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Review Article

The Impact of Insulin-Like Growth Factor on the Regeneration of Myelin Sheath

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Abstract
The regeneration of the myelin sheath, a critical process in restoring neuronal function after injury or disease, is influenced by various molecular factors. Insulin-like growth factor (IGF) has emerged as a key player in promoting myelin repair due to its roles in cellular growth, differentiation, and survival. This study investigated the impact of IGF on the regeneration of the myelin sheath, focusing on its effects on oligodendrocyte precursor cells, the primary contributors to remyelination. Experimental models revealed that IGF enhances oligodendrocyte precursor cell proliferation, migration, and differentiation into mature oligodendrocytes, which are essential for myelin production. Additionally, IGF could modulate phosphoinositide 3-kinase/protein kinase B and mitogen-activated protein kinase signaling pathways, which are crucial for neuroprotection and myelin repair. These findings underscore the therapeutic potential of IGF in conditions characterized by demyelination, such as multiple sclerosis (MS) and traumatic brain injury. Accordingly, further research is needed to optimize IGF delivery methods and evaluate their long-term efficacy and safety in clinical settings. Eventually, this study highlights IGF as a promising candidate for advancing regenerative therapies targeting myelin sheath restoration.
Keywords: Insulin-like growth factor, Myelin sheath regeneration, Oligodendrocyte precursor cells

Insulin-Like Growth Factor and Autoimmune Diseases

IGFs (IGF-I and IGF-II), along with their binding proteins, that is, IGF binding proteins (IGFBPs), and the receptors (IGF-IR types I and II) responsible for their signaling, play essential roles in normal development, growth, metabolism, and maintenance of internal stability. Furthermore, IGFBPs form a family of proteins that bind to IGFs. This family includes IGFBP1, IGFBP2, IGFBP3, IGFBP4, IGFBP5, and IGFBP6.[1-3]

Insulin-Like Growth Factor and Neurodegenerative Function

IGF-I functions as a pro-survival factor at the cellular level, primarily through the phosphatidylinositol 3-kinase/protein kinase B pathway to activate antiapoptotic cascades. Additionally, it boosts nerve cell metabolism, modulates neuronal excitability, and offers protection against nerve cell damage.[4-8] Brain and serum levels of IGF-I are functionally interconnected, and changes in brain IGF-I levels may be due to modifications in serum levels. The precise significance of fluctuations in IGF-I levels remains incompletely elucidated. However, it is notable that these levels undergo modifications in diverse pathological conditions. In light of IGF-I's pivotal function as a pro-survival signal in the maturing nervous system, it is conceivable that it assumes a commensurate role in the adult brain. Consequently, in the event of a pathological state, it is plausible that IGF-I levels may escalate to shield affected neurons, thereby conferring neuroprotective properties to serum IGF-I in the adult brain.[9-11]

The level of IGF-I can be affected by the primary cause of neuronal damage or as a result of it. The specific disease type determines which scenario occurs. For example, problems with IGF-I production in the liver due to liver damage, diabetes, or other conditions can lead to reduced IGF-I levels, which may cause neurological issues in conditions such as hepatic encephalopathy or diabetes. In cases of diabetes, it is well-documented that IGF-I levels in the blood decrease, and treatment with IGF-I can help with diabetic neuropathy. Additionally, reduced sensitivity to IGF-I in nerve cells may occur following inflammation or excitotoxic insult.[12] The text discusses the potential impact of IGF-I on cell survival in specific conditions. It proposes that IGF-I deficiency may be the root cause of neuronal dysfunction or death in some cases, while in others, this may contribute to the advancement of the disease. The passage suggests that the latter scenario is more prevalent, given the typical association of inflammation and excitotoxicity with neuronal death. Additionally, it refers to rare neurodegenerative conditions, such as ataxia telangiectasia, where diminished levels of IGF-I receptor, resulting from a protein mutation, lead to reduced

responsiveness to IGF-I in fibroblasts. This reduced sensitivity is likely also present in neurons and other cells bearing the IGF-I receptor in ataxia telangiectasia patients[11] (Figure 1).

