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What is the function of Matrix Metalloproteinase-2 and Matrix Metalloproteinase-9 in pain processes?.

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ABSTRACT

At the cellular level, the pathophysiology of neuropathic pain can be divided into two parts. The first is the early phase (several days) and the second is the late phase (ranging from weeks to months and years). Cancer cell growth in the periphery will cause nerve damage in the periphery and prolonged pain will cause changes in nerve transmission processes in the periphery and centre. This underlies the occurrence of peripheral neuropathic pain. Damage to peripheral nerve tissue will trigger peripheral sensitisation and then central sensitisation. After peripheral nerve cell damage (including axon damage), schwan cells will release MMP-9, initiating macrophage cell infiltration. Then there will be degradation of myelin basic protein. The presence of damaged axons will cause an increase in the number of sodium channels and hyperexcitability of ectopic signals from afferent nerve fibres. The result is a continuous action potential that eventually contributes to central sensitisation characterised by hyperalgesia and allodynia. This review summarizes that neuropathic pain occurs through hyperexcitability (hypersensitisation) of nerve cells is IL-1β, MMP-9 in the early phase, MMP-2 in the late phase and finally microglia and astrocyte cells.

Keywords

Matrix metalloproteinase (MMP), MMP-2, MMP-9, Neuropathic pain.

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INTRODUCTION

Matrix metalloproteinase (MMP) is a member or superfamily of the metzincin class of protease enzymes that has a zinc ion binding site as the site of activation of this enzyme. MMPs have the basic function of degrading a wide variety of extracellular matrix components. However, recent research has led us to utilise MMPs as regulators of extracellular tissues especially as extra- and intracellular signallers. MMPs determine many physiological functions, inflammation, homeostasis such as bone remodelling, angogenesis, immunity and wound healing. MMP activity is controlled by the activity of RNA transcription levels, propeptide activation and inhibition by MMP inhibitors. MMP dysregulation leads to many pathological conditions such as arthritis, inflammation and cancer [1].

MMP-9 plays a role in the early neuropathic phase with the end product being macrophage activation while MMP-2 plays a role in the late phase with the end product being astrocytes. The release of MMP-9 and MMP-2 will cause the activation of prointerleukin 1-β (inactive) to interleukin 1-β (active) and this will cause hyperexcitability of nerve cells and this is the precursor to the appearance of neuropathic pain [1,2].

PATHOPHYSIOLOGY OF PAIN

Pain originates from a stimulus that is terminologically referred to as a noxius stimulus. This stimulus is then captured by pain receptors known as nociceptors [3,4]. Nociceptors are receptors that specifically receive pain stimuli (noxious stimulus). These receptors are free nerve endings of A delta (Aδ) and C fibres. Pain captured by these receptors will be delivered to the central level through a process that we know as transmission and perception (pain pathway) [5].

MATRIX METALLOPROTEASE (MMP)

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These MMPs determine many physiological functions, inflammation, homeostasis such as bone remodelling, angogenesis, immunity and wound healing. MMP activity is controlled by the activity of RNA transcription levels, propeptide activation and inhibition by MMP inhibitors. MMP dysregulation leads to many pathological conditions such as arthritis, inflammation and cancer [6]. In the human body, there are 23 types of MMPs. This division is based on the structure and substrate specifications which are divided into several, namely: [7]

1. Collagenases consisting of MMP-1, MMP-8, MMP-13 and MMP-18
2. Gelatinase which consists of MMP-2 and MMP-9
3. Stromelysin which consists of MMP-3, MMP-10 and MMP-11
4. Membrane-type consisting of MMP-14 (MT1-MMP), MMP-15 (MT2-MMP), MMP-16 (MT3-MMP) and MMP-25 (MT6-MMP) and other MMPs 4.

In general, MMP consists of 3 domain structures consisting of: N-terminal peptide domain, internal catalytic domain, and C-terminal hemopexin domain. In general, MMPs are produced in an inactive state with cysteine residues located in the propeptide region. Activation of MMPs requires removal of the propeptide domain so that the catalytic active site becomes exposed [8].

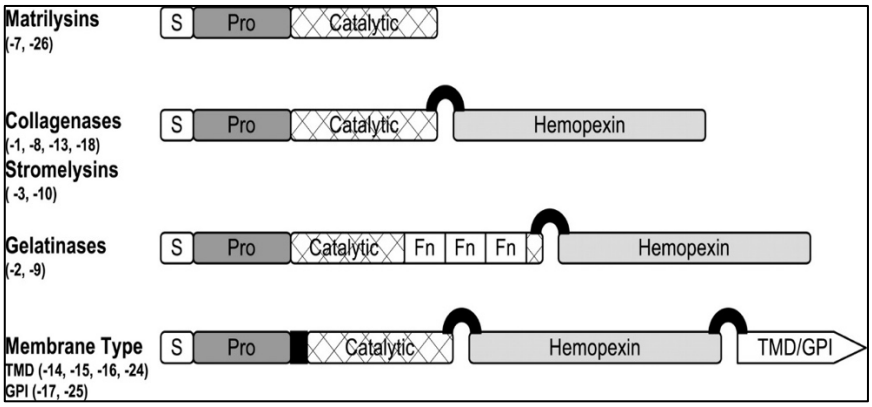

Figure 1. General protein structure of all MMPs

REGULATION OF MMP

The spectrum of MMPs is very broad, so MMPs are a collection of enzymes that have functions that are integrated with the body's homeostasis function and are related to the immune system between tissues and cells. Since it is known that excessive MMP function can cause a lot of damage, the body's physiological system regulates the activation of MMPs. MMP activation is largely regulated by four mechanisms, including:[6]

