NEW THERAPEUTIC OPPORTUNITIES SHARED BY INFLAMMATORY ARTHRITIS, OBESITY AND TYPE 2 DIABETES TO IMPROVE THE INFLAMMATORY RESPONSE

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Abstract. *Obesity is a pro-inflammatory condition associated with increased severity of various types of inflammatory arthritis. Weight loss is associated with improved disease activity in certain forms of inflammatory arthritis, such as rheumatoid arthritis and psoriatic arthritis. In addition, fundamental scientific experiments demonstrate the weight-independent anti-inflammatory and immunomodulatory effects of GLP-1 receptor agonists associated with inhibition of the NF-KB pathway, improved mitochondrial dysfunction induced by TNF-α, prevention of the expression of NOX-4 and oxidative stress, reduction of the expression of proinflammatory mediators such as IL-6 and IL-1β, and reduction of the expression of matrix metalloproteinases. Taking into account the chronic inflammatory background, shared by inflammatory arthritis, obesity, and type 2 diabetes, it is obvious that the inadequate behavior of any of these conditions can make the others worse.*

Key words: *obesity, inflammatory arthritis, rheumatoid arthritis, psoriatic arthritis, type 2 diabetes, GLP-1 receptor agonists, TNF-α, oxidative stress, proinflammatory mediators, oxidative stress, matrix metalloproteinases*

Rheumatoid arthritis and GLP-1 receptor agonists

Rheumatoid arthritis is a chronic systemic inflammatory autoimmune disease with unknown etiology. Its main clinical manifestation is symmetrical progressive erosive arthritis. In parallel, several extra-articular manifestations can also be observed. It is characterized by synovitis and joint damage. In the course of rheumatoid arthritis, synovium is transformed into hyperplastic invasive tissue, leading to the destruction of cartilage and bone. Fibroblast-like synoviocytes in the synovial membrane develop aggressive phenotypes and produce pathogenic mediators that lead to the onset and progression of the disease, playing a major role in the pathogenesis of rheumatoid arthritis. In rheumatoid arthritis, fibroblast-like synoviocytes acquire a phenotype resistant to apoptosis and lose their congenital ability for contact inhibition, leading to unobstructed proliferation of pathological fibroblast-like synoviocytes, the formation of invasive pannus, and subsequent mitochondrial dysfunction, oxidative stress, and positive inflammatory feedback. In addition, fibroblast-like synoviocytes produce cytokines and chemokines such as interleukin 1 beta (IL-1β), interleukin 6 (IL-6), and monocyte chemotactic protein 1 (MCP-1), as well as express cartilage-degrading enzymes like matrix metalloproteinases 3 and 13 (MMP-3 and MMP-13), and thus the cycles of inflammation and destruction of cartilage continue. Another important factor in the development of rheumatoid arthritis, which is tested as a potential therapeutic purpose, is the modulation of the pro-inflammatory signaling pathways, including the nuclear factor kB (NF-kB) and the P38/Mitogen-Activated Protein Kinase (MAPK). The prolonged activation of the NF-kB road is considered critically important for the pathogenesis of rheumatoid arthritis. The attraction of immune cells to the pannus further induces inflammation and promotes the release of cytokines and chemokines. HMG-1 is a chemokine that attracts large amounts of immune cells to the synovium in rheumatoid arthritis, where they release autoantigens that attack healthy bone and cartilage tissues. In addition, HMG-1 interacts with the Toll-Like receptors and leads to upregulation and activation of the proinflammatory pathway NF-kB [1, 7, 8].

It is proven that tumor necrosis factor alpha (TNF-α) is found in abundance in the synovium in rheumatoid arthritis. Numerous studies have shown the involvement of TNF-α in the maintenance of pathological inflammatory response by promoting the release of pro-inflammatory cytokines such as IL-1β and IL-6, reducing mitochondrial function, increasing the production of reactive oxygen species, regulating of expression of MMP-3 and MMP-13, and activating important inflammatory pathways like NF-kB и p38/MAPK. While therapies targeting TNF-α directly have been shown to be beneficial for some patients, other patients have a small or no response to such therapies. Therefore, new therapies are sought to treat this painful disease [1, 7, 8].

