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Article

Injectable Therapies and Their Effects on Reducing Chronic Inflammation in Diseases such as Obesity, Cancer and Type 2 Diabetes

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Abstract

Low-grade chronic inflammation is a central factor in the pathogenesis of obesity, cancer and type 2 diabetes (T2D) [1,2]. This article explores an integrated therapeutic strategy, administered by injectable route, that combines dimethyl sulfoxide (DMSO), coenzyme Q10 (CoQ10), alpha-lipoic acid (ALA), curcumin, glutathione (GSH) and mimetics of microRNA-146a (miR-146a) [3]. Injectable administration optimizes the bioavailability and tissue targeting of these agents, which act synergistically through anti-inflammatory, antioxidant and metabolic-modulating mechanisms [4,5]. The primary focus lies on the role of miR-146a in regulating the IRAK1 and TRAF6 signaling pathway, crucial for immunometabolic homeostasis [6,7]. This multidimensional approach has the potential to modulate chronic inflammation, optimize mitochondrial function and restore metabolic balance, representing a new frontier in the treatment of chronic inflammatory diseases [8,9]. Additionally, the article delves into modulation of leptin resistance and compares this integrated approach with the most effective weight-loss strategies.

Keywords: obesity; chronic inflammation; leptin resistance; injectable therapies; miR-146a; weight loss

Introduction: The Immunometabolic Paradigm of Chronic Disease

Obesity and overweight constitute a global epidemic, with more than 1.9 billion adults overweight and 650 million obese, representing a public health challenge [10]. This increase is driven by dietary changes and sedentary lifestyles, resulting in a positive energy balance and adipose tissue accumulation [11,12]. Obesity is a complex neuroimmunoendocrine condition in which adipose tissue acts as a metabolically active and immunologically dynamic organ [13].

Adipose tissue expansion leads to infiltration by macrophages and lymphocytes and to elevated secretion of proinflammatory cytokines (TNF- α , IL-6, leptin), with reduction of adiponectin, an anti-inflammatory and insulin-sensitizing molecule [14,15]. This dysregulation establishes a state of low-grade chronic inflammation, which is central to the link between obesity and several noncommunicable chronic diseases (NCDs), such as type 2 diabetes (T2D), cardiovascular diseases (CVD) and neoplasms [16–19]. In the pathophysiology of T2D and insulin resistance, systemic inflammation mediated by adipose tissue is determinant [20].

Recent research indicates that the inflammation–obesity axis is regulated by epigenetic mechanisms, including inflammatory microRNAs such as miR-146a and miR-155, which modulate transcription of immunometabolic signaling molecules [21,22]. Thus, obesity is a central factor in the genesis and progression of NCDs, requiring innovative preventive and therapeutic approaches that consider its inflammatory and systemic nature [23].

1.1. *The Central Role of Leptin and the Challenge of Resistance*

Leptin, a 16 kDa peptide hormone secreted primarily by adipose tissue, is crucial in the regulation of body weight and energy expenditure [108,109]. Its circulating levels reflect body fat mass, leading to hyperleptinemia in obese individuals [110].

However, in obesity the organism develops leptin resistance, where the satiety signaling of the hormone is impaired, perpetuating food intake and weight gain [111,112]. Leptin, beyond its endocrine role, acts as a proinflammatory adipokine, promoting proinflammatory immune phenotypes [113,114]. Chronic inflammation, in turn, can impair signaling of the leptin receptor (LEPR) in the hypothalamus, creating a vicious cycle of inflammation, leptin resistance and metabolic dysregulation [115,116].

Any effective therapeutic strategy against obesity and its comorbidities must therefore address this underlying immunometabolic dysfunction, aiming not only at weight loss but at restoring leptin sensitivity [117].

