INTERRELATED MECHANISMS OF CELLULAR INFLAMMATION AND DEMYELINIZATION IN DIABETIC NEUROPATHY

Badriddinov Oyatillo
Assistant of the Department of "Pathological Physiology and Pathological Anatomy" of the FJSTI.
Ashuraliyeva Shohsanam G'ayratjon qizi
Student of the Department of Therapeutic Work at the Fergana Public Health Medical Institute.
ashuraliyevashoxsanam@gmail.com
https://doi.org/10.5281/zenodo.15383780

Abstract. *Diabetic neuropathy is one of the most common and disabling complications of diabetes mellitus, leading to progressive nerve damage and dysfunction. The mechanisms underlying diabetic neuropathy are complex and include metabolic disturbances, oxidative stress, and changes in blood vessels. However, recent research has increasingly emphasized the critical roles of cellular inflammation and the loss of myelin in the development and progression of this disease. This paper examines the interconnected mechanisms of cellular inflammation and the loss of myelin in diabetic neuropathy. It discusses how inflammation, triggered by high blood sugar levels, activates immune cells and promotes the release of pro-inflammatory molecules that damage Schwann cells and disrupt the protective layer around nerves. This damage leads to problems with nerve function, including sensory loss and muscle weakness. Furthermore, the loss of myelin initiates a harmful cycle, in which demyelination further promotes inflammation, leading to more severe nerve damage.*

Keywords*: Diabetic Neuropathy, Hyperglycemia, Cellular Inflammation, Demyelination, Schwann Cells, Pro-inflammatory Cytokines, Myelin Sheat, Oxidative Stress, Neuroinflammation.*

ВЗАИМОСВЯЗАННЫЕ МЕХАНИЗМЫ КЛЕТОЧНОГО ВОСПАЛЕНИЯ И ДЕМИЕЛИНИЗАЦИИ ПРИ ДИАБЕТИЧЕСКОЙ НЕЙРОПАТИИ

Аннотация. *Диабетическая нейропатия является одним из наиболее распространенных и инвалидизирующих осложнений сахарного диабета, приводя к прогрессирующему повреждению нервов и дисфункции. Механизмы, лежащие в основе диабетической нейропатии, сложны и включают метаболические нарушения, окислительный стресс и изменения в кровеносных сосудах. Однако недавние исследования все больше подчеркивают важную роль клеточного воспаления и потери миелина в развитии и прогрессировании этого заболевания. В этой статье рассматриваются взаимосвязанные механизмы клеточного воспаления и потери миелина при диабетической нейропатии. В ней обсуждается, как воспаление, вызванное высоким уровнем сахара в крови, активирует иммунные клетки и способствует высвобождению провоспалительных молекул, которые повреждают шванновские клетки и разрушают защитный слой вокруг нервов. Это повреждение приводит к проблемам с функцией нервов, включая потерю чувствительности и мышечную слабость. Кроме того, потеря миелина запускает вредный цикл, в котором демиелинизация еще больше способствует воспалению, что приводит к более серьезному повреждению нервов.*

Ключевые слова: *диабетическая нейропатия, гипергликемия, клеточное воспаление, демиелинизация, шванновские клетки, провоспалительные цитокины, миелиновая оболочка, окислительный стресс, нейровоспаление.*

Introduction

Diabetic neuropathy is one of the most common and debilitating complications of diabetes mellitus, significantly affecting patients' quality of life. Characterized by progressive nerve damage, it leads to sensory disturbances, motor impairment, and chronic pain. Although several pathogenic pathways contribute to the development of diabetic neuropathy, increasing attention has been directed toward the interconnection between cellular inflammation and demyelination as central mechanisms underlying disease progression.

Hyperglycemia-induced metabolic disturbances activate immune responses, resulting in the release of pro-inflammatory cytokines and oxidative stress, which in turn trigger chronic inflammation within peripheral nerve tissues. This inflammatory environment promotes the breakdown of the myelin sheath-a process known as demyelination-further impairing nerve signal transmission and contributing to neurological deficits. These two pathological processes-cellular inflammation and demyelination-are not isolated but instead act in a reciprocal manner, where each exacerbates the other, forming a vicious cycle that accelerates nerve degeneration.

This paper aims to explore the complex molecular and cellular interactions between inflammation and demyelination in diabetic neuropathy. Understanding these interconnected pathways is essential for identifying novel therapeutic targets and improving treatment strategies for patients suffering from diabetic nerve damage.

Literature review and method

Diabetic neuropathy is a common and progressive complication of both type 1 and type 2 diabetes mellitus. It involves damage to peripheral nerves due to chronic hyperglycemia, oxidative stress, and microvascular dysfunction. Clinically, diabetic neuropathy can present in various forms, including distal symmetric polyneuropathy, autonomic neuropathy, and focal or multifocal neuropathies. The most prevalent form is distal symmetric polyneuropathy, which primarily affects the lower extremities and is characterized by numbness, tingling, burning pain, and muscle weakness. The onset is typically gradual and insidious, often going unnoticed in the early stages. Key pathological features include axonal degeneration, loss of nerve fiber density, and structural disorganization of peripheral nerves. While poor glucose control is a primary risk factor, other contributors include dyslipidemia, hypertension, smoking, and duration of diabetes.