Glucagon-like peptide 1 (GLP-1) is an intestinal hormone, an incretin secreted by L-cells in the distal ileum and colon under the influence of food passing through the gastrointestinal tract. Endogenous GLP-1 is rapidly degraded by an enzyme called dipeptidyl peptidase-IV (DPP-4), and endogenous GLP-1 has a short plasma half-life of about 2-3 minutes. GLP-1 exerts its function by binding to the GLP-1 receptor, which is a transmembrane G protein-coupled receptor. This receptor is widely expressed in the tissues of the body, in addition to the beta cells and alpha cells of the pancreas, it is also found in the central nervous system, enteric nervous system, lymphocytes, lungs, kidneys, liver, blood vessels, fibroblast-like synoviocytes and many more localizations in the human body, which are still being studied. Binding of GLP-1 to its receptor at the beta-cell level leads to stimulation of insulin secretion by a glucose-dependent mechanism, and at the alpha-cell level leads to suppression of glucagon secretion, which is associated with its hypoglycemic effect. In addition, GLP-1 delays gastric emptying, increases satiety, and reduces appetite. [1-6, 9, 10, 11]. Figure 1 and figure 2 represent the described.

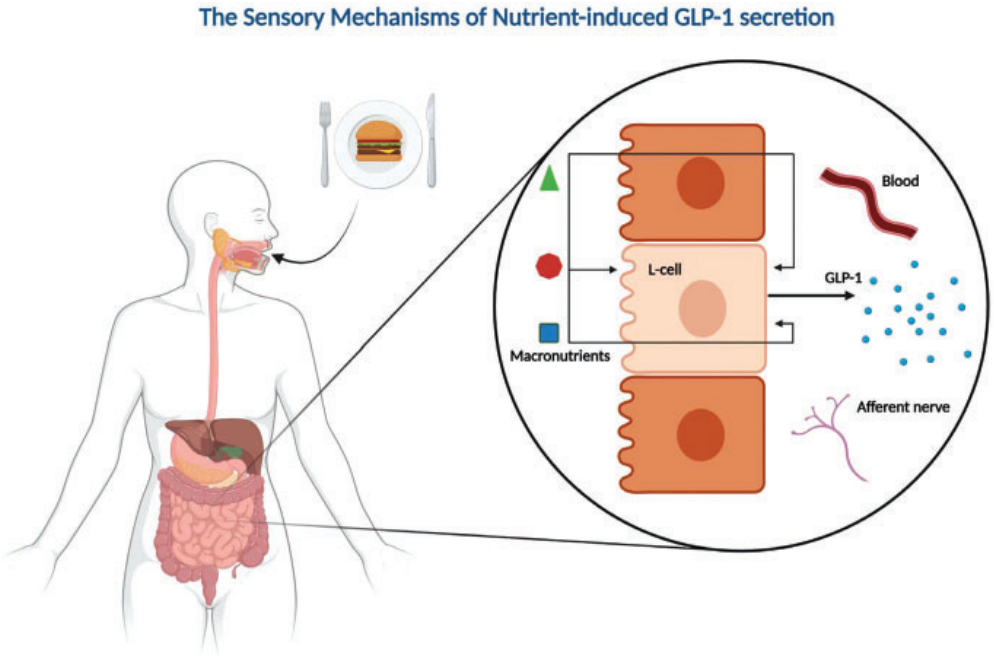


Fig. 1. The Sensory Mechanisms of Nutrient-induced GLP-1 secretion. (Hjørne AP, Modvig IM, Holst JJ. The Sensory Mechanisms of Nutrient-Induced GLP-1 Secretion. Metabolites. 2022 May 7;12(5):420 [11])