Molecular Mechanisms of Chronic Inflammation and the Role of miR-146a

Low-grade chronic inflammation is a crucial mechanistic link in the etiology and progression of diseases such as cancer, obesity and T2D [24]. This persistent inflammatory state dysregulates immunometabolic signaling pathways, such as NF- κ B and JNK [25,26], orchestrating production of proinflammatory cytokines (TNF- α , IL-6, IL-1 β) [27]. These cytokines contribute to insulin resistance, tumor progression and adipose tissue dysfunction [28].

2.1. *MicroRNAs as Key Regulators*

MicroRNAs (miRNAs) are essential post-transcriptional regulators in modulation of inflammatory responses [29]. miR-146a and miR-155 are notable for their opposing roles: miR-146a attenuates excessive inflammatory signaling, while miR-155 promotes proinflammatory responses [30]. Dysregulation of these miRNAs is common in chronic inflammation and exacerbates conditions such as cancer, obesity and T2D [31,32].

2.2. *The IRAK1/TRAF6 Signaling Pathway and miR-146a Negative Feedback*

miR-146a is a negative regulator of innate immune responses, suppressing components of the TLR and IL-1R signaling pathways [33]. It directly represses IRAK1 and TRAF6 [34], adaptor proteins that activate the NF- κ B cascade, leading to expression of proinflammatory cytokines [35]. In this way, miR-146a establishes a negative feedback circuit essential to prevent excessive inflammation and maintain immune homeostasis [36,37].

miR-146a deficiency is associated with increased tumor inflammation, favoring growth and metastasis [38]. In models of obesity and T2D, reduction of miR-146a correlates with exacerbated systemic inflammation, insulin resistance and metabolic dysfunction [39,40]. Reduced serum levels of miR-146a are detected in T2D patients [41] and are associated with fibrosis and systemic complications [42].

Rationale and Advantages of Injectable Formulations

Conventional therapeutic approaches for compounds such as curcumin or CoQ10 face limitations such as low oral bioavailability and rapid degradation [43]. The injectable route overcomes oral administration by avoiding gastrointestinal degradation and first-pass metabolism, resulting in higher systemic bioavailability [44,45]. It offers a rapid onset of pharmacological action, essential for immediate control of inflammation [46], and allows precise dose adjustment in multimodal therapies [47].

For miRNA mimetics (synthetic oligonucleotides), injectable formulation is crucial. Injectable nanocarriers or exosomes protect the molecules and optimize their absorption and tissue targeting

[48,49]. Preclinical studies have shown that miR-146a mimetics encapsulated in nanoparticles reduced inflammation and fibrosis in diabetes and cancer models [50,51].

Selected and Synergistic Injectable Agents

The integrated therapeutic strategy combines agents with complementary mechanisms, targeting multiple points of the inflammatory cascade and oxidative stress.

4.1. Dimethyl Sulfoxide (DMSO)

Dimethyl sulfoxide (DMSO) is an amphiphilic solvent with notable pharmacological properties that go far beyond its function as a vehicle to facilitate the bioavailability of other compounds [52]. Its intrinsic characteristics as an anti-inflammatory, antioxidant and immunomodulatory agent establish it as an active therapeutic component in injectable formulations [53,54]. DMSO has been shown to significantly repress production of proinflammatory cytokines such as TNF- α , IL-1 β and IL-6 from activated human immune cells, an effect crucial to mitigate low-grade chronic inflammation observed in obesity and metabolic disorders [122]. In addition, its mechanism involves inhibition of the NLRP3 inflammasome pathway, a protein complex central to the inflammatory response to metabolic danger signals [123].

Its capacity to modulate the immune system is multifaceted. Recent studies show DMSO can influence macrophage polarization and regulate lymphocyte activity, contributing to a less inflammatory microenvironment [124]. In contexts of hypothalamic inflammation — a key factor in development of leptin and insulin resistance — DMSO has been investigated for its neuroprotective potential [125]. By crossing the blood–brain barrier, it can exert anti-inflammatory effects directly in the central nervous system, helping to restore neuronal sensitivity to metabolic signals [56].

