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Adiponectin as an immunoregulatory factor in physical exercise – A brief overview

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ABSTRACT

Adiponectin, an adipokine abundantly produced by adipose tissue, is a well-established regulator of energy metabolism and insulin sensitivity. Beyond these metabolic roles, a growing body of evidence characterizes adiponectin as a potent immunoregulatory factor. This mini-review provides a brief overview of adiponectin's anti-inflammatory functions in both the peripheral and central nervous systems. We discuss its role in modulating innate and adaptive immunity, including suppressing pro-inflammatory cytokine production, promoting anti-inflammatory M2 macrophage polarization, and regulating T-cell function. Additionally, we discuss how adiponectin signaling through its receptors (AdipoR1 and AdipoR2) in microglia and astrocytes can counteract neuroinflammation, with relevance to neurological and behavioral conditions. Given the challenges in pharmacologically targeting the adiponectin signaling system, we explore physical exercise as a feasible therapeutic strategy to increase adiponectin levels. We highlight evidence that exercise-induced increases in adiponectin mediate significant anti-inflammatory effects, underscoring the potential of lifestyle interventions to modulate immune responses via adiponectin.

1. Introduction

Adipose tissue has been recognized as part of the endocrine system for over 30 years (Cook et al., 1987; Scherer, 2006), with adipocyte-released factors collectively referred to as adipokines (Scherer, 2006). Among these, adiponectin stands out as one of the most abundant plasma proteins acting in synergy with the insulin-signaling system to regulate energy metabolism (Scherer et al., 1995; Yamauchi et al., 2001, 2002). Beyond its vital role in supporting insulin signaling and fatty acid oxidation, adiponectin has been characterized as an essential anti-inflammatory adipokine with protective effects across different systems, including the circulatory (Ouchi et al., 1999, 2000), pulmonary (Salvator et al., 2021), and central nervous systems (Nicolas et al., 2017).

The effects of adiponectin are mediated mainly by activation of two specific receptors, adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2) (Tanabe et al., 2015). The adaptor protein containing a pleckstrin homology domain, a phosphotyrosine domain, and a leucine zipper motif (APPL1) couples receptor activity to the activation of downstream signaling pathways (Ruan and Dong, 2016). Such downstream pathways include activation of the peroxisome proliferator-activated receptor alpha (PPARα), a transcriptional factor that upregulates lipid metabolism (Contreras et al., 2013; Ruan and Dong, 2016), and the AMP-activated protein kinase (AMPK), an intracellular energy sensor that responds to ATP depletion (Hardie, 2007). Notably, both signaling pathways have also been implicated in the inflammatory response, as PPARα can downregulate the transcription of several pro-inflammatory factors (Contreras et al., 2013) and AMPK plays an important role in the metabolic programming of macrophages (Cui et al., 2023).

Although adiponectin production was initially thought to be exclusive of white adipose tissue (Scherer et al., 1995), more recent accounts demonstrate it is also produced by the bone marrow adipose tissue (Cawthorn et al., 2014) and, remarkably, lymphocytes (Danturti et al., 2017; Zhang et al., 2021), underscoring the relevance of the adiponectin signaling system in immunoregulation. In this mini-review, we briefly

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describe the findings characterizing adiponectin's immunoregulatory functions in the innate and acquired peripheral immune response. Moreover, as adiponectin receptors are found in microglia and astrocytes (Guillod-Maximin et al., 2009; Miao et al., 2021), and the low-molecular-weight isoforms of adiponectin cross the blood-brain barrier (Kos et al., 2007; Kubota et al., 2007), we review the recent investigations unravelling the adiponectin's role in counteracting neuroinflammation. Finally, as pharmacological targeting of the adiponectin signaling system remains challenging, we explore how lifestyle factors, such as physical exercise, have been suggested as a therapeutic strategy to increase adiponectin levels.

2. Adiponectin modulation of peripheral immunity

Adiponectin receptors are found in monocytes and lymphocytes (Pang and Narendran, 2008). Not surprisingly, adiponectin modulates the activity of both the innate and adaptive immune responses (Liu and Li, 2025). Its roles in regulating different immune responses are discussed in the following sections.

