THE EFFECT OF SUBCONJUNCTIVAL RESVERATROL INJECTION ON IL-6 AND TNF-A EXPRESSION ON FORM DEPPRIVATION MYOPIA

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ABSTRACT

This paper explores the relationship between inflammation and myopia, a prevalent refractive error with increasing global prevalence, particularly in Asia. It discusses the role of inflammatory cytokines, such as IL-6 and TNF-α, in the pathophysiology of myopia, highlighting evidence that myopic eyes exhibit elevated levels of these cytokines compared to non-myopic eyes. The review examines various studies that demonstrate how inflammation may contribute to ocular elongation and the progression of myopia through mechanisms involving the scleral extracellular matrix and immune cell activity. Additionally, the potential therapeutic effects of resveratrol, a polyphenolic compound with anti-inflammatory properties, are considered in the context of form deprivation myopia. The findings suggest that targeting inflammatory pathways may offer novel strategies for managing myopia and mitigating its rising incidence worldwide.

INTRODUCTION

A common type of refractive error, myopia represents a worldwide public health issue with significant social and economic consequences.[1] The prevalence of myopia in Asia has reached its highest recorded level. Sixty years ago, between 10 and 20 percent of people in China were nearsighted. Nowadays, up to 90% of people in their teens and twenties are myopic.[2] In Seoul, Korea, 96.5% of males aged 19 have myopia.[2] In other nations, including the United States and Europe, where myopia affects almost half of the youth, the prevalence is rising quickly.[2] In two schools in Tokyo, Japan, it was found that around 77% of students aged 6 to 11 and 95% of students aged 12 to 14 had myopia.[3] By 2050, it is projected that 50% of the global population will be affected by myopia, with 10% experiencing high myopia, according to Holden et al. Estimates indicate that myopia prevalence will surge from 22% in 2000 to double that figure, while cases of severe myopia are expected to rise fivefold from 2% in the same year.[4]

Research on myopia using animal models has been conducted for over four decades, despite the continuous increase in its prevalence. In 1977, Wiesel and Raviola pioneered the development of an animal model for myopia by inducing neonatal lid fusion in monkeys.[5] They subsequently suggested that myopia arises due to changes in visual input and neural regulation, based on their finding that myopia did not progress in rats raised in darkness. Their study indicated that axial myopia occurs when atypical visual experiences interfere with postnatal eye development, despite the refractive state being primarily influenced by genetic factors[6]. Wallman et al. utilized chicks raised with white translucent eye occluders, depriving them of visual input in the nasal, temporal, or entire retina, as models for myopia research.[7] As a result, myopia with a median of -15 diopters was confined to the visually deprived retinal

region. These findings suggest that acquired myopia may be induced by visual input. Even in humans, myopia has been observed to develop due to prolonged near-work activities.[8] Huang et al. examined the prevalence and progression of myopia in 9–11-year-olds in Taipei, Taiwan, using a questionnaire to collect 2-year refraction data every six months. They also looked at the protective behaviors of increasing time spent outside the home, pausing from near work every half hour, and extending proximity working distance based on parents' self-reports. For each habit, the risk ratios were 0.71, 0.89, and 0.77. Each action also significantly slowed the evolution of myopia from 6 to 24 months in a spherical equivalent study.[8]

Eye elongation causes myopia, which is linked to increased collagen I breakdown and reduced connective tissue production, changing the sclera's composition.[9] Recent studies indicate that the retina, photoreceptors, and retinal pigment epithelium regulate scleral tissue remodeling by activating signals that influence ocular development and axial length.[10] Various substances, such as collagen I, matrix metalloproteinase (MMP)-2, and transforming growth factor (TGF)-β, have been linked to myopia development in myopic eyes. TGF-β, produced by ocular tissues, is known to alter the scleral extracellular matrix (ECM), leading to a reduction in collagen synthesis.[10–12] Nuclear factor (NF)-κB activation increases collagen disruption by upregulating matrix metalloproteinase 2 (MMP2) expression and decreasing tissue inhibitor of MMP2 activity.[13] Through form deprivation-induced myopia, it has also been demonstrated that MMP2 is increased in the sclera of tree shrews and chicks.[14] Recent clinical and experimental studies have shown that atropine reduces the expression of c-Fos, NF-κB, interleukin (IL)-6, and tumor necrosis factor (TNF)-α in hamsters with monocular form deprivation (MFD)-induced myopia.[15] These results suggest that inflammation is a key factor in myopia development.