Insulin-Like Growth Factor 1 and Innate Immunity

IGF-1, in conjunction with colony-stimulating factors, such as interleukin (IL)-3, plays a role in regulating the body's innate immune system by influencing the growth and development of myeloid lineage cells. Research has indicated that growth hormone and IGF-1 can boost the numbers of immune cells in mice suffering from peritonitis. Nonetheless, the precise mechanisms by which IGF-1 impacts the variety of precursor cells in the bone marrow are not fully understood. It is highly probable that IGF-1 facilitates the growth and differentiation of these precursor cells while also governing bone size during the growth process. The presence of IGF-1 has implications for the bone marrow and the production of blood cells. Furthermore, IGF-1 may play a role in preventing specific myeloid lineage cells from undergoing apoptosis, with potential significance for the immune system. In vitro studies have demonstrated that IGF-1 can inhibit cell death in IL-3-dependent cell lines following removing IL-3. Conversely, heightened IGFBP expression may attenuate the local bioactivity of IGF-1 and decrease cellular susceptibility to proliferation or the initiation of an anti-apoptotic response.[13] The results indicate that IGF-1 plays a direct role in modulating hematopoiesis by stimulating cell proliferation and anti-apoptotic signaling. Furthermore, it is suggested that IGF-1's interaction with immunocompetent cells may influence the responsiveness of mature immune cells to antigens, as observed in various in vitro studies.[14]

Insulin-Like Growth Factor 1 and Neuroprotective Effects

The critical period of brain cell proliferation is predominantly observed during the fetal and neonatal stages. IGF-1 assumes a pivotal role in the process of differentiation, encompassing cell proliferation and survival throughout nervous system development. Notably, there is a heightened expression of IGF-1 receptors during this period, indicating a significant involvement of IGFs in developmental processes.[15] In the developing brain, the local production of IGF-1 is predominantly observed in neuronal-rich areas, notably the spinal cord, midbrain, cerebral cortex, hippocampus, and olfactory bulb.[16] Mice harboring null mutations in genes encoding IGF-1 could reduce brain size, hypomyelination, decreased density of oligodendrocytes, loss of neuron populations, and reduced glucose uptake. Conversely, transgenic mice that overexpressed IGF-1 exhibited brains that were 55% larger, with increased cell number and size compared to controls.[17] An increase of 130% in myelin content was observed in animals. Consistently, transgenic mice overexpressing the IGF-inhibitory IGFBP-1 exhibited a reduction in the percentage of myelinated axons and the thickness of myelin sheaths. A decrease in myelin protein expression accompanied this reduction. Notably, IGFs are known to play a crucial role in promoting the survival and differentiation of various types of neural cells, including sensory, sympathetic, and motor neurons.[18] Significant evidence supports a strong correlation between lower levels of circulating IGF-1 and the deterioration of cognitive functions in aging individuals.[7]

Insulin-Like Growth Factor Adaptive Immunity

IGF-1 is a peptide hormone that not only plays a vital role in regulating metabolism, growth, and development