2.1. Adiponectin's role in the innate immune response

Not long after its discovery (Scherer et al., 1995), the immunomodulatory properties of adiponectin began to be investigated. Given the inverse correlation between adiposity and circulating adiponectin levels (Arita et al., 1999; Bahceci et al., 2007), early investigations suggested that adiponectin could act as a protective factor in obesity-associated vascular diseases (Ouchi et al., 1999, 2000). In cultured human aortic endothelial cells, adiponectin was shown to prevent the tumor necrosis factor alpha (TNFα)-induced increase of monocytic adhesion (Ouchi et al., 1999) by blocking the activation of the nuclear factor (NF)-κB via a cyclic adenosine monophosphate (cAMP)-dependent pathway (Ouchi et al., 2000), which is known to be a key transcription factor leading to the activation of adhesion proteins in such endothelial cells. Moreover, adiponectin was also shown to suppress macrophage function, as evidenced by reduced phagocytic activity and decreased lipopolysaccharide (LPS)-induced expression of TNF-α mRNA in macrophages (Yokota et al., 2000). Conversely, evidence suggests that TNFα, which is often increased in obese subjects (Engeli et al., 2003), acts as a negative modulator of adiponectin levels (He et al., 2016; Lo et al., 2007).

Adiponectin's action on macrophage function has been further investigated, indicating that it induces macrophage polarization towards the anti-inflammatory M2 phenotype (Ohashi et al., 2010). Adiponectin-deficient mice exhibit increased pro-inflammatory markers associated with the M1 macrophage phenotype and reduced M2-associated anti-inflammatory markers (Ohashi et al., 2010). In contrast, treating cultured macrophages with adiponectin stimulates polarization towards the M2 phenotype (Ohashi et al., 2010). Such adiponectin-induced polarization has been shown to mediate several physiological processes, including the cold exposure-promoted browning of subcutaneous white adipose tissue (Hui et al., 2015), anti-inflammatory activity in the lungs (Salvator et al., 2021), and anti-tumor immunity (Braun et al., 2025).

In summary, adiponectin is an essential regulator of the innate immune response, as higher circulating levels suppress pro-inflammatory activity and shift the immune response towards an anti-inflammatory state.

2.2. Adiponectin's role in the adaptive immune response

The adaptive immune response largely depends on the activity of bone marrow- and thymus-derived lymphocytes, with both B and T cells expressing varying levels of adiponectin receptors (Pang and Narendran, 2008; Ramos-Ramírez et al., 2021; Wilk et al., 2011). Concerning T cells, adiponectin regulates the pro-inflammatory activity of effector T cells (Wilk et al., 2011) and the anti-inflammatory activity of regulatory T cells (Ramos-Ramírez et al., 2021). The antigen-specific activation of effector T cells upregulates the adiponectin receptor's synthesis and translocation to the cell surface (Wilk et al., 2011). Adiponectin treatment reduces proliferation and cytokine production by antigen-activated T cells (Wilk et al., 2011), thereby limiting the pro-inflammatory immune response. On the other hand, adiponectin increases the secretion of the anti-inflammatory cytokine interleukin (IL)-10 from regulatory T cells, although it does not alter cytokine synthesis (Ramos-Ramírez et al., 2021).

Adiponectin also regulates hematopoiesis (Crawford et al., 2010), while adiponectin receptors preserve the hematopoietic stem cells' self-renewal potential (Meacham et al., 2022). Remarkably, unstimulated bone marrow-derived lymphocytes (i.e., non-B and non-T cells) were shown to synthesize and secrete adiponectin, which regulates hematopoiesis (Crawford et al., 2010). Similar adiponectin synthesis and secretion were also observed in regulatory T cells residing in the thymic nurse cell complexes (Zhang et al., 2021), suggesting that the adiponectin-mediated modulation of the adaptive immune response may, to some extent, be independent of adiponectin derived from white adipose tissue.

3. Adiponectin's regulation of central immune response

It remains unclear whether adiponectin is expressed in the central nervous system; however, low-molecular-weight adiponectin does cross the blood-brain barrier (Kos et al., 2007; Kubota et al., 2007). Although central adiponectin levels are estimated to be a 1000-fold lower than that observed in serum (Kos et al., 2007), adiponectin receptors are ubiquitously expressed in the brain, including neurons (Clain et al., 2022; Repunte-Canonigo et al., 2010), astrocytes (Guillod-Maximin et al., 2009; Pratap and Holsinger, 2020; Wan et al., 2014), and microglia (Miao et al., 2021; Nicolas et al., 2017). Not surprisingly, the anti-inflammatory properties of adiponectin also extend to the regulation of neuroimmune response.