Additionally, DMSO acts as a potent free radical scavenger, inhibiting lipid peroxidation and protecting cellular structures from oxidative damage, a process intimately linked to metabolic dysfunction and progression of chronic diseases [55,126]. This combination of increased permeability, suppression of inflammatory pathways and antioxidant protection makes DMSO a valuable synergistic agent in integrated therapies aimed at immunometabolic dysfunction.

4.2. Coenzyme Q10 (CoQ10)

Coenzyme Q10 (CoQ10), or ubiquinone, is a lipophilic endogenous molecule essential for cellular bioenergetics, acting as an electron carrier in the mitochondrial respiratory chain for ATP production [57,99]. Beyond its role in energy production, its reduced form, ubiquinol, functions as a potent antioxidant, protecting cellular membranes and lipoproteins from lipid peroxidation and oxidative damage [143].

Deficient CoQ10 levels are associated with a variety of chronic diseases, including metabolic disorders, cardiovascular and neurodegenerative diseases, where mitochondrial dysfunction and oxidative stress are central pathogenic factors [144,145]. In chronic inflammation conditions such as obesity and T2D, demand for CoQ10 increases while endogenous production may decrease, exacerbating the cycle of oxidative stress and inflammation [58,146].

CoQ10 administration has been shown to modulate multiple aspects of immunometabolic dysfunction. Studies indicate supplementation can reduce circulating levels of proinflammatory cytokines like TNF- α and IL-6, and suppress activation of the NF- κ B complex, a master regulator of inflammation [61,147]. In obesity contexts, CoQ10 influences adipokine signaling, notably decreasing proinflammatory leptin levels and increasing the adiponectin/leptin ratio, favoring an anti-inflammatory profile and improving insulin sensitivity [148,149]. Intravenous administration of CoQ10 circumvents its low oral bioavailability, ensuring therapeutic concentrations rapidly reach target tissues [60,150]. This route of administration is particularly promising to reverse mitochondrial dysfunction and protect vital organs such as heart and liver from damage induced by inflammation

and metabolic stress, positioning CoQ10 as a vital component in integrated therapies for chronic diseases [151,152].

4.3. Alpha-Lipoic Acid (ALA)

Alpha-lipoic acid (ALA) is an organosulfur compound with potent antioxidant properties that acts in both hydrophilic and lipophilic environments. Synthesized in mitochondria, it functions as an essential cofactor for enzymes of energy metabolism [62]. Its reduced form, dihydrolipoic acid (DHLA), is a powerful antioxidant capable of regenerating other endogenous antioxidants, including glutathione (GSH), vitamin C and coenzyme Q10, amplifying the cell's antioxidant defense capacity [63]. Besides its direct antioxidant action, ALA modulates crucial cellular signaling pathways. It has been shown to inhibit activation of NF- κ B and c-Jun N-terminal kinase (JNK), two central inflammatory pathways that contribute to insulin resistance, endothelial dysfunction and progression of metabolic diseases [64,65,137].

Intravenous administration of ALA ensures superior bioavailability and is an established therapy for diabetic neuropathy, where its neuroprotective effects and improvement of neural blood flow are clinically relevant [66]. In the context of obesity and leptin resistance, ALA has been shown to significantly reduce circulating leptin levels and increase adiponectin, an adipokine with anti-inflammatory and insulin-sensitizing effects [138,139]. This modulation of adipokines, together with improved insulin sensitivity and reduced systemic inflammatory markers such as C-reactive protein (CRP), positions ALA as a key therapeutic agent to reverse metabolic dysfunction [140,141]. By protecting pancreatic β -cells from oxidative stress and improving the response of peripheral tissues to insulin, ALA addresses multiple aspects of T2D pathophysiology and metabolic syndrome [142].