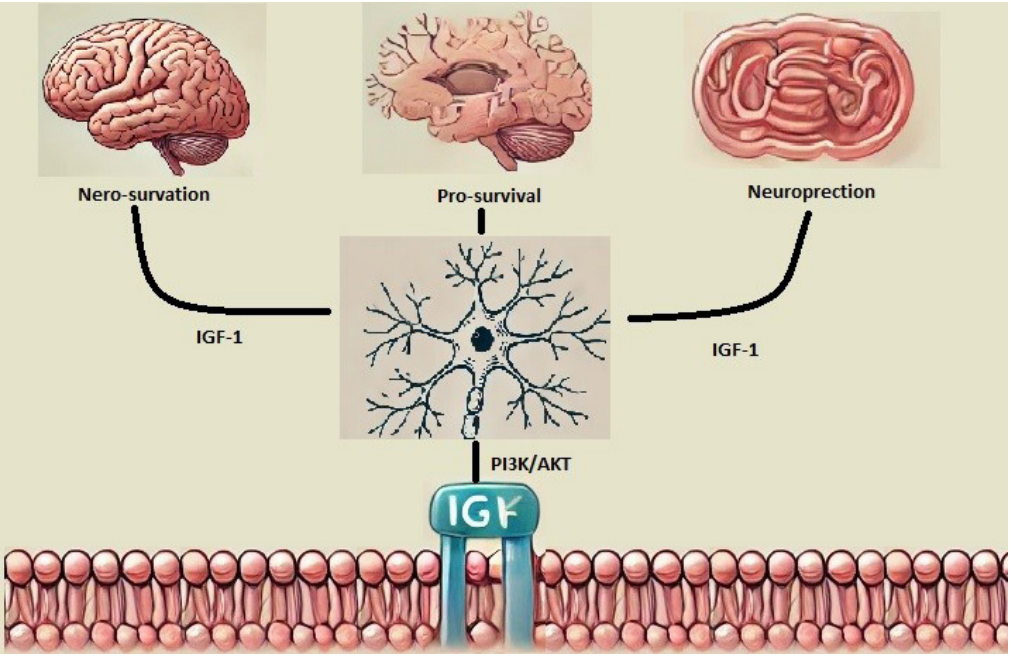

Figure 1. Insulin-Like Growth Factor and Neurodegenerative Function. *Note*. PI3K/AKT: Phosphoinositide 3-kinase/protein kinase B

but also has significant implications in shaping adaptive immunity.[14,19]. Recent studies have revealed the complex relationship between IGF-1, its receptor (IGF-IR), and various aspects of the adaptive immune system.[14,19] Research has shown that IGF-1 and IGF-IR play a significant role in shaping the function and growth of various adaptive immune cell types, such as T and B cells.[14,19] The IGF-1 pathway shares similar signaling components with cytokines, indicating its potential to influence the strength and effectiveness of adaptive immune responses.[14,19] Pro-inflammatory cytokines can diminish multiple components of the IGF-1 pathway.[14,19] The intertwining of IGF-1 signaling with adaptive immunity offers valuable insights into the organism's comprehensive management of energy resources, its ability to survive, and its mechanisms for defending against threats.[14,19] IGF-1 noticeably contributes to normal and pathological wound healing and tissue remodeling across various clinical conditions.[14,19] The IGF-1 pathway may have implications in the pathogenesis of autoimmune diseases, although the relationship with these processes is intricate and relatively unexplored.[14,19] The lymphoid tissues of genetically hypopituitary species with reduced IGF-1 levels show a decrease in cellularity, leading to immune dysfunction, as described by Heemskerk et al[14] Conversely, it is observed that IGF-1 offers protection against the development of insulin-deficient diabetes mellitus in experimental animals.[10]

However, antibodies targeting IGF-IR have been found in patients with Graves' disease, where the receptor is overexpressed by multiple cell types.[10] The potential implication of IGF-1 and IGF-IR in the pathogenesis of autoimmune diseases suggests that targeting this pathway presents an appealing therapeutic opportunity. IGF-IR has been the focus of drug development endeavors in the field of oncology, utilizing both small-molecule and monoclonal antibody methodologies.[10]

Recognizing the broader role of IGF-IR in regulating both normal and pathological adaptive immune responses may provide crucial opportunities for therapeutic intervention in several related diseases that have been particularly challenging to treat. Understanding that the IGF-1 pathway has the potential to influence adaptive immunity underscores the complex interconnectedness of human biology. This revelation also indicates that shared signaling pathways exist between growth factors and cytokines, implying nature's intricate mechanisms to harmonize metabolic processes, growth, and adaptive immune responses, ultimately benefiting the organism's overall health.

