REVIEW ARTICLE

Pulsed Magnetic Field Treatment for Calming Neuroinflammation in Pain Conditions

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ABSTRACT

Context • Neuroinflammation can be associated with inflammatory mediators, such as cytokines and chemokines, that follow damage, injury, infection, or illness in the peripheral nervous system (PNS) and/or the central nervous system (CNS). These can play strategic roles in the formation and continuation of abnormal pain behaviors. Pulsed magnetic field (PMF) treatments have attracted attention for the prevention and management of various pain conditions.

Objective • The review intended to examine the mechanisms underlying the documented anti-neuroinflammatory effects of PMF treatment and its beneficial effects for neuroinflammatory pain states.

Design • The research team performed a narrative review by searching for articles in the PubMed databases. The search used the keywords, pulsed magnetic field, neuroinflammation, cytokines, chemokines, pain, alone and in combination, without the restriction of the publication date.

Setting • This study was take place in faculty of medicine, Usak University, Usak, Turkey.

Results • Neuroinflammation is a very complex process with the contribution of many inflammatory cells and their mediators. PMF treatment may modulate the neuroinflammatory conditions in the central and peripheral neural tissues.

Conclusions • The noninvasive PMF therapy, which has parameters that can be controlled and which has no side effects, is a nonpharmacological therapeutic option with pain-relief ability through strong control of central and peripheral neuroinflammation. Further studies are needed to explore how PMF therapy controls central and peripheral neuroinflammation in various diseases and conditions. (*Altern Ther Health Med.* 2023;29(6):62-67).

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The immune system's activation following inflammatory stimuli, such as tissue damage, pathogens, irritants, or disease, can trigger numerous biochemical, cellular, and functional events in the central nervous system (CNS) and the peripheral nervous system (PNS), resulting in a multifaceted interaction between the three systems.[1,2,3] These interactions occur as a result of the regulatory effects of those systems on each other and play a key role in painful conditions.[2,3]

The immune system, CNS, and PNS have many molecular mechanisms and signaling pathways that play an important role in the physiological, biochemical, and behavioral consequences of the initiation and maintenance of pain conditions.[4] The neuroimmune system is an important signaling system that manages the interactions.[2,3]

Neuroinflammation can be defined as the inflammatory response of neural tissues after damage, injury, or various illnesses.[5, 6] Occurring in both the PNS and the CNS, it's characterized by enhanced vascular permeability, infiltration of leukocytes, activation of glial cells, and amplification of the generation of various inflammatory mediators, such as cytokines and chemokines.[5,6]

Pain conditions associated with excessive peripheral and/or central inflammatory mediators are a complex phenomenon, and many management choices are available, such as steroidal and nonsteroidal anti-inflammatory drugs, antidepressants, opioids, and anticonvulsants.[3,7] Targeting neuroinflammatory mediators, such as cytokines and chemokines, may provide a successful approach for the treatment and prevention of various pain conditions.

The toxicity and side effects of those medicinal treatments have led to researchers' increased interest in nonpharmacological,

safer therapeutic approaches for improving the quality of life of patients with pain. Growing lines of evidence from in-vivo and in-vitro experimental studies have reported that noninvasive, pulsed magnetic field (PMF) treatments, can serve as nonpharmacological options without side effects. PMF can relieve some pain conditions or restore neural function by modulating the cellular and functional interactions between the CNS and PNS and the immune system.[8-11]

The current review intended to examine the mechanisms underlying the documented anti-neuroinflammatory effects of PMF treatment and its beneficial effects for neuroinflammatory pain states. It presents an overview of the current literature regarding the effects of PMF treatment on cellular events occurring between the CNS and PNS and the immune system in pain conditions.

METHODS

Procedures

This study was take place in faculty of medicine, Usak University, Usak, Turkey. Studies on neuroinflammation and pulsed magnetic field treatments were searched for on PubMed using the keywords, pulsed magnetic field, neuroinflammation, cytokines, chemokines, pain, alone and in combination, without the restriction of the publication date.

The review includes articles published in the English language. This narrative review considers an overview of the available literature on the effects of PMF treatment on neuroinflammatory events in pain states rather than exploring several tightly formulated questions.