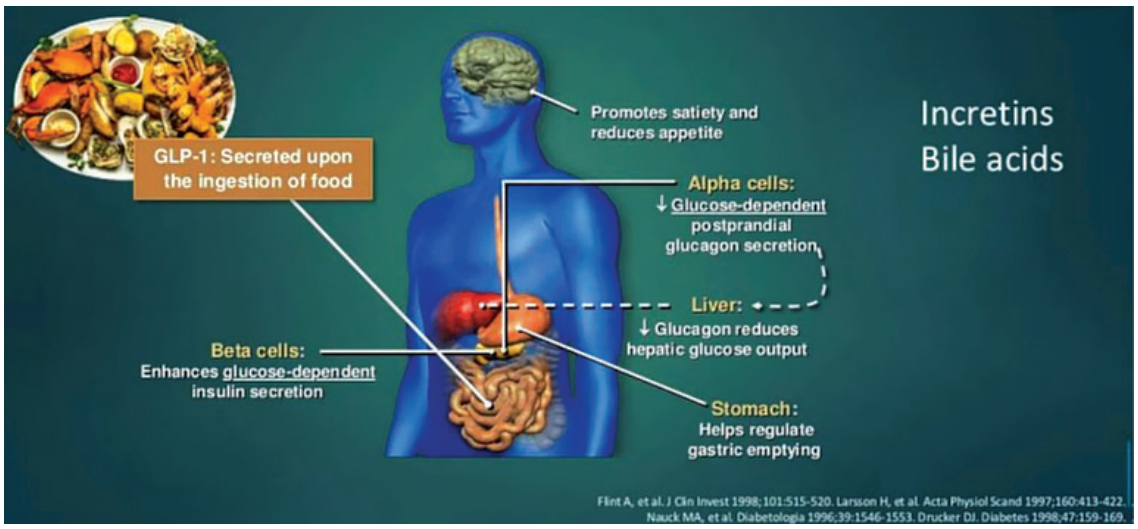


Fig. 2. Biological effects of GLP-1. Flint A et al. J Clin Invest 1998;101:515-520. (Larsson H, et al. Acta Physiol Scand. 1997;160:413-422. Nauck MA, et al. Diabetologia 1996; 39:1546-1553. Drucker DJ. Diabetes, 1998;47:159-169 [12-15])

In patients with type 2 diabetes mellitus, the level of endogenous GLP-1 is reduced. Therefore, GLP-1 receptor agonists are widely used in these patients, both for their hypoglycemic effect and for the additional advantage of appetite suppression, delayed gastric emptying, and weight reduction. These drugs have been modified to be resistant to the enzyme that degrades them, DPP-4. In addition, the many pleiotropic effects of GLP-1 receptor agonists are widely used, such as immunomodulation, anti-inflammatory effect, and neuroprotection. Thus, due to their anti-inflammatory properties, GLP-1-based therapies may be beneficial for patients with inflammatory arthritis [1-6, 9-11].

GLP-1 receptor agonists – improvement of mitochondrial dysfunction

Studies have been conducted on fibroblast-like synoviocytes isolated from the synovial tissues of the knee joint of volunteers. These fibroblast-like synoviocytes were treated with TNF-α in the presence or absence of a GLP-1 receptor agonist. The loss of mitochondrial membrane potential and the decrease in cytochrome C oxidase activity in fibroblast-like synoviocytes are indicators of mitochondrial dysfunction. In turn, TNF-α induces this mitochondrial dysfunction. Studies have shown that GLP-1 receptor agonists at higher doses improve mitochondrial dysfunction by returning mitochondrial membrane potential and cytochrome C oxidase activity to almost basal levels [1].