Resveratrol (3,5,4′-trans-trihydroxystilbene) is a polyphenolic phytoalexin that is a member of the stilbene family. Although peanuts, cherries, and tea all contain it, grape skins and seeds are the primary source.[16] Red wine contains this ingredient.[17] Many plant species produce it in reaction to UV radiation, diseases, stress, and damage.[18] When epidemiologists reported in 1981 that the French had a reduced death rate from coronary heart disease despite risk-increasing behaviors (smoking and consuming a lot of saturated fats), interest in RSV among academics surged dramatically. Moderate red wine drinking was cited as an explanation for this behavior. Resveratrol may play a role in regulating various intracellular enzymes, such as cyclooxygenases, lipoxygenases, kinases, and free radical scavengers.[19] Because of this, it has a variety of biological qualities, including anti-inflammatory, anti-glycation, antioxidant, neuroprotective, and anti-tumor actions.[20] However, the potential for using its qualities is restricted due to its rapid metabolism and low bioavailability, which is why RSV is still the focus of many therapeutic investigations.

According to recent research, resveratrol provides a number of therapeutic benefits for diabetes, cardiovascular disease, and cancer.[21] Reduced blood levels of inflammatory cytokines including TNF-α, IL-1β, and IL-6, as well as inhibition of the NF-κB pathway for cardiovascular illnesses in rats, are signs of resveratrol's actions.[22,23] Resveratrol safeguarded against vascular damage by increasing sirtuin 1 (SIRT1) expression while reducing NF-κB and P38 mitogen-activated protein kinase (MAPK) expression, thereby inhibiting inflammasome activation..[24,25] By blocking TNF-α-mediated MMP9 production, it also inhibited the human hepatocellular carcinoma cell's ability to invade. By suppressing the expression of pro-inflammatory cytokines (TNF-α and IL-6) and adipogenic genes (PPARγ, C/EBPα, FAS, and aP2), resveratrol demonstrated anti-obesity actions.[26] Additionally, it has been demonstrated that resveratrol activates Sir2, a conserved deacetylase for replicative lifetime in studies on aging.[27,28] Resveratrol's anti-inflammatory properties were associated with these benefits.[29,30] In this review article, we discuss the potential effect of resveratrol in supressing TNF-α and IL-6 expression in form deprivation myopia.

Evidence linking inflammation and myopia

A growing body of clinical data suggests that inflammation may play a role in the The pathophysiology of myopia suggests that a heightened inflammatory state within the circulatory system or the eye correlates with its severity. A large cross-sectional study in Korea found a significant association between higher white blood cell counts and an increased prevalence of myopia (19). Additionally, as myopia progressed, there was an observed rise in circulating neutrophils alongside a decline in monocytes, eosinophils, and lymphocytes (20). Moreover, patients with high myopia exhibited significantly elevated platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios in

peripheral blood (22, 23), indicating increased inflammation and dysregulation of serum immune cells in individuals with high myopia compared to normal subjects, which serve as markers of systemic inflammatory properties (21). The peripheral blood of individuals with pathological myopia showed significant increases in the complement profile and high-sensitivity C-reactive protein (24) which demonstrated that pathological myopia is associated with systemic immunological microinflammation. Furthermore, in a study of human blood metabolomics, Dai et al. (25) expounded on the significance of oxidative stress, inflammation, and metabolic alterations in extreme myopia.