RESULTS

Neuroinflammation and Pain

Inflammation is the body's immunological defense mechanism that includes the complex biological responses of the somatosensory, immune, autonomic, and vascular systems against tissue damage, injury, or invasion of bacterial and viral pathogens.[12] The inflammation plays central roles in the development of various pathophysiologies, including rheumatoid arthritis, multiple sclerosis, diabetes, cancer, and cardiovascular and respiratory diseases.[13]

Inflammatory processes include the activation and migration of immune-mediated inflammatory cells and the release of various inflammatory mediators at the site of inflammation, resulting in typical inflammatory signs, such as fever, redness, edema, and pain.[14]

Neuroinflammation is a highly complex process that includes the overproduction of free radicals, the activation of complex enzymes, and the release of various inflammatory mediators.[49] Neuroinflammation and oxidative stress are interrelated factors in the etiology of several diseases, including diabetes, neurodegeneration, and cancer.[50]

Oxidative stress is defined as the imbalance between the production and scavenging of reactive oxygen species.[50] The imbalance in redox homeostasis can trigger the synthesis and release of pro-inflammatory mediators and the infiltration of immune cells, which can further amplify oxidative stress.[51]

Thus, inflammation and oxidative stress are closely related pathophysiological events that are tightly linked with one another. Control of oxidative stress, which can cause damage to membrane lipids, proteins, and nucleic acids, is one of the most important requirements for the prevention and treatment of diseases.[49]

A large body of evidence has elucidated the role of neuroinflammation in the initiation and progression of chronic and/or acute pain, and neuroinflammation is one of the most important components of the inflammatory process. Neuroinflammation resulting from neuroimmune interactions is defined as localized inflammation in the PNS and CNS, and it serves as a driving force in the onset and maintenance of pain states.[15]

The main purpose of the immune system, which is defined as the body's biological defense system, is to distinguish self from non-self. It's made up of many different cells, organs, and tissues that work together to fight infection, cellular damage, and disease.[2,3] The immune system's cells, such as macrophages and neutrophils, play different roles to protect and notify the body against infection and disease.

The immune system and the CNS and PNS, which contain countless immune and neuronal cells, work together to provide the body's defenses against tissue damage, inflammation, or injury. Neuroimmune interactions—including CNS- and PNS-mediated regulation of immunity as well as immune-system-mediated regulation of CNS and PNS function—are mediated by complex mechanisms involving numerous cells and molecules.[3,5]

Several inflammatory and immune-like glial cells have been implicated in the pathogenesis of pain. They include mast cells, neutrophils, macrophages, T cells, peripheral glia, Schwann cells, and satellite glial cells in the PNS and microglia, astrocytes, and oligodendrocytes in the CNS.[12,15] Immune responses are modulated by the PNS, particularly the sensory and motor nervous system as well as systemic and peripheral release of immune-derived molecules that can regulate central and peripheral neuronal functions.[13,16]

Inflammatory mediators produced during inflammation can cause the activation and sensitization of nociceptors, thereby awakening the process that results in the perception of pain, which plays a vital protective role for an organism.[17,18] Nociceptors are primary afferent pain fibers with cell bodies located in the dorsal root ganglia (DRG) and trigeminal ganglia (TG). They respond to tissue damage and consist of unmyelinated C fibers and myelinated A-beta (Aδ) fibers.[19] These neurons signal through the activation or sensitization of various receptors, such as the G-protein-coupled receptor (GPCR), ionotropic receptor, and tyrosine kinase receptor, and are located on nerve terminals and cell bodies.