Central inflammatory response is exacerbated in adiponectin-deficient mice. LPS-induced inflammation results in increased microglial reactivity and production of pro-inflammatory cytokines (IL-6, IL-1β, and TNF-α) in several brain regions of adiponectin knockout mice compared to LPS-treated wildtypes (Nicolas et al., 2017). Moreover, in animal models of dementia, such as those induced by chronic vascular hypoperfusion or transgenic expression of Alzheimer's disease (AD) risk genes, the expression of pro-inflammatory markers in the brain (He et al., 2021) and the disease-associated behavioral deficits (Miao et al., 2021) are worsened by adiponectin deficiency. The clinical relevance of such findings is evident in the aging-associated reduction in circulating adiponectin levels (He et al., 2023). Among the elderly, reduced adiponectin levels are associated with increased expression of pro-inflammatory cytokines (He et al., 2023) and worsened cognitive performance in individuals with dementia (He et al., 2021).

In vitro studies demonstrate that incubation of adiponectin in cultured microglia reduces both baseline and LPS-induced production of pro-inflammatory cytokines (Nicolas et al., 2017). Similarly, incubation with AdipoRon, an adiponectin receptor agonist, reduces microglial reactivity to LPS exposure and increases the expression of the anti-inflammatory factor Arginase 1 (Arg1) (Miao et al., 2021). Such an anti-inflammatory response has been linked to the activation of the AdipoR1/PPARγ pathway, as disrupting either AdipoR1 or the PPARγ signaling blocked the effects of adiponectin and AdipoRon in vitro (Miao et al., 2021; Nicolas et al., 2017). Others have also demonstrated that increased microglial lysosomal activity (He et al., 2021) and mitochondrial function (He et al., 2023) are complementary mechanisms that mediate the anti-inflammatory effects of increased adiponectin signaling.

The relevance of adiponectin's regulation of central immune response has been demonstrated across several disease models,

including chronic vascular hypoperfusion (Miao et al., 2021), systemic LSP-induced inflammation (Nicolas et al., 2017), neonatal stroke (Xu et al., 2022), AD (He et al., 2021), and chronic corticosterone-induced depression (Chabry et al., 2015). Notably, anti-inflammatory effects have been observed across diverse treatment regimens and routes of administration. A single intracerebroventricular infusion of adiponectin has been shown to rapidly counteract the chronic corticosterone- and LPS-induced pro-inflammatory response (Chabry et al., 2015; Nicolas et al., 2017). Similarly, a single intranasal adiponectin infusion elicited rapid and long-lasting (4 weeks) anti-inflammatory effects by shifting the microglial profile from an M1 to an M2 state in an animal model of neonatal stroke, mediated by AdipoR1 (Xu et al., 2022). On the other hand, chronic AdipoRon treatment, ranging from three weeks (Miao et al., 2021) to months (He et al., 2021), counteracted the pro-inflammatory profile and improved the cognitive performance in animal models of dementia (He et al., 2021; Miao et al., 2021).

Despite such promising findings, the high endogenous levels of circulating adiponectin (Ouchi et al., 1999) and its relatively short life (~75 min) (Halberg et al., 2009) pose a challenge for the exogenous administration of adiponectin as a therapeutic intervention. Lifestyle changes that upregulate adiponectin expression have been suggested as a promising alternative to indirectly target the adiponectin signaling system for therapeutic purposes (Liu et al., 2019).

4. Physical exercise-induced upregulation of adiponectin signaling

The benefits of physical exercise extend way beyond local adaptations in skeletal muscles (Chow et al., 2022; Safdar et al., 2016). When plasma from physically active mice is transplanted into sedentary mice, neurological and cognitive deficits associated with aging and neuroinflammation are improved to levels comparable to those achieved through exercise (De Miguel et al., 2021; Horowitz et al., 2020). Since exercise essentially involves localized skeletal muscle contraction, the means by which physical exercise elicits such systemic effects have been intensely debated over the past 25 years (Chow et al., 2022; Lee et al., 2019; Muñoz-Cánoves et al., 2013; Pedersen and Febbraio, 2012; Sato et al., 2022; Steensberg et al., 2001). Since Pedersen and colleagues established the muscle as a secretory organ (Pedersen and Febbraio, 2012; Steensberg et al., 2001), several other organs were shown to release factors in response to exercise, such as adipokines, hepatokines, and bone-derived factors (Chow et al., 2022; Lee et al., 2019). Recently, researchers have collectively referred to such exercise-elicited factors as *exerkines* (Chow et al., 2022; Safdar et al., 2016).