1. Gene expression mechanism involving transcription and post-transcription regulation.
2. MMP production is determined by the location and type or tissue that produces the MMP known as compartmentalisation
3. Activation of proenzymes by unbinding the pro-domain
4. Inhibition by TIMPs (Tissue Inhibitors of Matrix Metalloprotease) and inhibition by non-specific proteinases such as a2-macroglobulin 4.

Once MMPs are activated, there is potential for a global proteolytic reaction in the extracellular environment through activation (MMP pro-form) activation and degradation of inhibitors or inactivation of other proteases.

MMP-9 AND MMP-2 IN NEUROLOGICAL DISEASES

The most widely discussed of the 23 MMPs associated with inflammation are MMP-9 and MMP-2. These two types of MMPs are found in the extracellular matrix, fluid in the brain and serum in blood vessels [8]. There are many mechanisms that can activate MMP-9 and MMP-2 but it is specifically known that MMP-9 and MMP-2 are activated by plasminogen/plasmin and MMP-14. MMP-9 and 2 activity can be detected using gelatin-substrate zymography assay. MMP-2 is present in many tissues and MMP-9 is easily stimulated by other mechanisms. MMP activity is regulated by an endogenous inhibitor, TIMP (tissue inhibitor of metalloproteinases) [9].

The activities of MMP-9 and MMP-2 are inhibited by TIMP-1 and TIMP-2, respectively. MMPs especially MMP-9 and MMP-2 also play an important role in neuroinflammation and are involved in various CNS diseases including Alzheimer's, amyotrophic lateral sclerosis, multiple sclerosis, brain and spinal cord trauma, epilepsy, and stroke [9].

By disrupting cell-cell and cell-matrix homeostasis, MMPs can also trigger anoikis-like pathways of brain cell death. Consistently, MMP-9 and MMP-2 are found in several matrix-targeted CNS diseases, MMPs can cause the release of extracellular growth factors and cytokines that are involved in various biochemical reactions of the body. In addition, the pathological process of MMP-9 and MMP-2 plays a role in many physiological processes, namely development and regeneration functions. Many sources say MMPs are involved in the process of neuropathic pain [9].

MMP-9 AND MMP-2 IN NEUROPATHIC PAIN

At the cellular level, the pathophysiology of neuropathic pain can be divided into two parts. The first is the early phase (several days) and the second is the late phase (ranging from weeks to months and years). Cancer cell growth in the periphery will cause nerve damage in the periphery and prolonged pain will cause changes in nerve transmission processes in the periphery and centre. This underlies the occurrence of peripheral neuropathic pain [9].

Damage to peripheral nerve tissue will trigger the emergence of peripheral sensitisation followed by central sensitisation. After peripheral nerve cell damage (including axon damage), schwan cells will release MMP-9, initiating macrophage cell infiltration. Then there will be degradation of myelin basic protein. The presence of damaged axons will cause an increase in the number of sodium channels and hyperexcitability of ectopic signals from afferent nerve fibres. The result is a continuous action potential that eventually contributes to central sensitisation characterised by hyperalgesia and allodynia [9].

Proinflammatory cytokines such as interleukin (IL)-1β appear after nerve tissue damage which plays a role in sensitisation in neuropathic pain. After nerve tissue injury, MMP-9 levels will increase in the dorsal root ganglion (lumbar ligament model 5) although MMP-9 and MMP-2 can be found in serum and cerebrospinal fluid [1]. Based on the lumbar ligament model 5, MMP-9 and MMP-2 may increase in the peripheral nerve tissue.

Intrathecal administration of MMP-9 according to studies that have been done, was found to have allodynia, and vice versa, MMP-9 inhibitors given intrathecally were found to cause a decrease in the incidence of neuropathic pain in the early phase. Therefore, it is concluded that MMP-9 causes neuropathic pain due to the activation of interleukin (IL)-1β which has previously been activated by MMP-9 from the inactive form (pro- interleukin (IL)-1β) to the active form of interleukin (IL)-1β. This interleukin (IL)-1β will later cause neuronal hyperexcitability by acting on neighbouring nociceptive receptor cells [1,9].