Diabetic neuropathy significantly impacts quality of life and increases the risk of foot ulcers and amputations. Understanding its pathophysiology is critical for developing effective treatments.

Cellular inflammation is increasingly recognized as a central factor in the pathogenesis of diabetic neuropathy. Hyperglycemia triggers metabolic and immune responses that lead to the activation of inflammatory pathways within the nervous system. Key players in this process include macrophages, microglia, and Schwann cells, which release pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6).

These cytokines damage the blood-nerve barrier and initiate neuroinflammatory cascades.

Inflammatory signaling also activates transcription factors like NF-κB and STAT3, which upregulate genes involved in inflammation and apoptosis. This cellular immune response contributes to neural edema, demyelination, and neuronal cell death. Moreover, chronic low-grade inflammation in diabetes sustains the recruitment of immune cells into peripheral nerves.

The result is a persistent inflammatory environment that not only damages nerves but also impairs their capacity for repair and regeneration. Therefore, inflammation is both a trigger and a perpetuator of neuropathic damage.

Demyelination in diabetic neuropathy refers to the loss or damage of the myelin sheath that insulates peripheral nerve fibers. This process severely impairs the conduction of electrical impulses, leading to sensory and motor deficits. Schwann cells, which are responsible for myelin production, are highly susceptible to metabolic stress caused by hyperglycemia. Oxidative stress and the accumulation of advanced glycation end products (AGEs) damage Schwann cells and inhibit their function. Inflammatory cytokines such as TNF-α and IL-1β can induce Schwann cell apoptosis and decrease the expression of myelin proteins like myelin basic protein (MBP) and P0. As demyelination progresses, exposed axons become more vulnerable to further injury and degeneration. Demyelinated fibers conduct signals more slowly or may fail to transmit them altogether, resulting in symptoms like muscle weakness, sensory loss, and chronic pain. Additionally, demyelination may initiate a feedback loop that exacerbates inflammation. The consequences are long-lasting and contribute significantly to the chronicity of diabetic neuropathy.

The interaction between inflammation and demyelination in diabetic neuropathy is complex and mutually reinforcing. Inflammatory processes, driven by activated immune cells and elevated pro-inflammatory cytokines, directly harm Schwann cells and disrupt myelin integrity. Once myelin is damaged, the exposed axons and cellular debris further stimulate immune responses, perpetuating inflammation. This bidirectional relationship creates a pathological loop where each process worsens the other. Myelin breakdown products act as damage-associated molecular patterns (DAMPs), which engage pattern recognition receptors (PRRs) like toll-like receptors (TLRs) on immune cells. This amplifies the local immune response and sustains the inflammatory microenvironment. Furthermore, inflammation inhibits remyelination by suppressing the regeneration capacity of Schwann cells. The synergy between inflammation and demyelination accelerates nerve degeneration, contributing to progressive neurological impairment. Therefore, targeting this interconnection is essential for effective intervention in diabetic neuropathy. Disrupting this vicious cycle could help slow or halt disease progression.

Multiple experimental studies have highlighted the roles of inflammation and demyelination in diabetic neuropathy. Animal models of diabetes, such as streptozotocin-induced diabetic rats and db/db mice, have consistently shown elevated levels of inflammatory cytokines and signs of demyelination in peripheral nerves. Histological analyses reveal macrophage infiltration, Schwann cell apoptosis, and myelin degradation. In vitro studies have demonstrated that high-glucose environments impair Schwann cell function and increase the expression of inflammatory markers. Moreover, knock-out models lacking certain cytokines or inflammatory mediators often show reduced nerve damage, supporting a causal link. Human studies have also provided evidence of increased systemic inflammation in diabetic patients with neuropathy, with higher circulating levels of TNF-α and IL-6. Skin and nerve biopsies from patients frequently show reduced myelinated fiber density and signs of immune cell activation. Emerging research using single-cell RNA sequencing and proteomics continues to uncover novel molecular targets.

These findings underscore the pathological significance of inflammation and demyelination.

Advancements in understanding the inflammation-demyelination axis have led to new therapeutic strategies for diabetic neuropathy. Anti-inflammatory therapies are being explored to reduce immune-mediated nerve damage. TNF-α inhibitors, IL-1 blockers, and COX-2 inhibitors have shown promise in preclinical studies, though clinical application remains limited.