Insulin-Like Growth Factor and Immunity

IGF-1 is a peptide hormone with a pivotal role in regulating immunity, alongside its ancient functions in metabolism, growth, and development.[10,14,20]

Recent research has brought to light the complex interplay between IGF-1, its receptor (IGF-IR), and multiple facets of the immune system.[20,21] Research has established that IGF-1 and IGF-IR play a substantial role in influencing the functionality and proliferation of a variety of immune cell types, notably T and B cells. The IGF-1 pathway shares common signaling components with cytokines, suggesting that it can modulate the magnitude and quality of immune responses.[20] Pro-inflammatory cytokines, on the other hand, have been found to dampen several components of the IGF-1 pathway.[20] The integration of IGF-1 signaling with immunity provides insights into the overall energetic economy, survival, and host defense of the organism.[20] IGF-1 plays an extremely important role in both regular and abnormal wound healing processes, as well as in tissue remodeling across a wide range of clinical situations.[20] Its association with these processes is intricate and not thoroughly investigated despite playing a role in the pathogenesis of autoimmune diseases.[21] Genetically hypopituitary species with reduced IGF-1 levels show decreased cellularity of lymphoid tissues and linked immune dysfunction.[19] The evidence suggests that IGF-1 has the potential to shield experimental animals from developing insulin-deficient diabetes mellitus.[21] In patients with Graves' disease, researchers have discovered the presence of antibodies that specifically target IGF-IR, which is overexpressed by various cell types in the body. The potential involvement of IGF-1 and its receptor (IGF-1R) in the development of autoimmune diseases indicates that targeting this pathway could offer a promising therapeutic approach. Efforts have been focused on the development of cancer drugs targeting IGF-IR, utilizing both small molecule and monoclonal antibody approaches.[21] Recognizing the extensive involvement of IGF-IR in regulating both normal and pathological immune responses presents significant prospects for therapeutic intervention in various associated diseases that have been proven particularly challenging to address.[21]

Insulin-Like Growth Factor and Neurodegenerative Disease

IGF-1 plays a pivotal role in the complex landscape of neurodegenerative diseases. Studies endeavor to offer a comprehensive portrayal of the intricate interplay between IGF-1 levels and neurodegenerative conditions, leveraging insights gleaned from cutting-edge research endeavors.[22,23] Neurodegenerative diseases, such as Alzheimer's disease (AD), are intricate conditions marked by the progressive degeneration of neurons and a decline in cognitive functions. Biomarkers, such as IGF-1, have instigated a significant paradigm shift in the approach to identifying and addressing these diseases. IGF-1, a peptide hormone crucial for the growth and preservation of the nervous system, has garnered substantial attention due to its potential impact on the pathogenesis of neurodegenerative diseases.[22,24] The results of a study on patients with AD revealed that there is a negative correlation between serum IGF-1 levels and age, disease

duration, and modified Rankin scale scores. These findings suggest that IGF-1 may play a potential role in the progression of AD.[2] Furthermore, another study indicated an inverse correlation between IGF-1 levels and the risk of developing AD in patients with mild cognitive impairment, as well as a poor cognitive outcome after 2 years.[25] The evidence strongly confirms a significant connection between IGF-1 levels and the development and advancement of neurodegenerative diseases. Higher IGF-1 levels are linked to a lower risk of neurodegenerative diseases, while lower levels are associated with a higher risk.[22,23] However, further investigations are necessary to validate the prognostic value of serum IGF-1 levels in neurodegenerative diseases and uncover the underlying sources of heterogeneity.[11]