Several studies (27–30) have reported that myopic eyes contain higher levels of inflammatory cytokines in the vitreous or aqueous humor compared to non-myopic eyes. In addition to their positive correlation with ocular axial length (AL), the concentrations of metalloproteinase-2 (MMP-2) and interleukin (IL)-6 in aqueous humor were significantly elevated in highly myopic eyes compared to control eyes (27). Moreover, while IL-1 receptor antagonist expression was notably lower in highly myopic cataract patients than in those with age-related cataracts, monocyte chemoattractant protein-1 (MCP-1) expression in the aqueous humor was significantly higher in the former group (28). Additionally, patients with high myopia (29) and highly myopic eyes with macular holes (MHs) (30) exhibited increased expression of inflammatory cytokines in the vitreous, including interferon gamma (IFN-γ), IL-6, interferon-inducible protein 10, eotaxin, MCP-1, macrophage inflammatory protein-1α (MIP-1α), and MIP-1β. The elevated presence of MIP, derived from lymphocytes, dendritic cells, and macrophages, suggests that immune cells play a role in myopia development.

The elevated levels of inflammatory cytokines in myopic eyes indicate a heightened ocular inflammatory state, suggesting that persistent subclinical inflammation may contribute to myopia progression. However, research on the link between inflammation and myopia has yielded conflicting results. Zhu et al. (34) found no significant correlation between axial length (AL) and inflammatory cytokines (IL-1β, IL-6, and tumor necrosis factor-alpha (TNF-α)) in the aqueous humor of cataract patients with AL ranging from 22.6 to 31.5 mm. These inconsistencies may stem from variations in inclusion criteria, testing methodologies, and sample sizes across different studies.

In various experimental myopia species, such as hamsters[15,31–33], tree shrews[34], mice[35], guinea pigs[36,37], and chicks[38], Research has shown that myopia development is associated with increased expression of ocular inflammatory cytokines. Furthermore, an elevated ocular inflammatory state has been found to promote myopia progression. During myopia induction, inflammatory cytokines are activated and migrate from the retina to the scleral layer. In the myopic eyes of Syrian hamsters subjected to form-deprivation myopia (FDM), pro-inflammatory cytokines such as IL-6, TNF-α, IL-1β, TGF-β, and MMP-2 were upregulated, whereas the anti-inflammatory cytokine IL-10 was downregulated.[39] These findings indicate that the MAPK and NF-κB pathways may play a role in inflammation-induced myopia. Meanwhile, inflammatory stimulators such as peptidoglycan and lipopolysaccharide were found to accelerate myopia progression, whereas the administration of the immunosuppressive drug cyclosporine A to the eye helped slow its development.[39] Several other studies have reported that hamsters experiencing myopia progression exhibit elevated levels of inflammation-related factors in their FDM eyes. Additionally, pro-inflammatory agents have been shown to enhance the expression of these factors in retinal pigment epithelium (RPE) cells in vitro.[31,32] RPE cells play a crucial role in myopigenesis by identifying key signaling molecules and influencing ion and fluid transport, thereby transmitting growth-regulating signals from the retina to the choroid and sclera.[40] Tree shrews subjected to 7- and 14-day FDM exhibited similar experimental results.[34]

Role of TNF-α in FDM

Produced mostly by T cells or innate immune cells, TNF-α is a proinflammatory cytokine that binds and activates two distinct receptors to induce a variety of biological effects.[41] When TNF-α binds to TNF receptor 1, it leads to the formation of complex I, which activates NF-κB and MAPKs, triggering tissue degradation and inflammation.[42] The activation of TNF receptor 2 also leads to the formation of complex I and the stimulation of downstream signaling pathways, which primarily regulate homeostatic biological activities.[42] Ocular TNF-α is primarily produced by microglia and Müller cells, leading to retinal pigment epithelium cell death and disruption of the blood-retinal barrier through the activation of the EGFR/p38/NF-κB/p62 pathway.[43] Additionally, it can accelerate the release of other proinflammatory molecules from Müller cells and promote glial cell proliferation.[44]