Adiponectin regulates energy metabolism, and energetically challenging activities, such as physical exercise, increase adiponectin levels (see Wang et al. 2025 for a recent meta-analysis). Nevertheless, it is worth noting that the effects of exercise on adiponectin levels may be influenced by training and exercise regularity. Aerobic exercise, particularly that performed at higher intensities (higher than 75% of the maximum heart rate reserve), increases circulating adiponectin levels (Numao et al., 2011; Racil et al., 2013; Schön et al., 2019). This has been shown in lean (Schön et al., 2019) and obese subjects (Numao et al., 2011; Racil et al., 2013) of both sexes. Likewise, resistance training has been shown to increase adiponectin levels shortly after a single exercise session in previously trained participants (Varady et al., 2010), and after a 12-week training protocol in previously untrained obese participants (Bagheri et al., 2025). Notably, the acute effects of resistance training are not detectable in untrained obese participants (Varady et al., 2010). Similarly, protocols utilizing high-intensity interval training (HIIT) elevate adiponectin levels after several weeks of training (Osalou et al., 2025; Shing et al., 2013), but not acutely (Kon et al., 2019; Williams et al., 2013). Therefore, even though adiponectin levels may acutely increase in response to a single bout of exercise in trained participants (Schön et al., 2019; Varady et al., 2010) or in those with chronic metabolic conditions (Chan et al., 2017; Wang et al., 2025), it is likely that a more significant increase will be seen with regular physical exercise. Moreover, current evidence suggests that the increase in circulating adiponectin levels in response to regular exercise is evident regardless of exercise modality (Wang et al., 2025).

The exercise-induced increase in adiponectin levels has been associated with improved mood (Chan et al., 2017) and cognition (Schön et al., 2019), suggesting crosstalk between circulating adiponectin and central nervous system functions. Indeed, our recent investigations indicate that exercise acutely increases brain adiponectin levels (Cheng et al., 2025). Since exercise reduces neuroinflammatory markers (Xiao et al., 2021), it is pertinent to suggest that adiponectin could mediate the anti-inflammatory effects of exercise in the central nervous system. Evidence for this hypothesis was provided by Liu and colleagues (Liu et al., 2024). Physical exercise counteracted chronic stress-induced central inflammation by shifting microglial phenotype toward the anti-inflammatory M2 state, thereby reducing levels of pro-inflammatory cytokines in the hippocampus. Moreover, these effects were shown to depend on AdipoR1 activation, as knocking it down blocked the exercise-induced anti-inflammatory response (Liu et al., 2024).

In summary, lifestyle interventions, such as physical exercise, can circumvent the challenges of pharmacologically targeting the adiponectin signaling system to modulate the immune response at both peripheral and central levels (Fig. 1).

5. Conclusion and future perspectives

Since its identification 30 years ago (Scherer et al., 1995), the synthesis, regulation, and function of adiponectin have been intensely investigated. In addition to being primarily synthesized by lymphocytes in white adipose tissue, it is now understood to be produced by lymphocytes and by bone marrow adipose tissue (Cawthorn et al., 2014; Danturti et al., 2017; Zhang et al., 2021). Such localized synthesis underscores the importance of adiponectin signaling in regulating the immune response. Moreover, the blood-brain barrier permeability to adiponectin and the expression of adiponectin receptors in central immune cells, including astrocytes and microglia, indicate that adiponectin's anti-inflammatory function extends to the brain. Indeed, increasing central adiponectin signaling has been an effective anti-inflammatory strategy in animal models of several diseases. Despite the limitations in pharmacologically targeting such signaling system, adiponectin levels appear to be tightly regulated by lifestyle factors. Remarkably, upregulating adiponectin levels through exercise counteracts stress-induced central inflammation (Liu et al., 2024).