Insulin-Like Growth Factor 1 in Acute Ischemic Stroke

IGF has emerged as a key factor in the context of ischemic stroke, demonstrating both protective and prognostic implications. IGF-1, a peptide hormone structurally similar to insulin, has been a focal point in several studies investigating its impact on stroke outcomes.[26] Research by Recent study highlighted that high levels of IGF-1 during acute stroke are associated with improved survival rates and reduced stroke severity.[27] The findings underscore the potential neuroprotective effects of IGF-1 in the context of stroke. Furthermore, the study evaluated the dynamic fluctuations in IGF-1 levels during the initial week following a stroke, revealing a correlation between reduced IGF-1 levels and favorable outcomes, such as decreased hospitalization duration and enhanced independence one month post-stroke.[27] A meta-analysis encompassing 17 studies reported that elevated serum IGF-1 levels were significantly linked to a lower risk of ischemic stroke and better post-stroke recovery.[28] This meta-analysis sheds light on the potential of IGF-1 as a biomarker for stroke risk assessment and outcome prediction. Shaheen et al, focusing on the Egyptian population, found a significant reduction in serum IGF-1 levels in acute ischemic stroke cases compared to controls.[26] Their findings underscored the independent risk factor role of low IGF-1 levels in ischemic stroke, emphasizing the importance of IGF-1 in stroke pathophysiology. Likewise, Denti et al explored the early determinants of stroke outcomes, specifically examining serum IGF-1 and IGF-binding protein 3 (IGFBP-3) concentrations post-stroke onset.[29] They aimed to unravel the predictive value of these biomarkers in understanding stroke prognosis and recovery trajectories. A systematic review by researchers in Western Sweden, Italy, China, and Denmark evaluated the association of IGF-1 with incident ischemic stroke and post-stroke outcomes.[28] The review highlighted a significant correlation between higher serum IGF-1 levels, reduced risk of ischemic stroke, and improved recovery post-stroke, emphasizing the potential of IGF-1 as a prognostic indicator. In conclusion, the intricate interplay between IGF and ischemic stroke unveils a promising avenue for further research and clinical applications. From its neuroprotective effects to its prognostic value, IGF-1 stands as a pivotal player in the landscape of stroke management and understanding.

Conclusion

IGF is a critical factor in the reconstruction of myelin, a vital component of the central nervous system. Myelin serves as a protective sheath for nerve fibers, ensuring the efficient transmission of electrical signals. The study explored the role of IGF in various diseases, including autoimmune diseases, neurodegenerative diseases, and ischemic stroke, highlighting its potential impact on cell survival and disease progression.

Demyelination, the loss of myelin, is a distinct feature of various neurological disorders, such as multiple sclerosis (MS). Research has confirmed the significant role of IGF in myelin production and regeneration. Notably, IGF-I promotes the differentiation of oligodendrocyte progenitor cells and supports myelination, underscoring its efficacy in promoting remyelination. Additionally, IGF-I exhibits a protective effect against Schwann cell death and facilitates the myelination of peripheral sensory axons.

The potential therapeutic value of IGF-I in the context of MS has garnered attention. Studies have demonstrated that IGF-I promotes myelin production by oligodendrocytes and is upregulated at the peripheries of demyelinated plaques. Nevertheless, diminished IGF1R expression in oligodendrocytes within MS lesions may impact IGF bioactivity.

Intriguingly, research has indicated that the intrathecal delivery of IGF-1 enhances myelin repair in both young and aged rats, suggesting its potential therapeutic application in MS. Furthermore, systemic treatment with IGF-1 has shown promise in reducing demyelination and promoting clinical recovery in the experimental models of MS. IGF-I exerts a pivotal role in the promotion of myelin production and regeneration, rendering it a propitious therapeutic target for the reconstruction of myelin in neurological disorders such as MS. This study investigated the potential impact of IGF-I on the immune system, emphasizing its role in shaping adaptive immunity and influencing the strength and effectiveness of adaptive immune responses. The IGF-1 pathway shares similar signaling components with cytokines, representing its potential to influence the magnitude and quality of immune responses.

In summary, this brief review presents evidence that IGF-I has a positive effect on the reconstruction of myelin sheets. Elevated levels of IGF-1 have been observed in MS lesions, which may contribute to increased myelin production and remyelination. Additionally, IGF-1 has been found to protect against Schwann cell death and promote the myelination of peripheral sensory axons.

Authors' Contribution

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Software: Navid Shomali.
Supervision: Navid Shomali.
Validation: Tannaz Haghgoui.
Visualization: Mahdiye Shirafkan.
Writing–original draft: Tannaz Haghgoui.
Writing–review & editing: Navid Shomali.

Competing Interests

None.

Ethical Approval

Not applicable.

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