A pro-inflammatory and neuroprotective cytokine, TNF-α is essential for many physiological and immunological processes linked to tissue regeneration, neuronal injury, and retinal ischemia. Two different receptors, a 55 kDa receptor 1 (TNF-R1) and a 75 kDa receptor 2 (TNF-R2), mediate the different functions of TNF-α, depending on which receptor is activated. While TNF-R1 activation results in the recruitment of immune cells that induce inflammation, TNF-R2 stimulation is neuroprotective and encourages tissue regeneration. Furthermore, TNF-R1 can directly cause oxidative stress by triggering enzymes that produce reactive oxygen and nitrogen species. According to Kondkar et al. (2018), TNF-α may have a causal role in neurodegenerative diseases by interacting with inflammation and oxidative stress to cause neurodegeneration.[45]

Recent findings suggest that the inflammatory role of the tumor necrosis factor family is more significant than the apoptotic function of its individual members. Interactions among cells within the scleral extracellular matrix modify the biomechanical and biochemical properties of the sclera, potentially causing ocular elongation and contributing to myopia development.[46]

Several proteins implicated in the inflammatory response, including c-Fos, NFκB, IL-6 (interleukin 6), and tumor necrosis factor-α (TNF-α), were shown to be expressed by Lin et al. According to the study, myopic hamsters have higher amounts of these proteins. Researchers also discovered that hamsters' eyes treated with lipopolysaccharide and peptidoglycan had higher production of these proteins, which was associated with a faster onset of myopia. Furthermore, hamsters given the anti-inflammatory medication cyclosporine showed a reduction in the production of inflammatory proteins and a concomitant slowdown in the course of myopia.[46,47]

Role of IL-6 in FDM

During inflammation, innate immune cells produce IL-6, a cytokine that exhibits both pro-inflammatory and anti-inflammatory properties. While IL-6 trans-signaling, mediated by its attachment to the soluble IL-6 receptor, promotes inflammation, the classical pathway, where IL-6 binds to the membrane-bound IL-6 receptor, demonstrates anti-inflammatory effects.[48] It mediates downstream reactions by activating Janus kinase (JAK), which in turn stimulates MAPKs and NF-κB.[49] In the human retina, IL-6 trans-signaling can result in oxidative stress, inflammation, endothelial cell dysfunction, and neovascularization.[50] Chronic inflammatory disorders, including inflammatory ocular illness, have been linked to the development of dysregulated and persistent IL-6 production.[51,52]

Due to its dual role as both a pro-inflammatory and anti-inflammatory mediator, IL-6 has been implicated in the pathophysiology of various eye disorders. The IL-6 gene, located on chromosome 7p21.9, contains multiple polymorphisms that regulate IL-6 protein production. Among these, the IL-6-174 G/C polymorphism (rs1800795) is particularly significant, as it influences baseline IL-6 levels by modulating IL-6 promoter activity. Several studies have also associated this polymorphism with the development and progression of ocular diseases.[53]

Chronic inflammatory conditions affecting the choroid and retina are often associated with a gradual shift toward myopia over time in clinical observations of retinal diseases. Persistent, low-grade inflammation in the retina and choroid may contribute to progressive scleral expansion and axial elongation, particularly if choroidal inflammation weakens the sclera, causing it to stretch—similar to what is observed in Vogt-Koyanagi-Harada disease. Furthermore, a potential link may exist between genetically predisposed subclinical inflammation in the retina/choroid and the development of myopia, as well as related retinal degeneration. The retinal nerve shares several morphological and physiological traits with the vertebrate brain, including a robust endothelial barrier. Chronic inflammation has also been associated with various neurodegenerative conditions, such as Alzheimer's disease and dementia.[54,55]