In addition, the release of MMP-9, interleukin (IL)-1β, p38MAPK will activate microglia (characterised by an increase in microglia markers CD 11b and Iba1) in the spinal cord. The activation of microglia will cause degradation of the extracellular matrix of nerve tissue which will be followed by degradation of myelin, all of which will lead to hyperexcitability of nerve cells, triggering neuropathic symptoms [1,9].

This increase in MMP levels will occur in the early phase but will decrease in the late phase. From several experiments, it can be proven that injecting p38 inhibitors can slow down the onset of the late phase of

neuropathic pain. Taken together, these important data suggest a role for MMP-9 and interleukin (IL)-1β in the development of neuropathic pain through the generation of interleukin (IL)-1β and activation of microglial cells. Microglials emerge after two days post-nerve injury where these microglia originate from pERK (phosphorylated extracellular regulated kinase) [1,9].

The neuropathic pain model experiment (rat lumbar nerve ligation) showed a significant role of phosphorylated extracellular regulated kinase (pERK) in the neuropathic pain process. In nerve injury it was found that pERK appears several hours after nerve injury and is a marker of nerve injury in the early phase (Ji et al., 2009; Lakhan and Avramut, 2012). After 5-6 days, the levels of MMP-9 will decrease, replaced by an increase in MMP-2 levels. Increased levels of MMP-2 mark the start of the advanced phase of neuropathic pain [1,9].

Increased MMP-2 will activate interleukin (IL)-1β from the originally inactive pro-form of interleukin (IL)-1β. However, the activation of interleukin (IL)-1β will activate MMP-2 which will be directly released by astrocyte cells in an autocrine manner (Figure 2). MMP-2 will activate the action of astrocytes but astrocytes can also be activated through ERK [10]. Astrocyte activation (characterised by increased astrocyte markers GFAP and S-100) can appear at peak levels in the late phase. Astrocytes in the spinal cord produce molecules such as phophorylated c-Jun N-terminal kinase (pJNK), basic fibroblast growth factor (bFGF) (Fig. 2) [1,9].

The effect of increasing astrocytes is actually the same as the effect of increasing microglial cells. Experiments that administer astrocyte inhibitors such as alpha aminoadipate and JNK inhibitors can be very effective in reducing advanced neuropathic pain. Inhibition of the pERK pathway has also been shown to inhibit the early or late phase of neuropathic pain which can be very useful for reducing neuropathic pain [1,9].

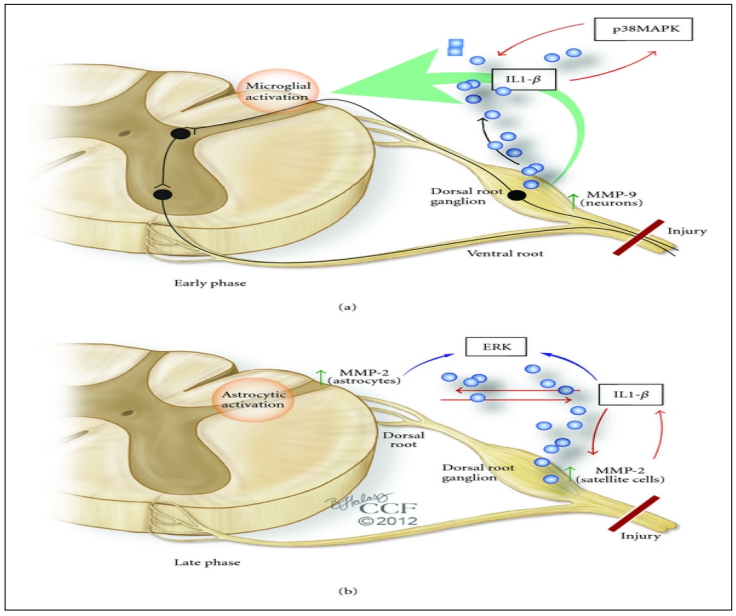

Figure 2. MMPs in DRGs of the lumbar nerve ligase model [1].

Microglia activation plays an important role for the creation of neuropathic pain in the early phase and the role of astrocytes in the late phase. From this information, it can be seen that what causes neuropathic pain through hyperexcitability (hypersensitisation) of nerve cells is IL-1β, MMP-9 in the early phase, MMP-2 in the late phase and finally microglia and astrocytes [1,9].

All experiments produced uniform results, namely an increase in MMP-9, MMP-2, microglia and astrocytes in the nerve site that was given the "injury". So in this case it can be concluded that MMP-9, MMP-2, microglia and astrocytes can be found in peripheral tissues. The increase in MMP-9, MMP-2, macrophages and astrocytes not only increased in peripheral tissues but also reached the level of the spinal nerve ganglion, namely the dorsal root ganglion (DRG) [10].

CONCLUSION

This review summarizes that neuropathic pain occurs through hyperexcitability (hypersensitisation) of nerve cells is IL-1β, MMP-9 in the early phase, MMP-2 in the late phase and finally microglia and astrocyte cells.

DECLARATIONS

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

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