Nevertheless, certain divergences in the adiponectin's anti-inflammatory functions warrant further research. In astrocytes, increased adiponectin signaling can elicit a pro-inflammatory response, with increased expression of pro-inflammatory cytokines, including IL-6 (Wan et al., 2014). Moreover, AdipoR2 expression levels increase in activated astrocytes in animal models of AD, which may reflect increased energetic demands associated with the pro-inflammatory phenotype of reactive astrocytes (Pratap and Holsinger, 2020). Such paradoxical effects have been discussed in the literature (Kalkman, 2021; Menzaghi and Trischitta, 2018; Waragai et al., 2020), although only conjectural explanations have been proposed. For instance, the adiponectin-elicited release of IL-6 from astrocytes is consistent with the intriguing finding that adiponectin's insulin-sensitizing effects in the liver were associated with the release of macrophage-derived IL-6 through activation of the pro-inflammatory NF-κB (Awazawa et al., 2011). Notably, this effect was independent of AdipoR1 or AdipoR2, suggesting the existence of a third, unknown pathway (Awazawa et al., 2011). Some have also pointed to a paradoxical hyperadiponectinemia in cognitive impairment and AD pathogenesis (Wennberg et al., 2016). This could be explained by potential upregulation of adiponectin synthesis induced by AD-associated insulin resistance (Waragai et al., 2020). Indeed, genetic modifications of insulin receptors in adipose

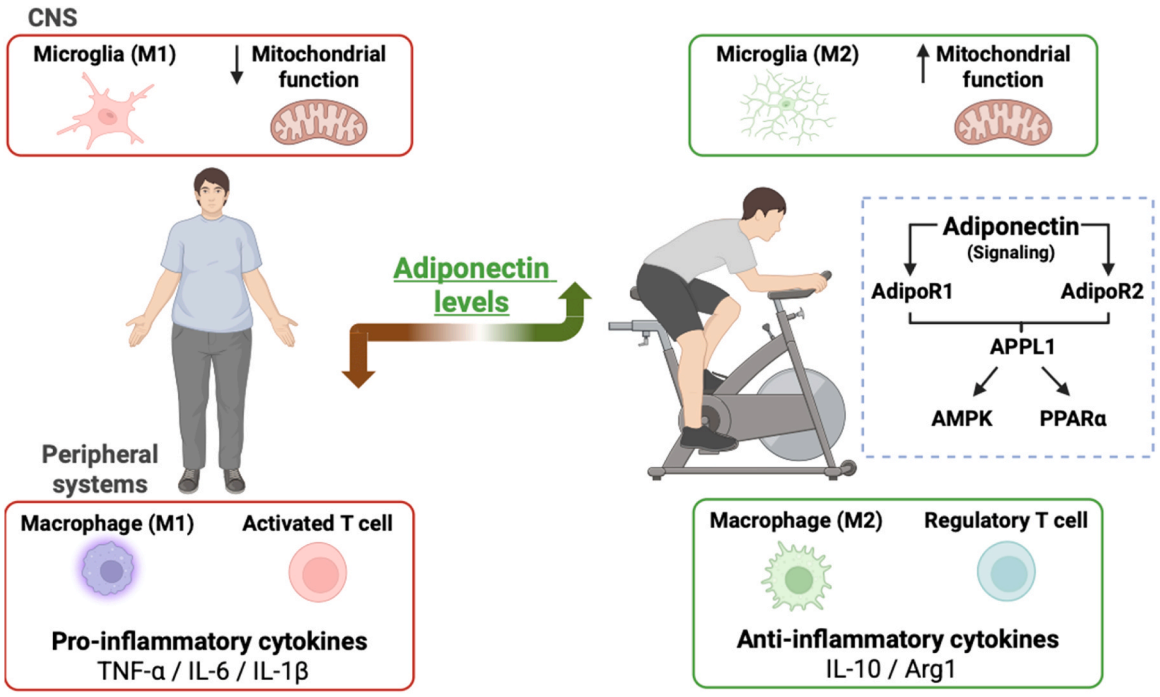

Fig. 1. Adiponectin regulates peripheral and central immune response. Increased circulating adiponectin levels, which can be achieved through lifestyle interventions such as physical exercise, counteract inflammatory responses in peripheral and central tissues. Adiponectin signaling stimulates polarization of macrophages and microglia toward the anti-inflammatory M2 phenotype, promotes the release of anti-inflammatory cytokines by regulatory T cells, and improves mitochondrial function.

tissue and insulin resistance lead to a compensatory increase in circulating adiponectin levels (Yamauchi and Kadowaki, 2013), which may eventually contribute to adiponectin resistance (Lin et al., 2007). Providing more substantial mechanistic explanations for the adiponectin paradox is therefore crucial for harnessing the therapeutic properties of adiponectin.

CRediT authorship contribution statement

Douglas A. Formolo: Writing – original draft, Writing – review & editing, Conceptualization. **Suk-Yu Yau:** Conceptualization, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

None.

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