The trabecular meshwork (TM) and endothelial cells of Schlemm's canal (SC) in the anterior segment of the human eye have been found to produce IL-6 locally. Immunohistochemical analysis of human choroidal fibrovascular tissue demonstrates strong positive staining in stromal cells and retinal pigment epithelial (RPE) cells under pathological conditions such as wet age-related macular degeneration (AMD), indicating that ocular IL-6 production contributes to disease pathophysiology. Although serum IL-6 levels often show variability when compared to intraocular fluid measurements, increased IL-6 concentrations have also been identified in the serum, tears, and intraocular fluid of patients with ocular diseases. Based on this mechanism, intraocular IL-6 levels may serve as a reliable

marker for early detection of ocular inflammation and monitoring disease progression, as aqueous and vitreous humors provide a more precise reflection of the eye's immune status than serum.[53]

The potential effect of resveratrol in FDM

In traditional medicine, resveratrol, which is extracted from Polygonum cuspidatum roots, is used to treat cardiovascular disease, inflammation, and carcinogenesis.[56] In the beginning, resveratrol was described as a phytoalexin that gave the plant resistance to microbial or fungal diseases as well as stressful stimuli like UV light or damage.[57] Despite being present in many foods, it is most well-known for being a component of grapes and wines. Romero-Pérez et al. showed that because the skin is removed sooner in the white wine manufacturing process, red wines have a greater resveratrol concentration than white wines.[58]

Resveratrol has been shown to possess therapeutic properties in various diseases, exhibiting anti-inflammatory, antioxidant, and anti-neoplastic effects. Some studies suggest that resveratrol increases the expression and activity of the protein deacetylase enzyme silent information regulator 2/sirtuin-1 (SIRT1), a crucial molecule that regulates the body's response to diet and physical activity, particularly in the context of metabolic disorders.[59–61] Treatment with resveratrol enhanced the lifespan of mice on a high-calorie diet by reducing insulin-like growth factor-1 (IGF-1) levels while improving insulin sensitivity.[61–63] Moreover, resveratrol has been found to lower body weight, fat mass, and plasma concentrations of MCP-1, TNF-α, and triglycerides in connection with metabolic syndrome. Its anti-inflammatory effects on cardiovascular diseases involve the regulation of nitric oxide synthase (iNOS) and IL-1β mRNA expression in coronary artery endothelial cells, along with the inhibition of intracellular adhesion molecule 1 (ICAM-1).[64] Heart failure can be caused by cardiovascular disorders. One study found that oral resveratrol treatment greatly reduced the infiltration of mast cells and macrophages in C57BL/6 mice with heart failure produced by transverse aortic constriction surgery.[65]

Resveratrol also demonstrates anti-inflammatory effects both in vitro and in vivo by suppressing Aβ-induced microglial activation through the downregulation of the TLR4/NF-κB/STAT signaling pathway[65]. The findings above highlight that resveratrol's beneficial effects are largely attributed to its anti-inflammatory properties, including the reduction of circulating inflammatory markers such as TNF-α, IL-1β, and IL-6, as well as the inhibition of the p38–MAPK and NF–κB pathways.[66] Nevertheless, the benefits of resveratrol for eye health remain inconclusive due to conflicting evidence. A recent study suggests that resveratrol suppresses the upregulation of SIRT-1 and Ku70, thereby preventing retinal mitochondrial activation. This inhibition also restricts the translocation of BAX into the mitochondria.[67]

CONCLUSION

In summary, the findings discussed in this paper underscore the crucial involvement of inflammation in the development of myopia, indicating that increased levels of inflammatory cytokines like IL-6 and TNF-α are linked to the advancement of this refractive condition. The findings indicate that myopic eyes exhibit a heightened inflammatory state, which may contribute to ocular elongation and the associated structural changes in the sclera. Furthermore, the potential therapeutic effects of resveratrol in modulating inflammatory responses and its implications for myopia management are discussed, emphasizing the need for further research to explore its efficacy and mechanisms of action. Overall, this review underscores the complex interplay between inflammation and myopia, paving the way for novel therapeutic strategies targeting inflammatory pathways to mitigate the rising prevalence of myopia globally.

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