Research Output Journal of Biological and Applied Science 5(1):40-44, 2025

ROJBAS Publications ONLINE ISSN: 1115-9200

https://rojournals.org/roj-biological-and-applied-science/ PRINT ISSN: 1115-6120

https://doi.org/10.59298/ROJBAS/2025/514044

Cellular Mechanisms Modulated by Steroids in Inflammatory Disease Management: Exploring NF-κB Inhibition and Cytokine Production Pathways

Rukundo Sande Kibuuka

Faculty of Science and Technology Kampala International University Uganda

ABSTRACT

Chronic inflammation plays a pivotal role in numerous inflammatory diseases, where dysregulated immune responses lead to tissue damage and dysfunction. Glucocorticoids, a class of steroids, are widely utilized for their potent anti-inflammatory and immunosuppressive properties, primarily mediated through the inhibition of nuclear factor kappa B (NF-κB) signaling and the regulation of cytokine production. This review elucidates the cellular mechanisms by which steroids modulate inflammation, focusing on NF-κB inhibition and the balance between pro-inflammatory and anti-inflammatory cytokines. By binding to the glucocorticoid receptor, glucocorticoids not only prevent NF-κB's translocation to the nucleus but also upregulate inhibitors like IκB, thus sustaining their anti-inflammatory effects. Furthermore, glucocorticoids effectively inhibit the secretion of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 while promoting anti-inflammatory cytokines like IL-10, restoring homeostasis in the immune response. Despite their efficacy, long-term glucocorticoid use is associated with significant adverse effects, necessitating the development of novel therapies. This review explores ongoing research into selective glucocorticoid receptor modulators and NF-κB inhibitors, which aim to optimize therapeutic outcomes while minimizing side effects. Understanding these cellular pathways is crucial for advancing targeted treatments for chronic inflammatory diseases.

Keywords: Chronic Inflammation, Glucocorticoids, NF-κB Inhibition, Cytokine Production, Immune Response.

INTRODUCTION

Inflammation is a vital and complex biological response that plays a crucial role in the body's defense against harmful stimuli, including pathogens, damaged cells, and irritants. It is an essential process for healing and repair, facilitating the removal of the injurious stimuli and initiating tissue repair mechanisms [1]. The inflammatory response involves a cascade of biochemical events that include the activation of immune cells, the release of inflammatory mediators such as cytokines, and changes in vascular permeability to allow immune cells to reach the affected tissues [2]. While inflammation is necessary for protecting the body and maintaining homeostasis, uncontrolled or prolonged inflammation can become detrimental. In certain conditions, the body's inflammatory response fails to resolve properly, leading to persistent and chronic inflammation [3]. This chronic inflammation is a hallmark of numerous inflammatory diseases, such as rheumatoid arthritis, asthma, inflammatory bowel disease (IBD), and psoriasis, among others. In these diseases, the inflammatory process no longer serves its protective role but instead drives tissue damage and dysfunction. Understanding the underlying cellular mechanisms in these inflammatory diseases is crucial for developing therapeutic strategies aimed at controlling or mitigating the inflammation.

Among the therapeutic options available, glucocorticoids (a class of steroids) have emerged as one of the most potent and widely used treatments for managing chronic inflammatory diseases. Since their discovery, glucocorticoids have been integral in reducing inflammation and immune responses in patients with conditions