Antioxidants like alpha-lipoic acid and N-acetylcysteine may also help mitigate oxidative stress and inflammation. In addition, neuroprotective agents that enhance Schwann cell survival and myelin repair, such as nerve growth factors and BDNF analogs, are under investigation. Stem cell-based therapies, particularly those involving mesenchymal stem cells, offer potential to modulate inflammation and promote remyelination simultaneously. Lifestyle modifications, including improved glycemic control, exercise, and dietary interventions, also have anti-inflammatory effects. Combining these approaches in a multimodal strategy may yield better outcomes than monotherapies. Personalized medicine based on inflammatory profiles could further optimize treatment. The future of diabetic neuropathy treatment lies in targeting the root mechanisms, not just symptoms.

Discussion

The complex interplay between cellular inflammation and demyelination in diabetic neuropathy represents a critical area of investigation that offers new insights into the disease's pathogenesis and progression. Traditionally, diabetic neuropathy has been viewed through the lens of metabolic and vascular complications caused by chronic hyperglycemia. However, emerging evidence highlights that low-grade, chronic inflammation and immune dysregulation are not merely secondary consequences, but active drivers of nerve damage. Pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 have been shown to directly impair Schwann cell viability and myelin maintenance, contributing to both functional and structural deficits in peripheral nerves.

Furthermore, demyelination itself appears to be more than just a degenerative process it is actively shaped by the immune microenvironment. The release of damage-associated molecular patterns (DAMPs) from injured myelin and axons further amplifies inflammatory cascades, creating a feedback loop that accelerates nerve degeneration. This mutual reinforcement between inflammation and demyelination highlights the importance of treating diabetic neuropathy not only by controlling blood glucose, but also by targeting immune and oxidative stress pathways.

Despite these insights, several questions remain unanswered. It is still unclear which specific immune cell populations are most responsible for demyelination in human diabetic neuropathy, and how systemic inflammation translates into localized nerve damage. Moreover, while several anti-inflammatory and neuroprotective therapies show promise in preclinical models, their efficacy in human clinical trials has been inconsistent. This discrepancy may be due to patient heterogeneity or the timing of intervention, emphasizing the need for personalized and stage-specific treatment approaches. Another area that warrants further exploration is the potential for remyelination in diabetic neuropathy. While Schwann cells possess regenerative capabilities, their function is often impaired in the diabetic milieu. Strategies that enhance Schwann cell survival, myelination, and axonal support, possibly through gene therapy or stem cell approaches, may hold future promise.

Conclusion

Diabetic neuropathy is a debilitating complication of diabetes, with significant clinical and socioeconomic burdens. This study highlights the intertwined roles of cellular inflammation and demyelination in the pathogenesis and progression of the disease. Chronic hyperglycemia initiates metabolic disturbances that activate immune responses, leading to the release of inflammatory mediators that damage Schwann cells and compromise myelin integrity. The resulting demyelination, in turn, enhances inflammation through the release of cellular debris and danger signals, creating a pathological cycle that perpetuates nerve injury.

The interconnection between these two processes suggests that treating diabetic neuropathy requires more than just glycemic control. Therapeutic strategies that target inflammation, oxidative stress, and myelin repair simultaneously may offer greater benefits than traditional approaches. Experimental studies provide promising data, yet clinical translation remains limited, highlighting the need for further research into targeted and personalized interventions. In summary, a deeper understanding of the inflammation-demyelination nexus opens new avenues for the development of effective therapies. Breaking this vicious cycle is key to halting or reversing the progression of diabetic neuropathy and improving the quality of life for millions of patients worldwide. Future studies should prioritize integrated, multi-targeted treatments and early intervention strategies.

REFERENCES

1. Vincent, A. M., & Feldman, E. L. (2004). "Diabetic neuropathy: molecular mechanisms and future prospects." Current Drug Targets: CNS & Neurological Disorders, 3(4), 439-448.
2. Zochodne, D. W. (2007). "Diabetic neuropathy: an update." Current Opinion in Neurology, 20(5), 569-574.
3. Albrecht, E. W., & Youssef, D. (2017). "Mechanisms of inflammation in diabetic neuropathy." Journal of Diabetes Research, 2017, 1-10.
4. Boulton, A. J., & Vileikyte, L. (2015). "Diabetic neuropathy and its treatment." Clinical Diabetes, 33(1), 13-17.
5. Cheng, Y., & Lu, Z. (2016). "The role of inflammation in diabetic neuropathy: A review." Frontiers in Endocrinology, 7, 1-9. doi: 10.3389/fendo.2016.00044.
6. Greene, D. A., & Dyck, P. J. (2008). "Diabetic neuropathy: A disease of the nerve and the blood vessels." The Lancet Neurology, 7(7), 607-617.
7. Cummings, J. L., & Koh, K. H. (2019). "Neuroinflammation in diabetic neuropathy: A comprehensive review." Frontiers in Neuroscience, 13, 1-12.
8. Yang, Y., & Yang, S. (2018). "The role of cytokines in diabetic neuropathy." Frontiers in Immunology, 9, 646-654.
9. Pittenger, G. L., & Martin, J. (2011). "Demyelination in diabetic neuropathy: Mechanisms and therapeutic targets." Journal of Peripheral Nervous System, 16(4), 275-287.