These receptors are directly bound and activated by a variety of inflammatory mediators, including pro-inflammatory cytokines and chemokines.[18,19] Some studies have suggested that neuroimmune interactions are modulated by various mediators, such as cytokines, neurotransmitters, neurosteroids, neuropeptides, cyclic nucleotides, and calcium

and protein kinases, and that they mediate crosstalk among physiological systems in pain conditions.[20,21]

Central and Peripheral Inflammatory Profiles

Excessive inflammatory responses in the PNS and CNS can be detrimental and cause abnormal cellular functions. Evidence from clinical and experimental studies have indicated that neuroinflammation can be associated with cytokine-chemokine networks in the CNS and/or PNS that play key roles in the formation and continuation of pain behaviors.[22]

Neuroinflammation is mediated by different peripheral and central immune cells such as macrophages, neutrophils, microglia and astrocytes.[23] Cytokine produced by these cells is involved in the development and coordination of peripheral and central inflammatory responses. Cytokines are protein molecules of low molecular weight and glycoprotein molecules that play a role in the functions of immune system cells and of many cells that carry receptors for them, such as nervous-system and endocrine-system cells.[6]

The cytokines that play a fundamental role in the inflammatory process in the development of pain are pro-inflammatory cytokines that increase and maintain the inflammatory process and anti-inflammatory cytokines that negatively modulate the inflammatory response.[24] Increasing evidence about inflammatory mechanisms in pain states with different origins has led to an increasing number of studies that use treatments that target inflammatory cells and/or release central or peripheral neuroinflammatory biomarkers as part of therapeutic strategies.[24]

Specific cytokines and their neutralizing antibodies have been the subject of studies of treatments for many diseases in which inflammatory mechanisms are involved, such as stroke, Alzheimer's disease, autoimmune diseases, wound healing, and amyotrophic lateral sclerosis, and the studies have reported that local or systemic distribution of anti-inflammatory cytokines or inflammatory-cytokine antagonists can be effective in the treatment of pain types relevant to inflammation.[25]

The severity and intensity of the inflammatory process mainly depends on the imbalance between the activation of the cascade of pro-inflammatory cytokines and the induction of anti-inflammatory cytokines. The release of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin 1beta (IL-1β), IL-6, and IL-17, induces the production of several mediators that are involved in the induction of inflammatory responses. That release is followed by release of anti-inflammatory cytokines, such as IL-4 and IL-10, that inhibit the production of inflammatory cytokines.[22,26]

In addition to cytokines, chemokines are also released from the cells during inflammation in neuronal tissues. Chemokines have been described as small chemotactic cytokines. They play key roles in directing the circulation of immune cells to sites of inflammation and to functions in the CNS and PNS, by coordinating immune-cell responses in various pain conditions.[23]

The C-X-C motif chemokines ligands 1 and 8 (CXCL1 and CXCL8) and the C-C motif chemokines ligands 2 and 3 (CCL2 and CCL3) are produced by neutrophils, monocytes, macrophages, or microglia in the peripheral nerves and spinal cord. Numerous studies have demonstrated that progressive increases in such chemokines can contribute to neuronal inflammation during pain conditions.[22,27] One study found that injured sciatic nerves can produce hundreds of times the normal amount of chemokines (CXCL1 and CXCL2) that bind to the surfaces of neutrophils and attract immune cells to injured tissue.[26]

The emergence and persistence of abnormal pain responses in conditions that cause neuroinflammation is due to inflammation-related changes in the biochemical environment of primary afferent fibers—peripheral sensitization—and the spinal cord—central sensitization.[28] The central and peripheral sensitization together produce abnormal pain responses, manifested as allodynia and hyperalgesia.

One of the hallmarks of neuroinflammation is the activation of glial cells in the dorsal root ganglia, spinal cord, and brain and the production of pro-inflammatory cytokines and chemokines that cause peripheral and central sensitization in the PNS and CNS. While peripheral sensitization commonly results from the interactions between the nociceptors and inflammatory markers in the inflamed site, central sensitization facilitates the processing of pain transmission at the spinal level.[29,30]

Numerous studies investigating pain mechanisms and treatment options have demonstrated key cell functions, such as microglial activation, for modulation of pain in the CNS. Microglial cells, also known as macrophages residing in the CNS, play a crucial role in pain-signaling processes. In the event of injury, infection, or disease, microglia upregulate inflammatory signals, causing neuroinflammation in the CNS.[3,5]

Many studies have reported that activated microglial cells can release immune-regulatory biomarkers, such as pro-inflammatory cytokines and chemokines. These cytokines and chemokines can affect the signaling cascade, primary afferent neurons, interneurons, and pain-projection neurons and can modulate pain sensitivity.[31] An increase in pro-inflammatory cytokines in the spinal cord can modulate electrical-signal transmission by increasing excitatory synaptic transmission and decreasing inhibitory synaptic transmission.[32]