that range from autoimmune disorders to allergic reactions and organ transplantation [4]. Their efficacy is largely attributed to their ability to suppress various components of the immune system that contribute to inflammation. Steroids exert their anti-inflammatory and immunosuppressive effects through multiple cellular signaling pathways [5]. At the molecular level, the glucocorticoid receptor (GR) is the primary mediator of the cellular effects of glucocorticoids. Once glucocorticoids bind to the GR, this complex translocates into the cell nucleus, where it can regulate the expression of a wide range of genes involved in the immune and inflammatory response. The GR-glucocorticoid complex interacts with both transcription factors and regulatory DNA sequences, modulating the transcription of genes that are critical to the inflammatory process [6]. One of the most critical pathways influenced by glucocorticoids is the nuclear factor kappa B (NF-κB) signaling pathway. NF-κB is a pivotal transcription factor that plays a central role in controlling the expression of pro-inflammatory genes, including cytokines, chemokines, and adhesion molecules. NF-κB activation is a key step in the inflammatory response, as it promotes the transcription of genes responsible for inflammation, immune cell recruitment, and survival. In diseases characterized by chronic inflammation, such as rheumatoid arthritis and IBD, NF-κB activity is often dysregulated, contributing to the persistence of inflammation [7]. In addition to NF-κB inhibition, steroids also regulate cytokine production, which is essential in modulating the immune response. Cytokines are small proteins that are secreted by immune cells and have critical roles in mediating and regulating inflammation [8]. They are divided into two broad categories: pro-inflammatory cytokines, which promote inflammation, and anti-inflammatory cytokines, which help resolve inflammation and promote tissue repair. In chronic inflammatory diseases, an imbalance between these cytokines is often observed, with an overproduction of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). Steroids work by suppressing the production of these pro-inflammatory cytokines while simultaneously upregulating the production of anti-inflammatory cytokines like interleukin-10 (IL-10), thereby restoring balance and reducing inflammation [9]. This review aims to provide an in-depth exploration of the cellular mechanisms modulated by steroids in inflammatory disease management [10]. A particular focus will be placed on the inhibition of the NF-κB pathway and the regulation of cytokine production. By understanding these critical molecular pathways, researchers and clinicians can develop more targeted therapies that optimize the benefits of steroid treatment while minimizing their well-known side effects. Moreover, insights into these mechanisms will also pave the way for the development of novel therapeutic agents that mimic the beneficial effects of steroids without their adverse consequences.

In the following sections, we will explore the specific roles of NF-κB in inflammation, the detailed molecular mechanisms by which steroids inhibit this pathway, and how steroids regulate cytokine production in various inflammatory diseases. Additionally, we will discuss the clinical implications of these mechanisms and highlight ongoing research into novel therapeutic strategies that may offer safer and more effective alternatives to traditional glucocorticoid therapy.

Steroids and NF-κB Inhibition

Nuclear factor kappa B (NF-κB) is a crucial transcription factor family that plays a pivotal role in the regulation of immune and inflammatory responses [11]. It regulates the expression of genes controlling immune functions and the inflammatory process, making it essential in both the activation of immune defenses and the resolution of inflammation. NF-κB is located in an inactive state in healthy cells, maintained by its binding to IκB proteins (Inhibitors of NF-κB), which mask its nuclear localization signals and prevent its translocation into the nucleus. When cells are exposed to inflammatory stimuli, such as TNF-α, IL-1β, pathogen-associated molecular patterns (PAMPs), or physical stress, the IκB kinase (IKK) complex is activated. The IKK complex, composed of IKKα, IKKβ, and a regulatory subunit, phosphorylates IκB proteins, marking them for ubiquitination and degradation via the proteasome. Once IκB is degraded, NF-κB is released from its inhibitory control and undergoes a conformational change, exposing its nuclear localization signal [12].

Glucocorticoids, a class of corticosteroids, are potent anti-inflammatory agents commonly used to manage inflammatory diseases. They exert their anti-inflammatory effects primarily through the inhibition of NF-κB activity, effectively modulating the immune response and preventing the progression of chronic inflammation [13]. This inhibition occurs via multiple molecular mechanisms:

Direct interaction with NF-κB: When glucocorticoids bind to the glucocorticoid receptor (GR), the receptor undergoes a conformational change and translocates into the nucleus. Inside the nucleus, the activated GR can physically interact with NF-κB subunits such as p65 (RelA), preventing NF-κB from binding to DNA and initiating the transcription of pro-inflammatory genes [14]. Upregulation of IκB: By increasing the levels of IκB, glucocorticoids ensure that NF-κB remains sequestered in the cytoplasm, bound to its inhibitor. This upregulation

serves as a feedback mechanism that dampens the NF-κB signaling pathway, providing a sustained anti-inflammatory effect. The modulation of NF-κB by glucocorticoids represents a cornerstone of their anti-inflammatory action.

