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Review

Chronic Inflammation Effect on Nerve Regeneration in Dental Tissues

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Abstract

Nerve regeneration in dental tissues is crucial to restore function and preserve oral health. But the regenerative process is seriously hampered by chronic inflammation, which can be brought on by autoimmune diseases, trauma, or recurring infections. Neuronal apoptosis, delayed axonal regrowth, and compromised neurotrophic support are all caused by inflammatory mediators, including pro-inflammatory cytokines, reactive oxygen species, and matrix metalloproteinases. In dental tissues, these pathological alterations result in fibrosis, sensory dysfunction, and protracted healing. Neurotrophic factor supplementation, stem cell-based strategies, and targeted anti-inflammatory treatments may all aid in the restoration of nerve function in dental tissues that have been chronically inflamed, according to recent research. Developing successful regenerative therapies in dentistry requires an understanding of the relationship between inflammation and nerve regeneration. The mechanisms through which chronic inflammation hinders nerve regeneration are examined in this review, with particular attention paid to oxidative stress, extracellular matrix changes, and inflammatory signaling pathways.

Keywords: *Nerve regeneration, Chronic inflammation, Oxidative stress, Reactive Oxygen Species (ROS)*

Introduction

The nervous system within the dental tissues is crucial for pain perception, mechano-sensation, and tissue hemostasis to maintain appropriate function and responsiveness to external stimuli (1). Long-term functional impairment, delayed healing, and sensory abnormalities can result from damage to dental nerves caused by infection, trauma or chronic inflammation (2). Chronic inflammation is harmful and prolonged, forming a microenvironment that actively inhibits nerve regeneration, whereas acute inflammation is a self-limiting process intended to remove damaging stimuli and promote tissue repair. In the end, this chronic inflammatory response hinders the functional recovery of dental tissues by interfering with synaptic connectivity, axonal growth, and neuronal survival (3, 4). In dental tissues, persistent bacterial infections are one of the main causes of chronic inflammation, especially in conditions like periodontitis and pulpitis (5, 6).

The immune system is continuously activated by these infections, which cause oxidative stress, extracellular matrix (ECM) remodeling, and the release of inflammatory mediators, all of which obstruct nerve repair processes (7). When microbial antigens remain in infected tissues, inflammation cannot be resolved, which prolongs the activation of immune cells like neutrophils, dendritic cells, and macrophages (8, 9). In addition to infectious causes, chronic inflammation is exacerbated by autoimmune disorders, systemic inflammatory diseases, and repetitive mechanical trauma, all of which make nerve regeneration even more difficult (10). On a molecular level, neuroinflammation and nerve degeneration are largely caused by pro-inflammatory cytokines like interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) (11, 12). These cytokines interfere with axonal repair processes, inhibit neurotrophic signaling, and reduce neuronal survival. Because TNF-α binds to neuronal receptors and triggers apoptosis pathways, which result in axonal degeneration, it is especially neurotoxic (13). The same is true for IL-1β which exacerbates tissue damage by encouraging immune cell recruitment and microglial activation (14). Because it interferes with neuronal repair and disrupts synaptic plasticity, IL-6, which is involved in normal inflammatory resolution, becomes harmful in chronic inflammation. A neurotoxic environment that inhibits appropriate nerve regeneration in dental tissues is produced by the cumulative action of these cytokines.

Oxidative stress, a consequence of the overproduction of reactive oxygen species (ROS), is another important factor in inflammation-induced nerve damage (15, 16). Chronic inflammatory conditions cause mitochondria in Schwann cells and neurons to malfunction, which impairs lipid peroxidation, energy metabolism, and neuronal apoptosis (17, 18). Nerve recovery becomes more challenging as oxidative stress worsens neurodegeneration (19). Chronic inflammation also causes dysregulation of Schwann cells, which are responsible for neurotrophic support and axonal remyelination. Schwann cells become reactively inflammatory rather than repair-promoting, which decreases their capacity to support nerve regeneration.

Considering these difficulties, creating successful treatment plans requires an awareness of the cellular and molecular processes that underlie inflammation-induced neurodegeneration (20). Anti-inflammatory medications, neurotrophic factor supplements, and stem cell-based regenerative techniques may be able to prevent inflammation-induced nerve degeneration, according to recent research (21, 22). The immunomodulatory and neuroprotective qualities of novel treatments utilizing mesenchymal stem cells (MSCs) and dental pulp stem cells (DPSCs) present promising paths toward the restoration of nerve function in inflammatory dental tissues (23, 24). This review examines important molecular pathways, cellular interactions, and therapeutic developments. It investigates how chronic inflammation affects nerve regeneration in dental tissues by examining the relationship among immune dysregulation, oxidative stress, and extracellular matrix remodeling and seeks to offer a thorough grasp of how long-term inflammation hinders nerve

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regeneration and how new treatments could improve healing.