GLP-1 receptor agonists – prevention of NOX-4 expression and oxidative stress

NOX-4 is involved in the release of superoxide from fibroblast-like synoviocytes. In studies, isolated fibroblast-like synoviocytes were treated with TNF-α, resulting in upregulation of NOX-4, which was improved by the administration of a GLP-1 receptor agonist. In addition, oxidative stress has been identified as a major player in the progression of rheumatoid arthritis. It has been found that in fibroblast-like synoviocytes treated with TNF-α in the presence of a GLP-1 receptor agonist, GLP-1 prevents oxidative stress in a dose-dependent manner. It has been found that in rheumatoid arthritis, GLP-1 restores the balance between oxidants and antioxidants, which is so important for maintaining homeostasis in various tissues and cells [1].

GLP-1 receptor agonists – attenuation of HMG-1 release

HMG-1 is an important chromatin protein that has a regulatory role by interacting with various transcription factors. In rheumatoid arthritis, it acts as a cytokine mediator of inflammation. Exposure of human fibroblast-like synoviocytes to TNF-α increases the release of HMG-1. However, in the presence of a GLP-1 receptor agonist, this effect of TNF-α is attenuated, and at higher doses of GLP-1, the level of HMG-1 returns to almost basal levels [1].

GLP-1 receptor agonists – reduction of expression of proinflammatory mediators

It has been shown that the proinflammatory cytokines IL-6 and IL-1β play an important role in the induction and maintenance of the pathological inflammatory response in rheumatoid arthritis. In addition, the chemokine MCP-1 (monocyte chemoattractant protein 1) selectively attracts immune cells to the synovium in rheumatoid arthritis, thereby exacerbating inflammation and enhancing joint destruction. In studies conducted on fibroblast-like synoviocytes treated with TNF-alpha, the results of real-time PCR and Western blot analysis showed that treatment with a GLP-1 receptor agonist reduced the expression of IL-6, IL-1β, and MCP-1 in a dose-dependent manner [1].

GLP-1 receptor agonists – reduction of matrix metalloproteinase expression

MMP-3 (matrix metalloproteinase-3) and MMP-13 are the two main collagenases involved in the degradation of the cartilage matrix in rheumatoid arthritis and are released from fibroblast-like synoviocytes in response to pro-inflammatory factors, including TNF-α. A study in which isolated fibroblast-like synoviocytes were treated with TNF-α in the presence of a GLP-1 receptor agonist showed that the GLP-1 receptor agonist reduced the expression of MMP-3 and MMP-13, both at the mRNA and protein levels, in a dose-dependent manner [1].

GLP-1 receptor agonists – inhibition of the activation of pro-inflammatory signaling pathways

Under normal physiological conditions, NF-κB is sequestered in the cytoplasm by its inhibitor IκBα. However, upon exposure to proinflammatory cytokines, IκBα is phosphorylated and degraded, thereby allowing translocation of p65 protein to the nucleus and activating the NF-κB proinflammatory pathway. Scientific experiments have shown that GLP-1 receptor agonists inhibit the NF-κB pathway by preventing phosphorylation and degradation of IκBα in rheumatoid arthritis. In addition, GLP-1 receptor agonists also inhibit activation of the proinflammatory p38/MAPK pathway [1]. Figure 3 represent the described.