Evidence from some studies has indicated that minocycline, a tetracycline derivative, can alleviate abnormal pain behaviors caused by various pain states, by selective inhibition of microglial activation, a function different from antibiotic activity.[33,34] Moreover, some studies found that anti-Ly6G and liposome-encapsulated clodronate (dichloromethylene bisphosphonate) can have anti-inflammatory properties and provide pain relief.[35,36] Anti-Ly6G—the rat anti-mouse Ly6G mono clonal antibody, clone 1A8—is a specific antibody for depletion of neutrophils, and

liposome-encapsulated clodronate is an agent for the depletion of systemic macrophages via apoptosis. Those studies found that the anti-Ly6G and liposome-encapsulated clodronate down-regulated the central and peripheral inflammatory cytokines and chemokines in experimental pain models, such as for diabetic neuropathy and peripheral acute inflammatory pain.[35,36]

These results indicate that central and/or peripheral inflammatory mediators and/or the systemic and/or resident immune-system cells that produce them, can be therapeutic targets in the treatment of many inflammatory conditions and various related pain behaviors.

Pulsed Magnetic Field

Magnetic fields. Some studies to date have found that magnetic fields and magnetic forces can affect the functioning of living systems and can have the ability to create various changes within the systems.[37,38] A living organism, which is approximately 70% water and has conductive properties, can create its own electricity, and therefore, its own magnetic field.

The magnetic force induced by a magnetic field is among one of the fundamental forces of nature that affect all structures, from atoms to molecules, from cells to organs.[39] Magnetic fields are everywhere, from DNA where electrical activity occurs, to cells, organs, and systems.

A magnetic field can affect ionic transport, biopotentials, oxygen utilization, the kinetics of reactions, chemical processes, and molecular and cellular pathways and is effective in the realization and regulation of all vital functions, from cellular behavior to the regulation of physiological functions.[38-40]

The effectiveness and key roles of magnetic fields in the functioning of a biological system have led to the idea that different applications of their power can be used externally in the treatment of different diseases.[40] Studies on the subject have increased rapidly.

In studies conducted to investigate the biological effects of PMF, systems are used that can produce a regular electromagnetic field and can change parameters, such as wave form, intensity, and frequency when necessary, to obtain accurate, stable, and reproducible results.[38,41,42]

A PMF consisting of a pair of Helmholtz coils is frequently used in research on biological effects; the pair consists of two identical circular coils, which are parallel to each other, and the circular centers, which are on the same axis. The distance of the coils to each other is designed to be equal to the circles' radiuses. In such a system, by passing the same amount of current through the two coils in the same direction, a uniform magnetic field is created in a cylindrical region on the axis that passes through the circles' centers, in the area between the coils.[42-44]

Pain caused by factors such as a metabolic disorder or trauma is an important clinical problem. In clinical applications, pain treatments are generally performed with pharmacological applications, such as analgesics, narcotics, anticonvulsants, anti-inflammatories. Despite the wide variety of applications, the inadequacy of the results obtained and the various side effects of pharmacological applications has led to a search for safer and more effective nonpharmacological alternative treatments for pain management.

Although questions regarding their mechanisms of action still exist, interest has been increasing regarding noninvasive PMF applications as an alternative nonpharmacological approach for the treatment of various pain conditions.

Anti-inflammatory potential. PMF treatments have received much more attention from researchers as potential therapeutic options without side effects in the prevention and treatment of various pain conditions.

Some experimental and clinical studies have been conducted that have investigated the mechanisms of action of PMF and have reported therapeutic potentials for PMF treatments.[8,39,40] These studies have evaluated PMF for the management of disease in clinical cases, or they have established animal models, related to such topics as regeneration after nerve injury, management of depression, repair of bone fractures, and wound healing.