Methods

To find peer-reviewed research on chronic inflammation and nerve regeneration in dental tissues published between 2015 and 2024, this literature review used PubMed, ProQuest, Web of Science, and Google Scholar. Using keywords like "chronic inflammation," "nerve regeneration," "dental pulp neurodegeneration," "oxidative stress," and "cytokine-mediated neurotoxicity," the search focused on studies looking at molecular pathways, cellular responses, and possible therapeutic approaches. Only studies that focused on acute inflammation were excluded; studies that examined the effects of inflammation on nerve repair in dental tissues in vitro, in vivo, and in clinical settings were included. Key inflammatory mediators such as tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6 were included in the extracted data along with oxidative stress, Schwann cell dysregulation, and extracellular matrix remodeling. Anti-inflammatory drugs, neurotrophic factor supplements, stem cell therapy, and biomaterial scaffolds were among the therapeutic approaches that were assessed. To determine common mechanisms of inflammation-induced nerve degeneration and evaluate the efficacy of different treatments, the chosen studies were critically examined. This review summarizes the available data to shed light on how chronic inflammation affects nerve healing and possible methods to promote dental tissue regeneration.

Discussion

Nerve regeneration in dental tissues is impaired and neurodegeneration is inflammation-mediated

Chronic inflammation modifies the molecular and cellular mechanisms that promote neuronal survival and axonal growth, creating an environment not conducive to nerve regeneration in dental tissues (25, 26). Chronic inflammation lasts longer and gradually injures the nervous system, unlike acute inflammation, which is necessary for tissue repair since it clears infections and starts the healing process (27, 28). Complete functional recovery is prevented by the overexpression of inflammatory mediators as a result of the chronic activation of immune responses, which disrupts neurodegenerative processes (29). Chronic inflammation suppresses nerve regeneration primarily through the ongoing release of pro-inflammatory cytokines like interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) (30). Through the induction of synaptic dysfunction, axonal degeneration, and neuronal apoptosis, these cytokines disrupt the delicate balance between nerve injury and repair (31). By acting through neuronal receptors promoting caspase activation, causing programmed cell death, and triggering intracellular apoptotic mechanisms, TNF-α alone has been found to cause neurotoxicity (32). In the same way, IL-1β participates in neuronal damage by facilitating immune cell infiltration and perpetuating microglial activation that advances the inflammatory cascade (33). As a result of interference with neurotrophic signaling and Schwann cell-mediated axonal regeneration, IL-6 despite its dual pro-inflammatory and regenerative roles, becomes primarily neurotoxic during chronic inflammatory conditions (34). Oxidative stress is a key player in inflammation-mediated neurodegeneration in combination with cytokine imbalance. Neurons, Schwann cells, and support tissues have oxidative insults due to overexpression of ROS and nitrogen species due to chronic inflammation (35, 36). Axonal transport impairment and ensuing neurodegeneration are the result of mitochondrial DNA mutations, defective energy production, and impaired calcium homeostasis in neurons that are under oxidative stress, which is highly vulnerable (37, 38). A self-sustaining cycle of neuronal damage is created when both mitochondrial dysfunction and oxidative stress are present (39). Damaged mitochondria release more ROS that further exacerbate nerve damage. Oxidative stress, as indicated by studies, not only inhibits the survival of neurons but also triggers the activation of glial cells and the secretion of neurotoxic factors that further inhibit the potential for regeneration (40). Chronic inflammation exerts negative effects on cellular components essential for nerve regeneration along

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with molecular disruptions. Schwann cells, which have a central role in the repair of axons and remyelination in chronically inflamed tissues, experience dramatic functional alterations (41). Schwann cells usually support neuronal regeneration through the secretion of brain-derived neurotrophic factors (BDNFs) and nerve growth factors (NGFs), which promote neuronal survival and axonal outgrowth (42, 43). Schwann cells, however, change from a pro-regenerative phenotype to a reactive inflammatory phenotype in inflamed tissue (44, 45). This leads to less secretion of neurotrophic factors, increased production of inflammatory mediators, and impaired remyelination. By damaging the supporting cellular network necessary for regeneration, this change also interferes with the process of nerve repair.

Remodeling of the extracellular matrix and establishment of a resistance to regeneration microenvironment

