• Review Article •

Growth hormone-releasing hormone in retinal disorders and uveitis: an updated review

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Abstract

● Growth hormone-releasing hormone (GHRH) is a hypothalamic releasing hormone that plays a crucial physiological role in regulating the synthesis and release of anterior pituitary hormones. In recent years, studies have found that GHRH possesses functions like anti-inflammation, promoting cell proliferation, and facilitating cell migration. It participates in regulating the development of uveitis and diabetic retinopathy. Additionally, it also has an impact on the development of retinal ganglion cells by modulating the inflammatory response and mediating the immune response. Given the important roles of GHRH in ophthalmic diseases, elucidating the molecular regulation of the GHRH-GHRH receptor (GHRHR) signal and the innovative development of intervention pathways that directly or indirectly target GHRH serve as strong evidence of how basic research guides innovation and translation. In this review, research reports on GHRH in ophthalmic diseases including retinal diseases and uveitis were summarized and analyzed.

● **KEYWORDS:** growth hormone-releasing hormone; retinal diseases; uveitis; diabetic retinopathy

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INTRODUCTION

Growth hormone-releasing hormone (GHRH), also known as growth hormone-releasing factor (GRF), is a 44-amino-acid peptide secreted by the hypothalamus that stimulates the production of growth hormone (GH) in the liver and other tissues by binding to its receptor. However, GHRH and its specific receptor are expressed not only in the pituitary gland, but also in other peripheral tissues[1]. GHRH regulates the secretion of GH and directly binds to the GHRH receptor on cells in peripheral tissues to promote cell proliferation. In addition, GHRH has anti-inflammatory effects; thus, GHRH agonists have been investigated for the treatment of various animal models of diseases, such as experimental myocardial infarction, vascular calcification, diabetes, and lung injury[2-5]. Prior studies have demonstrated that GHRH receptors are expressed in various ocular tissues, including the cornea, conjunctiva, lens, ciliary body, and retina. Therefore, research on GHRH and its analogs in ophthalmology has drawn growing attention from the medical community. Studies on uveitis, glaucoma, traumatic optic neuropathy, diabetic retinopathy (DR), and optic neuropathy have also been conducted. Among these, the neuroprotective effect of GHRH is of particular interest. Various ophthalmic diseases can lead to optic neuropathy, including glaucoma, ocular trauma, inflammation, and ischemic retinopathy, of which glaucoma is the most common. Optic neuropathy is a prevalent ophthalmic disorder characterized by the degeneration of retinal ganglion cells (RGCs) and their axons, and it is a major contributor to irreversible blindness and visual impairment. The pathogenesis of optic nerve diseases has not been fully clarified. Currently, treatment is mainly symptomatic[6-7], and there is no effective therapeutic modality[8]. In recent years, some researchers have discovered that GHRH not only exerts an anti-inflammatory effect but also has a certain protective impact on RGCs. Therefore, GHRH may offer a new targeted approach for the clinical treatment of ophthalmology-related diseases[9]. This article reviews the latest research on the role of GHRH in ophthalmic diseases, including but not limited to retinal diseases and uveitis.

OVERVIEW OF GHRH

GHRH is a peptide hormone secreted by the hypothalamus. It acts on the anterior pituitary gland, stimulating pituitary cells to secrete GH into the bloodstream, thereby promoting the growth and development of the organism. Similarly, GHRH also plays a crucial physiological role in regulating the

synthesis and secretion of hormones from the anterior pituitary gland in the hypothalamus[10]. GH can directly act on various tissues and organs. It stimulates the liver to produce insulin-like growth factor-1 (IGF-1) and promotes cell division. This forms an important GHRH-GH-IGF-1 neuroendocrine axis in the body[11]. The concentration of GH in the body is regulated by both GHRH and growth inhibitors to maintain human growth, development, and homeostasis[12]. GHRH is not only a neurohormone secreted by the hypothalamus but also a substance that can be produced by tumor cells and normal body cells, including placental cells, periosteal myeloid-derived cells, and germ cells[13-14]. Additionally, GHRH belongs to the secretin superfamily of peptide hormones, and the amino-terminal sequence of 29 amino acids is sufficient for the full biological activity of GHRH.

Owing to the short half-life and low bioactivity of natural GHRH, in recent years, researchers have used molecular biology methods to synthesize a variety of artificial GHRH analogs that have a longer half-life and higher bioactivity than natural GHRH[15-16].

PROTECTIVE MECHANISMS OF GHRH IN OPHTHALMIC DISEASES

Anti-inflammatory Mechanisms Among the intrinsic mechanisms associated with anti-inflammation, GHRH plays an extrapituitary function in regulating inflammatory processes in different organs and diseases[17]; moreover, it also has a physiological role in regulating the synthesis and release of anterior pituitary hormones. Hypothalamic hormones include GHRH, luteinizing hormone-releasing hormone (LHRH), gastrin-releasing peptides (GRP), thyrotropin-releasing hormone (TRH), and growth inhibitors. In addition, the receptors of these hormones, including GHRH receptor (GHRHR), LHRH receptor, GRP receptor, TRH receptor, and growth inhibitory receptor, are also expressed in the hypothalamus[18-19]. Meanwhile, the above receptors are also expressed in a variety of ocular tissues, including the cornea, conjunctiva, lens, ciliary body, and retina[20]. In addition, it has been reported that the GHRHR pathway of the GHRH-GH-IGF-1 axis is involved in the regulation of ocular physiological and pathological processes[21].

