correlation between Alzheimer's disease and MMP found that amyloid β stimulated the expression and activity of MMP-2,3,9 in astrocyte culture [22]. As such, targeting these MMPs specifically could be successful in finding treatment for AD.

Regulation of MMP Activity

MMP activity is tightly regulated at multiple levels to ECM homeostasis. Dysregulation of these control mechanisms contributes to neuroinflammation and neurodegenerative processes. Endogenously, MMPs are regulated by both activation of precursor zymogens and TIMPs. Many MMPs are secreted as inactive pro-enzymes and require proteolytic cleavage of the pro-domain to become active. Certain MMPs also activate one another. For example, MMP-3 and MMP-10 can cleave and activate the pro-forms of MMP-1, MMP-8 and MMP-13. In the laboratory, experimental activation can be achieved with multiple treatments with thiol reagents, mercurial compounds, or chaotropic agents that perturb the intermediate states of pro-MMPs [23]. Other oxidants such as hypochlorous acid and peroxynitrite react with the cysteine switch motif of pro-MMPs, thereby triggering activation. Endogenously, MMP levels are regulated by TIMPs between the states of matrix formation and destruction [24]. TIMPs are natural tissue-specific proteins that specifically inhibit MMPs by binding active MMPs in a 1:1 stoichiometric ratio, preventing substrate access. Although controlled balance between MMPs and TIMPs is essential for carrying out ECM remodeling events, the use of TIMPs as pharmacological agents to regulate MMP levels is limited by their short half-life in vivo [25]. As such, multiple pharmacologic small molecules MMP inhibitors have been developed in an attempt to downregulate MMP levels.

Pharmacological strategies have focused largely on broad-spectrum MMP inhibition. One well-known antibiotic agent, doxycycline, is a broad spectrum MMP inhibitor. Doxycycline potently inhibits stromelysin, gelatinase and collagenase at IC50 values of 32μM, 56μM and 452μM respectively [26]. It inhibits MMP activity and downregulates MMP transcription through direct binding to the zinc ion domain which disrupts MMP interaction with its substrates [27]. At low doses, doxycycline is a potent MMP inhibitor in both clinical and in vitro conditions. It has been shown by Castro et al. in mouse studies that during cases of increased MMP-2 levels in hypertension, administration of doxycycline consecutively for 8 weeks completely prevented any vascular alterations [28]. In part, this may be due to the effect of doxycycline in reducing MMP-2 levels which in turn prevented vascular hypertrophic remodeling and increased vascular collagen and elastin composition [28]. Moreover, doxycycline could effectively reduce elevated MMP-2, MMP-9 and MMP-14 levels. The use of doxycycline greatly reduces neuronal damage in brain ischemia as well as remodeling. In a study by Lee et al. focusing on the cerebral ischemia, revealed that while gelatinase MMPs (MMP-2,9) were upregulated during ischemia, administration of doxycycline could reduce MMP-9 activity, laminin degradation and neuron loss, thus suggesting that doxycycline performs a neuroprotective role in cerebral ischemia [29].

However, broad specificity MMP inhibitors are limited in its use due to inhibition of both matrix degradation and tissue repair which is associated with severe side effects and off-target interactions in musculoskeletal system and gastrointestinal disorders. As such, novel therapeutics have focused on designing selective MMP inhibitors. Beyond classical broad-spectrum inhibitors such as doxycycline, recent studies have explored natural compounds, synthetic small molecules and structural innovations to improve the safety and selectivity of MMP inhibitors. Studies have found that natural marine and terrestrial compounds are capable of modulating MMP-2 and MMP-9 activity. Ciccone, et al. [4] highlighted flavonoids, polyphenols and other bioactive molecules possessing dual antioxidant and anti-inflammatory effects not only suppress MMP activity but also reduce oxidative stress, a key driver of neurodegeneration in AD [4]. The dual mechanism of natural inhibitors offer a safer adjunct to synthetic molecules. Efforts in medicinal chemistry have also yielded potent and selective MMP inhibitors, overcoming the limitation of broad-spectrum agents. Selective MMP inhibitors function by either binding to exosites, allosteric blocking of active sites or inhibiting activation of pro-MMPs.

Although the design of selective MMP inhibitors are challenging due to their high sequence similarities at the active site of MMPs, multiple small molecules have been developed (Table 4) and are currently in pre-clinical or clinical trials. For instance, AZD1236 is a non-hydroxamate selective MMP-9 and MMP-12 inhibitor with nanomolar potency designed to treat moderate to severe COPD [30]. Although safe for use, the therapeutic efficacy has not yet been proved in the current Phase II trial [30]. Overall, selective MMP inhibitors are favored over broad spectrum inhibitors because of their ability to prevent off-target toxicities and improved efficacy. Fields (2019) summarized that early clinical trials of MMP inhibitors in cancer and COPD revealed that non-selective inhibitors caused musculoskeletal syndrome and gastrointestinal toxicity, due to off-target inhibition of MMPs which are essential for normal tissue repair [27]. Since then, modern strategies focus on targeting alternative zinc-binding groups, allosteric inhibition and exosite targeting to improve specificity. Selective inhibition allows for attenuation of disease-related processes without affecting normal neuronal plasticity.

Table 4: Small molecule inhibitors of MMP and respective assays.

Small Molecule Inhibitors of MMP									
Drugs	**2**	**3**	**7**	**-8**	**9**	**10**	**1 2**	**1 4**	**Assay**
Doxycycline	×	×	×	×	×	×	×	×	Activity Assay
Actininon	×	×	×	×	×	×	×		Gelatin Zymography
AZD1236	×				×				TAILS Assay
PF-356231							×		Invasion Assay & Angiogenesis Assay
444264, Calbiochem	×	×	×						Fluorescent Substrate
444244, Calbiochem	×								Fluorescent Substrate
444241, Calbiochem	×				×				Fluorescent Substrate
444225, Calbiochem		×							Fluorescent Substrate

Note: Data from Calbiochem.

Assays for Measuring MMP Activity

MMP activity can be monitored at the mRNA, protein and activity levels although it is difficult to measure individual MMP activity through enzymatic assays as a result of their overlapping specificity and latent forms [31]. MMP mRNA expression is commonly studied by reverse transcriptase polymerase chain reaction (RT-PCR). With MMP-specific PCR primers, RT-PCR yields a single product at the predicted size for each MMP to detect the specific mRNA of MMPs with high specificity and quantitatively measure the expression pattern of MMPs [32]. Fluorogenic MMP substrates and substrate zymography are the most common techniques to study and up-regulate MMP activity in vitro [33]. Fluorogenic MMP substrate technique utilizes fluorescently dyed artificial MMP substrates connected to a quencher [31]. As such, this measures the activity when MMPs actively cleave the substrates, destroying the quencher and displaying fluorescence [31]. Substrate zymography is specifically used to study ECM degrading enzymes from cell or tissue cultures. It measures the degradation of MMP substrates to determine whether a particular MMP is active or latent [31].

Conclusion

Evidence from experimental and clinical studies highlights the central role of MMP-2, MMP-3 and MMP-9 in Alzheimer's disease related neuroinflammation. Such MMPs are also involved in BBB disruption, synaptic remodeling and amplification of inflammatory signaling. Pharmacological approaches have shifted from broad-spectrum inhibition toward selective targeting MMPs with greater speci-

ficity and safety profiles. MMP inhibition has the potential to emerge as a viable strategy to reduce neuroinflammation and slow the progression of AD.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2025.63.009903

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Submission Link: https://biomedres.us/submit-manuscript.php