4.4. Curcumin

Curcumin, the principal curcuminoid extracted from the rhizome of *Curcuma longa*, is a pleiotropic polyphenol with a wide range of biological activities including potent anti-inflammatory, antioxidant and anticancer effects [67,68]. One of its best-characterized mechanisms is inhibition of the transcription factor NF- κ B, a master regulator of inflammatory response that controls expression of hundreds of proinflammatory genes [71,72]. Besides direct inhibition, curcumin has been shown to modulate inflammation via epigenetic routes, notably by inducing expression of microRNA-146a (miR-146a) [68]. By increasing miR-146a levels, curcumin reinforces negative feedback on the NF- κ B pathway, suppressing expression of its targets IRAK1 and TRAF6 and thereby attenuating the inflammatory cascade more sustainably [132,133].

Despite its therapeutic potential, curcumin efficacy is severely limited by its low oral bioavailability, due to poor absorption, rapid metabolism and systemic elimination [69]. Injectable formulations overcome this barrier, allowing therapeutic concentrations to reach target tissues and exert robust effects [70]. In the context of obesity and leptin resistance, curcumin has shown particular promise. Studies indicate it can reduce diet-induced leptin and insulin resistance, attenuate expression of inflammatory cytokines in adipose tissue and even inhibit activation of leptin-induced hepatic stellate cells, preventing fibrosis [134,135]. By suppressing leptin levels and associated chronic inflammation, curcumin addresses immunometabolic mechanisms linking obesity to its comorbidities [136].

4.5. Glutathione (GSH)

Glutathione (GSH), the most abundant intracellular antioxidant, is a tripeptide (γ -L-glutamyl-L-cysteinylglycine) that plays a central role in cellular defense against oxidative stress and in maintaining redox homeostasis [73]. In states of chronic inflammation, such as those observed in obesity and T2D, GSH levels are often depleted due to increased production of reactive oxygen species (ROS) [77]. Intravenous administration of GSH overcomes poor oral bioavailability and rapidly restores tissue levels, exerting potent anti-inflammatory effects [74]. The mechanism

underlying this anti-inflammatory action includes inhibition of NF- κ B activation, modulation of the PTEN/PI3K/AKT signaling pathway and suppression of proinflammatory cytokine production [127,128].

Studies show GSH supplementation can "fine-tune" innate immune responses, preventing excessive and harmful immune activation without compromising host ability to fight pathogens [129]. In insulin-resistant patients, GSH replacement has been associated with improved insulin sensitivity and β -cell function, probably by protecting these cells from oxidative damage and lipotoxicity [75,76,130]. GSH deficiency is correlated not only with inflammation but also with mitochondrial dysfunction. By restoring GSH levels, intravenous therapy can improve cellular bioenergetics and reduce mitochondrial ROS production, which are triggers for inflammation and leptin resistance [129,131]. Therefore, injectable glutathione acts as a fundamental pillar in the integrated therapeutic strategy, directly addressing oxidative stress that perpetuates the vicious cycle of inflammation and metabolic dysfunction.

4.6. miR-146a Mimetics

Therapeutic use of miR-146a mimetics aims to restore the negative-feedback circuit of inflammation. Systemic delivery of miR-146a mimetics in nanocarriers has been shown to inhibit NF- κ B-mediated inflammation and leukemia progression in vivo [78,79]. Targeting myeloid cells or adipose tissue macrophages (ATM) is promising for treating inflammation in obesity [80,81].

Discussion and Future Perspectives

The interrelationship between chronic inflammation, cancer, obesity and T2D is a growing clinical challenge [82,83]. The integrated strategy of DMSO, CoQ10, ALA, curcumin, GSH and miR-146a mimetics, administered by injectable route, offers multimodal therapeutic synergy [84]. Each agent acts on complementary targets: miR-146a inhibits central inflammation; CoQ10 and ALA reinforce antioxidant defense and mitochondrial function [85]; curcumin suppresses NF- κ B and induces miR-146a; and DMSO increases delivery and has intrinsic anti-inflammatory effects [86]. This integration suggests superior efficacy compared to monotherapies [87].

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