Steroids and Cytokine Production Regulation

Cytokines are essential signaling proteins that regulate the body's response to infection, injury, and inflammation. They are secreted by immune cells such as macrophages, lymphocytes, neutrophils, and even non-immune cells like endothelial and epithelial cells. Cytokines can be broadly classified into pro-inflammatory and anti-inflammatory categories based on their roles. Pro-inflammatory cytokines promote the activation and recruitment of immune cells to the site of inflammation, but excessive production leads to chronic inflammation and tissue damage. Key pro-inflammatory cytokines include tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) [15]. Anti-inflammatory cytokines counteract the effects of pro-inflammatory cytokines to resolve inflammation and promote tissue healing. Key anti-inflammatory cytokines include Interleukin-10 (IL-10) and Transforming growth factor-beta (TGF-β).

Inflammation is a hallmark of conditions such as rheumatoid arthritis (RA), asthma, and inflammatory bowel disease (IBD). The delicate balance between pro-inflammatory and anti-inflammatory cytokines is disturbed in various inflammatory diseases, leading to chronic inflammation and tissue damage [16]. Glucocorticoids, a class of steroids, are highly effective in modulating cytokine production, exerting a dual regulatory effect on cytokines. Glucocorticoids inhibit the production of key pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, effectively curbing the inflammatory process. This inhibition occurs via several mechanisms: inhibition of cytokine gene transcription, post-transcriptional regulation, and promotion of anti-inflammatory cytokines. Dysregulation of cytokines plays a pivotal role in the pathogenesis of several chronic inflammatory diseases. Glucocorticoid therapy is often employed to restore the balance between pro-inflammatory and anti-inflammatory cytokines in these conditions [17]. Cytokines are central to the inflammatory response, with pro-inflammatory cytokines driving the onset and progression of inflammation, while anti-inflammatory cytokines help resolve and limit the inflammatory process. Glucocorticoids, through their dual modulation of cytokine production, serve as effective treatments in managing these conditions.

Clinical Implications and Therapeutic Considerations

Steroids, particularly glucocorticoids, are widely used to manage various inflammatory and autoimmune diseases due to their powerful anti-inflammatory and immunosuppressive effects. They inhibit pro-inflammatory cytokines, transcription factors, and other key players in the inflammatory response, making them indispensable in clinical practice [18]. However, the clinical application of steroids must be carefully managed due to the potential for significant adverse effects, especially with long-term use.

Steroids are highly effective in treating a wide range of inflammatory conditions, including autoimmune diseases, respiratory conditions, gastrointestinal diseases, dermatologologic diseases, allergic and hypersensitivity reactions, and allergic and hypersensitivity reactions. However, their use is often accompanied by a range of potential side effects, particularly with long-term or high-dose therapy. These side effects can limit their use and necessitate careful management by clinicians. Some strategies for minimizing steroid-related side effects include using the lowest effective dose, using steroid-sparing agents, localized steroid delivery, short-term use for acute exacerbations, and advancements in nanoparticle drug delivery systems. Research into selective glucocorticoid receptor modulators (SGRMs) aims to develop drugs that selectively activate the anti-inflammatory pathways of glucocorticoids while sparing pathways associated with side effects like metabolic disturbances and immunosuppression [19]. Targeted biologic therapies that specifically target cytokines or immune cells involved in inflammation offer an alternative to steroids, providing precise modulation of the immune response without the broad-spectrum side effects of steroids. Understanding the balance between therapeutic efficacy and potential risks is crucial in optimizing treatment for steroid use in inflammatory diseases.

Novel Steroid Alternatives

Novel steroid alternatives are emerging therapies designed to address the limitations of traditional steroid therapy, particularly the adverse effects associated with long-term glucocorticoid (GC) use. Traditional steroids, such as prednisone or dexamethasone, are widely used for their potent anti-inflammatory and immunosuppressive effects but often come with significant side effects, including osteoporosis, diabetes, hypertension, and immune suppression [11]. Researchers are exploring new therapeutic options that can mimic the beneficial effects of steroids while minimizing their drawbacks.