Inflammation and a wide variety of pain conditions are closely linked.[3,4] One of the key features of PMF treatment is the anti-inflammatory reaction it elicits by suppressing, among other things, pro-inflammatory cellular markers including cytokines and gene expression, which characterize both acute and chronic phases of inflammation in various pathological states.[41-44]

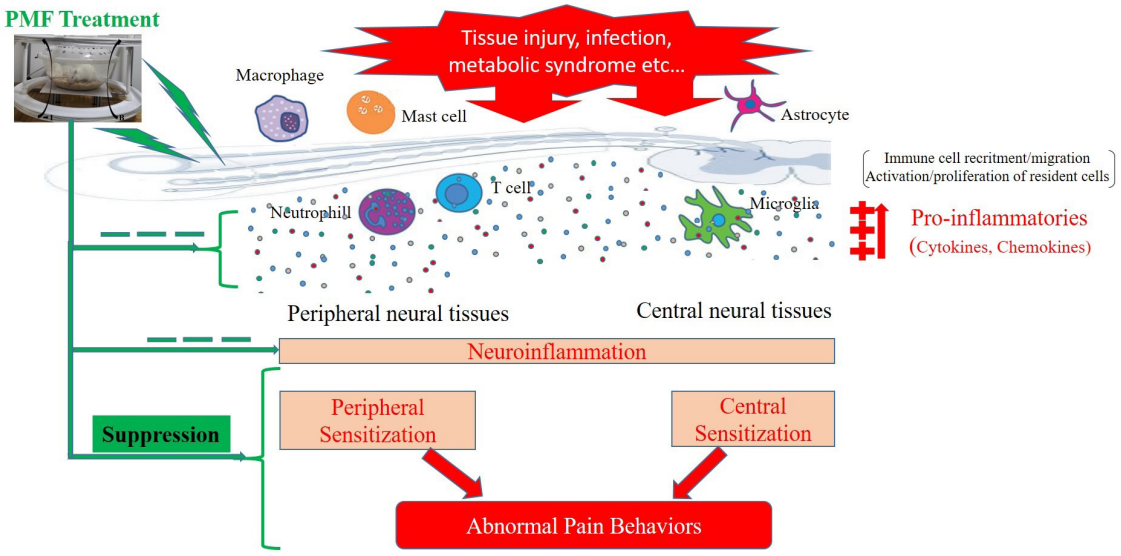
Some studies using different mammalian cell-culture models in vitro have also reported on the effects of PMF treatment on the progression of inflammation.[44,45] In addition, one study found that administration of PMF can cause a significant reduction in inflammation in human cell cultures related to pathology caused by COVID-19.[46]

Some studies have reported that PMF application can reduce the levels of chemokines, such as CCL3, CCL2, CXCL1 and CXCL8, and cytokines, such as TNF-α, IL-1β, and IL-6, which increase due to diabetes in the sciatic nerve and spinal cord.[43,44] It has been suggested that PMF treatments administered to diabetic rats may reduce the formation of pro-inflammatory cytokines by causing increased production of anti-inflammatory cytokines that act as an endogenous feedback inhibitor to maintain a balanced immune response in these neuronal tissues.

Moreover, numerous data from in vivo and in vitro animal and human studies indicate that PMF treatments can upregulate various growth factors, modulate the immune cells activities, increase the blood flow, reduce the oxidative stress and improve the abnormal sensory perceptions with its anti-angiogenic, anti-oxidative and anti-apoptotic actions in neuronal tissues during the diabetes.[47]

One study conducted for another chronic pain model found that PMF treatment could suppress the increase in pro-inflammatory cytokines, including TNF-α, IL-1β, and

Figure 1. PMF treatment and the inflammatory process



IL-17, and could increase the level of anti-inflammatory cytokines, such as IL-4 and IL-10, in central and peripheral neural tissues of rats with injured sciatic nerves.[9]

As stated previously, the increase in pro-inflammatory cytokines and the deterioration of the balance between pro-inflammatory and anti-inflammatory cytokines is one of the most important mechanisms of chronic-pain development. The increase in the levels of pro-inflammatory chemokines and cytokines that are produced in the spinal cord and sciatic nerve after disease or injury, can lead to the emergence of abnormal pain responses, and PMF treatment can ameliorate the neuropathic pain behaviors by balancing the pro-inflammatory and anti-inflammatory responses in the CNS and PNS.[22, 24, 26]