In the direction of axonal elongation and regulation of cellular interactions, the extracellular matrix (ECM) supplies the structural and biochemical support for nerve regeneration. The ECM is, however, subject to severe remodeling when there is persistent inflammation that negatively affects the repair of nerves (46). Axonal outgrowth is physically inhibited by the thick scar tissue formed by the excessive deposition of fibrotic materials like collagen types I and III brought on by an extended inflammatory response (47). When fibrotic tissue builds up neurons are unable to move through injured areas resulting in partial nerve recovery and long-term sensory impairment (48). Overexpression of matrix metalloproteinases (MMPs), especially MMP-9 and MMP-13, which break down vital ECM proteins and neurotrophic factor-binding sites is another important factor causing ECM disruption (49). Laminin and fibronectin, which are essential for neuronal adhesion and axonal migration, are broken down by MMP overactivity (50). In addition to impeding effective nerve repair, the excessive breakdown of these structural proteins creates an unstable regenerative microenvironment. While the removal of damaged tissue during the early phases of healing is necessary, persistent MMP activity overexpression in chronic inflammation sets off a destructive cycle in which the extracellular matrix is unable to support neuronal regeneration. Chronic inflammation not only causes fibrotic alterations but also modifies the bioavailability of neurotrophic factors which are necessary for nerve repair. Neuronal survival and axonal extension depend on the release of NGF, glial cell line-derived neurotrophic factor (GDNF), and ciliary neurotrophic factor (CNTF), all of which are inhibited by oxidative stress and inflammatory cytokines (51, 52). Unfinished nerve recovery results from the reduction of these growth factors, which restricts the capacity of regenerating axons to form new synaptic connections. Chronically inflamed dental tissues develop a regeneration-resistant microenvironment as a result of this imbalance between excessive ECM remodeling fibrosis and growth factor depletion (53, 54).

Possible therapeutic approaches to reverse inflammatory nerve damage

In an attempt to avert inflammation-induced neurodegeneration and restore neuronal function in dental tissues, several therapeutic approaches have been investigated due to the broad implications of chronic inflammation on nerve regeneration. One such approach involves the use of anti-inflammatory medications to regulate cytokine function and reduce neurotoxicity (55). Pharmacological agents against the TNF-α and IL-1β signaling pathways have demonstrated potential in preclinical studies through Schwann cell-mediated induction of nerve regeneration, reducing neuroinflammation and maintaining axonal integrity (56, 57). Cytokine selective inhibitors were found to have neuroprotective effects by restoring neurotrophic factor expression and preventing excessive activation of immune cells (58). Another approach includes the application of antioxidant-based therapy to scavenge oxidative stress. N-acetylcysteine, resveratrol, and curcumin are a few of the molecules that have been studied for their ROS-scavenging properties, their capacity to promote neuronal survival, and their ability to enhance mitochondrial function (59). These antioxidants have demonstrated efficacy in

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preclinical models by blocking lipid peroxidation, maintaining calcium homeostasis, and safeguarding the structural integrity of neuronal membranes (60, 61). Reducing oxidative stress may be a significant step in avoiding long-term neurodegenerative effects of chronically inflamed dental tissues as evidenced by the potential role of antioxidant therapy in nerve regeneration (62, 63). In instances where there has been damage to nerve function due to inflammation, regenerative medicine techniques, more precisely stem cell therapy, have been shown to have great promise (4, 64). Due to their immunomodulatory characteristics, bone marrow adipose tissue and dental pulp-derived mesenchymal stem cells can reduce inflammation while at the same time inducing nerve regeneration (65, 66). The neurotrophic factors BDNF, NGF, and GDNF released by these stem cells facilitate Schwann cell function, axonal extension, and neuronal differentiation (67, 68). Based on experimental research, stem cell transplantation may improve nerve repair by restoring deficient neuronal populations, minimizing fibrosis, and modulating immune responses (69). However, the optimization of delivery methodologies with assurance of long-term viability of transplanted cells and resolution of ethical and legal issues related to stem cell-based therapies are difficult. Besides pharmacological and regenerative medicine strategies, biomaterial scaffolds have been investigated as vehicles for neurotrophic factors and stem cell delivery. Biodegradable scaffolds composed of collagen, hyaluronic acid, or chitosan offer structural support and allow the controlled delivery of regenerative molecules (70). The scaffolds augment the regenerative capacity of inflammatory dental tissue by mimicking the natural extracellular matrix and supporting neuronal adhesion (71, 72). Preclinical investigations show that therapies based on scaffolds can optimize the success of nerve repair by improving axonal guidance, stabilizing the presence of neurotrophic factors, and guarding against injury caused by inflammation (73).

Conclusion

Chronic inflammation in extreme manners restrains nerve regeneration in dental tissues, disturbs cytokine signaling, increases oxidative stress changes and Schwann cell function, and remodels the extracellular matrix. Extended neurodegeneration ensues from the prolonged activity of inflammatory mediators like interleukin-1 beta, interleukin-6, and tumor necrosis factor-alpha that compromise neuronal survival and axonal regrowth. To comprehensively realize the precise effects of inflammatory mediators on dental nerve regeneration, more studies have to be conducted despite the promising results of anti-inflammatory drugs, stem cell therapies, and neurotrophic factor supplements. The major aims of future studies should include elucidating the molecular mechanisms responsible for inflammation-induced neurodegeneration and determining long-term effects on nerve function. To develop clinically useful treatments that restore normal sensory and functional capacity in chronic inflammatory dental disease patients, there will be a need to enhance regenerative strategies and optimize therapeutic interventions.

Disclosure

Statement

The authors declare that they have no conflict of interests.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical Consideration

Not applicable.

Data Availability

The contributions presented in the study are included in the article further inquiries can be directed to the corresponding author.

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