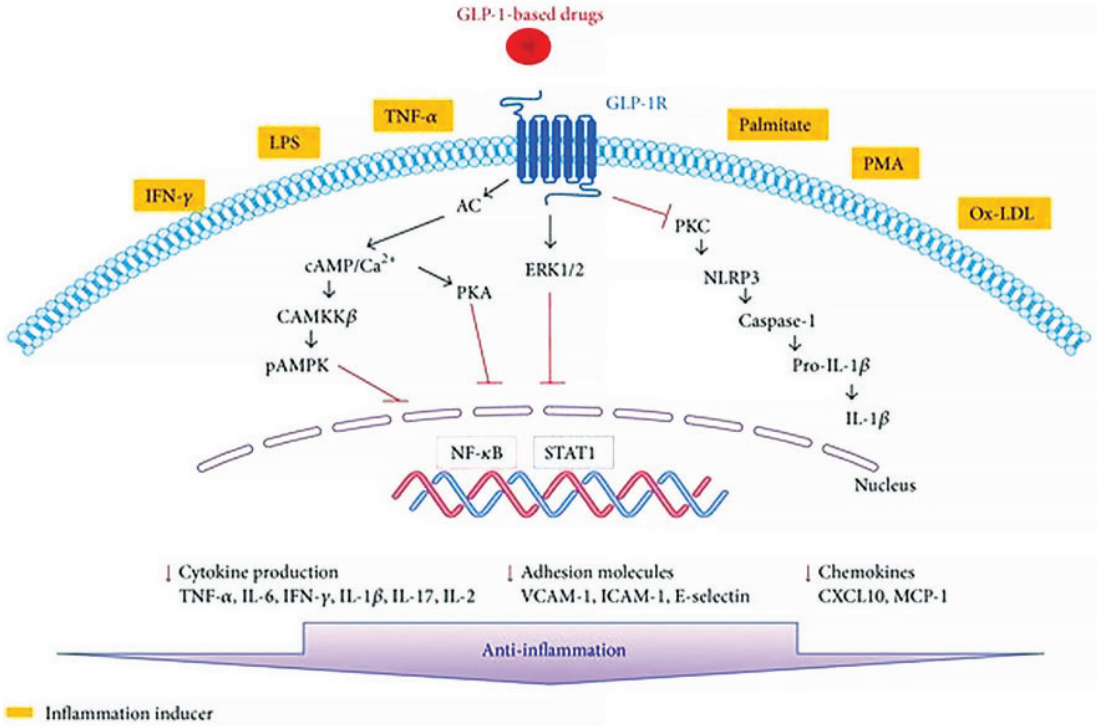


Fig. 3. Molecular Signaling Underlying the Anti-Inflammatory Effects of GLP-1 Receptor Agonists (Lee YS, Jun HS. Anti-Inflammatory Effects of GLP-1-Based Therapies beyond Glucose Control. Mediators Inflamm. 2016;2016:3094642 [5])

Results from conducted scientific experiments show that GLP-1 receptor agonists have a positive effect on multiple factors in rheumatoid arthritis. GLP-1 receptor agonists can improve the inflammatory response in rheumatoid arthritis by improving mitochondrial dysfunction, reducing NOX-4 expression and oxidative stress, decreasing the expression of cytokines, chemokines, and degrading enzymes, and inhibiting the activation of proinflammatory signaling pathways [1].

Psoriatic arthritis, psoriasis, and GLP-1 receptor agonists

Psoriatic arthritis is a heterogeneous disease characterized by joint involvement and active or latent psoriasis. It usually presents as a peripheral or axial polyarthritis with chronic joint damage. Due to the complex mechanism and stimulation of various metabolic pathways in psoriatic arthritis, it is often accompanied by multiple comorbidities. Among the most common are metabolic syndrome, hepatic steatosis, osteoporosis, type 2 diabetes mellitus, and others [2-6, 9, 10].

Data from conducted studies show an improvement in PASI (Psoriasis Area Severity Index), as well as an improvement in the dermatological quality of life index. The current limiting factors in establishing the direct impact of GLP-1 receptor agonists on patients with psoriatic arthritis are related to the small sample size. Nevertheless, the positive impact of GLP-1 receptor agonists on weight reduction and appetite control has been confirmed, allowing the treatment of obesity to be more effective. Because of the adverse effects of obesity on psoriatic arthritis and psoriasis, these drugs may indirectly improve both conditions. Thus, GLP-1 receptor agonists may be a suitable option for obese patients with psoriatic arthritis because of their ability to reduce low-grade inflammation caused by excessive fat tissue [2-6, 9, 10].

GLP-1 receptor agonists as modulators of innate immunity

It is also important to note that recent studies have shown that GLP-1 receptor agonists exert regulatory functions on innate immune cells, particularly macrophages, leading to reprogramming of macrophages to an M2 phenotype. M2 macrophages suppress inflammation, promote tissue healing, and tolerate self-antigens and certain neoantigens [2-6, 9, 10].