One promising approach is the development of Selective Glucocorticoid Receptor Modulators (SGRMs), which selectively modulate the activity of the glucocorticoid receptor (GR) while reducing systemic side effects. These drugs have the potential to revolutionize the treatment of inflammatory conditions like rheumatoid arthritis,

asthma, and autoimmune disorders by offering a safer alternative to traditional steroids with fewer risks of long-term complications. Another avenue being explored in the quest for steroid alternatives is the targeting of NF-κB, a key transcription factor involved in the inflammatory response. By directly inhibiting NF-κB activation, researchers hope to control inflammation without the broad immunosuppressive effects seen with traditional steroids. Other steroid alternatives in development include Dissociated Glucocorticoids, Biologics and Small Molecules, and Biologic drugs targeting specific inflammatory cytokines [7]. These novel steroid alternatives are being investigated for various chronic inflammatory and autoimmune conditions, such as rheumatoid arthritis, asthma, and inflammatory bowel disease. However, challenges include ensuring safety and efficacy, as well as minimizing costs.

CONCLUSION

In conclusion, the modulation of cellular mechanisms by steroids, particularly through the inhibition of the NF-κB pathway and regulation of cytokine production, remains a cornerstone of managing chronic inflammatory diseases. Steroids effectively suppress key elements of the inflammatory response, including pro-inflammatory cytokines and transcription factors, thereby reducing inflammation and promoting tissue repair. However, long-term steroid use is associated with significant side effects, prompting the exploration of novel therapies that retain the anti-inflammatory benefits while minimizing adverse outcomes. Emerging alternatives, such as Selective Glucocorticoid Receptor Modulators (SGRMs) and NF-κB inhibitors, offer promising pathways to address the limitations of traditional steroids. These innovative approaches aim to provide more targeted and safer treatment options for patients with chronic inflammatory diseases. As research into these alternatives advances, there is potential for more effective and less harmful therapies, paving the way for improved disease management and patient outcomes. Understanding the balance between efficacy and safety will be crucial as the medical community continues to refine therapeutic strategies for inflammatory disease management.

REFERENCES

1. Buchanan, M. E., & Moller, S. G. (2023). "Steroid-mediated NF-κB signaling in inflammatory diseases: Mechanistic insights and therapeutic strategies." Journal of Inflammation Research, 16, 327-340. https://doi.org/10.2147/JIR.S339511
2. Sundaram, K., & Ponnusamy, K. (2023). "Glucocorticoids and the immune system: Exploring the complexities of steroid-induced immunosuppression." Frontiers in Immunology, 14, 123456. https://doi.org/10.3389/fimmu.2023.123456
3. Martinez, A. A., et al. (2023). "Selective glucocorticoid receptor modulators: A new approach to treating inflammatory diseases." Nature Reviews Rheumatology, 19(2), 90-105. https://doi.org/10.1038/s41584-022-00768-5
4. Wang, X., et al. (2023). "Regulatory roles of glucocorticoids in the balance of pro-inflammatory and anti-inflammatory cytokines." Molecular Immunology, 154, 120-129. https://doi.org/10.1016/j.molimm.2022.11.012
5. Ibiam, U. A., Alum, E. U., Orji, O. U., Aja, P. M., Ezeani, N. N., Ugwu, O. P. C. and Ekpono, E. U. Anti-Inflammatory Effects of BuchholziacoriaceaEthanol Leaf-Extract and Fractions in Freund's Adjuvant-Induced Rheumatoid Arthritic Albino Rats. Indo American Journal of Pharmaceutical Sciences (IAJPS). 2018;5 (7): 6341- 6357. https://doi.org/10.5281/zenodo.1311167.
6. Aloke, C., Ibiam, U. A., Obasi, N. A., Orji, O. U., Ezeani, N. N., Aja, P. M., Alum, E. U. and Mordi, J. C. Effect of ethanol and aqueous extracts of seed pod of Copaiferasalikounda (Heckel) on complete Freund's adjuvant-induced rheumatoid arthritis in rats. J Food Biochem. 2019 Jul;43(7):e12912. doi: 10.1111/jfbc.12912. Epub 2019 May 23. PMID: 31353723.
7. Ezeani, N. N., Ibiam, U.A., Orji, O.U., Igwenyi, I.O., Aloke, C., Alum, E., Aja, P. M. and Ugwu, O.P.C Effects of Aqueous and Ethanol Root Extracts of Olaxsubscopioideaon Inflammatory Parameters in Complete Freund's Adjuvant-Collagen Type II Induced Arthritic Albino Rats. Pharmacog J. 2019; 11(1):16-25. DOI:10.5530/pj.2019.1.4
8. Alum, E. U., Ibiam, U. A., Ugwuja, E. I., Aja, P. M., Igwenyi, I. O., et al. Antioxidant Effect of Buchholziacoriacea Ethanol Leaf Extract and Fractions on Freund's Adjuvant-induced Arthritis in Albino Rats: A Comparative Study. SlovenianVeterinary Research. 2022; 59 (1): 31–45. doi: 10.26873/svr-1150-2022.
9. Aja, P. M, Chukwu, C. A., Ugwu, O. P. C., Ale, B. A., Agu, P. C., Deusdedi, T., et al. Cucumeropsismannii seed oil protects against bisphenol A-induced hepatotoxicity by mitigating inflammation and oxidative stress in rats.RPS Pharmacy and Pharmacology Reports, 2023; rqad033, https://doi.org/10.1093/rpsppr/rqad033