Other studies have found that PMF treatment can suppress the increase in the levels of chemokines, such as CXCL1 and CCL3, in the neural tissues of rats with a sciatic-nerve injury and can prevent the infiltration of immune cells and the migration of neural progenitors.[9,44]

Recently, some studies have also suggested anti-inflammatory properties for PMF treatments in a peripheral inflammatory-pain model.[10,43] Acute peripheral inflammatory pain is mainly characterized by hypernociceptive responses, also referred to as hyperalgesia or allodynia, due to the changes in sensitization of primary sensory nociceptive fibers and of the spinal cord.[29] Studies performed with this model have shown that CCL3 and CXCL1 chemokines and pro-inflammatory cytokine levels, such as TNF-α, IL-1β, IL-6, and IL-17, have increased in the inflammation region and in the spinal-cord tissues of inflamed rats.

Pro-inflammatory chemokines and cytokines, which increase the release of inflammatory cells to the inflammation area with the activation of the immune system after exposure to inflammatory agents, can cause more leukocyte migration to the region and increase pro-inflammatory cells.[43,44]

A cytokine can create a synergistic effect by stimulating the expression of other cytokines, and after the release of different and more cytokines, it can provide more than the sum of the effects of each cytokine alone. These findings suggest that cytokines and chemokines released by immune-system cells, such as macrophages, neutrophils, and microglia, can play an important role in the emergence of painful responses due to peripheral inflammation.

Also, some in-vivo and in-vitro studies have shown that PMF can ameliorate inflammatory conditions due to modulation of cellular functions.[41,48] The suppressive effects of PMF application on the increase in the levels of CCL3 and CXCL1 chemokines and of pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, and IL-17, at the inflammation site and in spinal-cord tissues suggests that PMF treatment can produce anti-inflammatory effects by modulating the functions of immune-system cells in the inflammatory process (Figure 1).

Some in-vitro and in-vivo studies have also shown that PMF treatment can alleviate oxidative stress by reducing oxidants and/or increasing antioxidants in various experimental models and have reported that it can have anti-oxidative effects.[52-55]

Contradictory findings for PMF treatments. Although some studies have shown that PMF treatments can relieve pain and improve functioning in different pain conditions, various contradictory findings have been reported that have found that treatment with PMF and/or the addition of it to standard treatment procedures, provides no beneficial effects.[8,11,47] Contradictory findings have also been reported for various pain conditions, such as painful diabetic polyneuropathy, chronic pain, and chronic and tonic muscle pain, with some researchers showing positive[9,38,39] and others showing negative[56-58] findings.

The fact that optimal treatment parameters for PMF haven't yet been determined may have led to the different results. The magnetic fields applied in magneto-therapy for pain have a frequency below 100 Hz and a magnetic flux density between 0.1 mT and 30 mT, in accordance with the generally accepted criteria in physical medicine.[59] However, the effects of PMF may not depend solely on its frequency or

intensity. If PMF is configured with the right form, intensity, frequency, or sequence, it may have many benefits for improving the biological system in various pain conditions.

Despite conflicting findings, the use of PMF, a noninvasive, safe, and easy treatment, as an alternative to conventional pharmacological therapy in the treatment of various pain and inflammatory conditions has increased significantly in recent years.

Clinical Significance and Future Perspectives

Central and peripheral neuroinflammation resulting from neuroimmune interactions not only serves as a driver for pain after different exposures but is also important in the emergence of many diseases, from Alzheimer's disease to psychiatric diseases.[1-3] Neuroinflammatory reactions, in which inflammatory mediators produced by multiple cell types can play an important role, include a range of biochemical and cellular changes, which are associated with pain conditions.[12] Thus, targeting excessive neuroinflammation can be a promising approach to alleviate abnormal pain behaviors and also control the progression of neuroinflammation-based diseases.

CONCLUSIONS

The noninvasive PMF therapy, which has parameters that can be controlled and which has no side effects, is a nonpharmacological therapeutic option with pain-relief ability through strong control of central and peripheral neuroinflammation. Further studies are needed to explore how PMF therapy controls central and peripheral neuroinflammation in various diseases and conditions.

AUTHORS' DISCLOSURE STATEMENT

The author indicates that he has no potential conflicts of interest.

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