Conclusion

All these findings suggest that GLP-1 receptor agonists may have potential as safe and effective

therapies for the treatment of certain inflammatory arthritis conditions, such as rheumatoid arthritis and psoriatic arthritis. Further studies are needed to better understand the precise mechanisms driving these promising results.

References

1. Tao Y, Ge G, Wang Q, et al. Exenatide ameliorates inflammatory response in human rheumatoid arthritis fibroblast-like synoviocytes. IUBMB Life. 2019 Jul;71(7):969-977. doi: 10.1002/iub.2031.
2. Karacabeyli D, Lacaille D. Glucagon-Like Peptide 1 Receptor Agonists in Patients With Inflammatory Arthritis or Psoriasis: A Scoping Review. J Clin Rheumatol. 2024 Jan 1;30(1):26-31. doi: 10.1097/RHU.0000000000001949.
3. Grygiel-Górniak B, Skoczek W. Molecular Background and Clinical Implications of Glucose Disorders in Patients with Psoriatic Arthritis. J Clin Med. 2023 Sep 7;12(18):5814. doi: 10.3390/jcm12185814.
4. Chen J, Mei A, Wei Y, et al. GLP-1 receptor agonist as a modulator of innate immunity. Front Immunol. 2022 Dec 8;13:997578. doi: 10.3389/fimmu.2022.997578.
5. Lee YS, Jun HS. Anti-Inflammatory Effects of GLP-1-Based Therapies beyond Glucose Control. Mediators Inflamm. 2016;2016:3094642. doi: 10.1155/2016/3094642.
6. Mehdi SF, Pusapati S, Anwar MS, et al. Glucagon-like peptide-1: a multi-faceted anti-inflammatory agent. Front Immunol. 2023 May 17;14:1148209. doi: 10.3389/fimmu.2023.1148209.
7. Wu Z, Ma D, Yang H, et al. Fibroblast-like synoviocytes in rheumatoid arthritis: Surface markers and phenotypes. Int Immunopharmacol. 2021 Apr;93:107392. doi: 10.1016/j.intimp.2021.107392.
8. Li J, Tang RS, Shi Z, Li JQ. Nuclear factor-κB in rheumatoid arthritis. Int J Rheum Dis. 2020 Dec;23(12):1627-1635. doi: 10.1111/1756-185X.13958.
9. Xu X, Lin L, Chen P, et al. Treatment with liraglutide, a glucagon-like peptide-1 analogue, improves effectively the skin lesions of psoriasis patients with type 2 diabetes: A prospective cohort study. Diabetes Res Clin Pract. 2019 Apr;150:167-173. doi: 10.1016/j.diabres.2019.03.002.
10. Costanzo G, Curatolo S, Busà B, et al. Two birds one stone: semaglutide is highly effective against severe psoriasis in a type 2 diabetic patient. Endocrinol Diabetes Metab Case Rep. 2021 Aug 1;2021:21-0007. doi: 10.1530/EDM-21-0007.
11. Hjørne AP, Modvig IM, Holst JJ. The Sensory Mechanisms of Nutrient-Induced GLP-1 Secretion. Metabolites. 2022 May 7;12(5):420. doi: 10.3390/metabo12050420.
12. Flint A, Raben A, Astrup A, Holst JJ. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. J Clin Invest. 1998 Feb 1;101(3):515-20. doi: 10.1172/JCI990.
13. Larsson H, et al. Glucagon-like peptide-1 reduces hepatic glucose production indirectly through insulin and glucagon in humans. Acta Physiol Scand. 1997;160:413-422, https://doi.org/10.1046/j.1365-201X.1997.00161.x.
14. Nauck MA, Effects of subcutaneous glucagon-like peptide 1 (GLP-1 [7–36 amide]) in patients with NIDDM.et al. Diabetologia 1996; 39:1546-1553.
15. Drucker DJ. Glucagon-like peptides. Diabetes. 1998 Feb;47(2):159-69. doi: 10.2337/diab.47.2.159.

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