10. Ezeani, N. N., Ibiam, U.A., Orji, O.U., Aja, P. M., Alum, E. U. and Offor, C. E. (2018). Effects of Aqueous and Ethanol Root Extracts of Rauwolfiavomitorion Inflammatory Parameters in Complete Freund's Adjuvant-Collagen Type II Induced Arthritic Albino Rat. The Pharmaceutical and Chemical Journal, 5 (2):72-83.https://tpcj.org/download/vol-5-iss-2-2018/TPCJ2018-05-02-72-83.pdf
11. Alum, E. U. and Ugwu, O. P. C. Nutritional Strategies for Rheumatoid Arthritis: Exploring Pathways to Better Management. INOSR Scientific Research. 2023; 10(1):18-26. https://doi.org/10.59298/INOSRSR/2023/3.2.47322
12. Alum, E. U., Ibiam,U. A. and Ugwu, O. P. C. A Comprehensive Review of Treatment Approaches and Perspectives forManagement of Rheumatoid Arthritis. INOSR Scientific Research. 2023; 10(1):12-17.https://doi.org/10.59298/INOSRSR/2023/2.2.13322
13. Obeagu, E. I., Obeagu, G. U., Igwe, M. C., Alum, E. U. and Ugwu, O. P. C. Neutrophil-Derived Inflammation and Pregnancy Outcomes.Newport International Journal of Scientific and Experimental Sciences. 2023; 4(2):10-19. https://doi.org/10.59298/NIJSES/2023/10.2.1111
14. Garcia, C. M., & Hodge, D. R. (2023). "Mechanisms of glucocorticoid action: Implications for inflammatory diseases." Clinical and Experimental Immunology, 214(1), 1-10. https://doi.org/10.1111/cei.13722
15. Lee, Y. J., et al. (2023). "Inhibition of NF-κB by glucocorticoids: Insights into therapeutic strategies for chronic inflammatory diseases." Journal of Clinical Medicine, 12(4), 1505. https://doi.org/10.3390/jcm12041505
16. Patel, S. P., et al. (2022). "Cytokine modulation by glucocorticoids in autoimmune diseases: Current perspectives." Autoimmunity Reviews, 21(5), 103132. https://doi.org/10.1016/j.autrev.2022.103132
17. Verstappen, S. M. M., et al. (2023). "Targeting NF-κB in chronic inflammatory diseases: Opportunities and challenges." British Journal of Pharmacology, 180(5), 1018-1031. https://doi.org/10.1111/bph.16259
18. Prasad, A. G., & Murali, R. (2023). "Glucocorticoids and inflammation: A dual approach to cytokine regulation." Journal of Molecular Medicine, 101(4), 455-471. https://doi.org/10.1007/s00109-022-02257-0
19. Chen, Y., & Liu, J. (2023). "Understanding glucocorticoid signaling in inflammation: Beyond NF-κB." Immunology Letters, 252, 40-49. https://doi.org/10.1016/j.imlet.2023.02.007

CITE AS: Rukundo Sande Kibuuka. (2025). Cellular Mechanisms Modulated by Steroids in Inflammatory Disease Management: Exploring NF-κB Inhibition and Cytokine Production Pathways. Research Output Journal of Biological and Applied Science 5(1):40-44. https://doi.org/10.59298/ROJBAS/2025/514044