It has been reported that after optic nerve injury, subcutaneous administration of the GHRH agonist MR-409 or GHRH antagonist MIA-602 promoted RGC survival, which was related to the increased retinal phosphorylation of protein kinase B (Akt/PKB) by both GHRH agonists and antagonists[22]. Beyond this, the GHRH agonist MR-409 promoted retinal microglia activation, and the GHRH antagonist MIA-602 significantly decreased the expression of inflammation-related genes interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α). Moreover, it has also been reported that GHRH antagonists reduce endotoxin-stimulated GH and IGF-1 elevation and attenuate the inflammatory response by decreasing macrophage and leukocyte infiltration and inhibiting the production of TNF-α and IL-1β[23]. In addition to the above eye-related findings, Leone *et al*[24] constructed a colon cancer mouse model with a GHRH gene knockout. They found that after GHRH knockout, the mice showed a higher disease activity index and more obvious weight loss. The total number of tumors significantly increased, especially that of large-sized tumors located in the distal colon, and the mice showed a higher inflammatory response. Furthermore, it has been suggested that GHRH knockout promotes colon cancer development through an inflammatory mechanism.

Promoting Cell Proliferation and Migration GHRH receptors can be expressed in several extra-hypothalamic tissues, including the heart, lung, kidney, small intestine, pancreas, eye, and mesenchymal stem cells (MSCs)[25]. It has also been reported that GHRH can act on cells expressing GHRH receptors to promote cell proliferation and inhibit apoptosis. For example, GHRH agonists can effectively improve the proliferation and metabolism of pancreatic B cells and promote insulin secretion[26]. In addition, GHRH agonists can also promote the repair of cardiac tissues in acute myocardial infarction model rats, improve cardiac ejection fraction, and reduce the area of myocardial infarction[27]. Meanwhile, Schally *et al*[28] showed that when they were investigating the proliferative effects on tumor cells, the GHRH agonist MR-409 not only increased the proliferative viability of NCIH446 small-cell lung carcinoma, HCC827, NCI-H460 non-small-cell lung carcinoma, and other cancer cell lines, but also stimulated the cell-cycle transition of tumor cells from the G1 to the S phase and reduced apoptosis. In contrast, the GHRH antagonist MIA-602 effectively inhibited tumor cell proliferation and promoted apoptosis.

Because GHRH plays a significant role in stimulating cell proliferation and inhibiting apoptosis, researchers have speculated that this mechanism may be related to the enhancement of the properties and functions of MSCs[29]. MSCs can enhance cellular activity, promote cell proliferation, reduce levels of oxidative stress factors, and down-regulate the expression of apoptotic signaling[30]. MSCs exert therapeutic effects by secreting various cytokines to reduce cellular damage. Prior studies have shown that MSCs can produce a large number of exosomes. These exosomes contain a variety of biological substances, such as proteins, mRNAs, microRNAs, signaling molecules and other biologically active substances. They are released into the corresponding tissues and play a role in damage repair[31]. Recent studies have shown that injecting GHRH agonists into the ischemic hind-limbs of mice can stimulate the proliferation of mouse MSCs and

inhibit apoptosis, thereby enhancing their therapeutic effect on tissue injury in mice[32].

GHRH stimulates MSC proliferation by activating a variety of signaling pathways. First, GHRH promotes the increase of cyclic adenosine monophosphate (cAMP) through the activation of adenylate cyclase and the activation of proteinkinase A (PKA), which in turn increases the Ca^{2+} influx[33]. Second, GHRH and its agonists promote cell proliferation by activating the Janus kinase 2-signal transducer and activator of transcription 3 (JAK2-STAT3) and Rat sarcoma viral oncogene homolog-rapidly accelerated fibrosarcoma kinase-extracellular signal-regulated kinase/mitogen-activated protein kinase (Ras-Raf-ERK/MAPK) signaling pathways[34]. Third, the promotion of cell proliferation and survival by GHRHR may be associated with the activation of the phosphoinositide 3-kinase-Akt/PKB (PI3K-Akt/PKB) signaling pathway[16]. Akt serves as a central regulator of insulin and IGF-1 signaling and promotes the translocation of connexins to the nucleus to enhance the expression of cellular myelocytomatosis oncogene (c-MYC) and vascular endothelial growth factor proteins, thereby regulating cell proliferation in MSCs[35]. The protective mechanisms of GHRH are summarized in Figure 1.

GHRH AND OCULAR DISEASES

GHRH and its receptors are expressed in a variety of ocular tissues. Dubovy *et al*[20] analyzed human post-mortem eyes and confirmed that GHRH is expressed in the human corneal epithelium, corneal endothelium, trabecular meshwork, ciliary body, optic nerve, and neural retina. Their findings suggested the involvement of the GHRH-GHRHR signaling pathway in the mechanisms underlying human ocular pathologies.

GHRH and Diabetic Retinopathy DR is one of the most common and severe complications of diabetes, affecting approximately 30% to 40% of diabetic patients[36]. Studies predict that the number of DR patients will increase from about 103 million in 2020 to 130 million in 2030, and reach 161 million by 2045[37-38]. It is the leading cause of irreversible blindness in diabetic patients. Patients with DR show obvious thinning of the inner retinal layer, including the retinal nerve fiber layer and the ganglion cell layer[39]. Functional assessments show decreased contrast sensitivity, electrophysiological defects, visual field deficits, and impaired pupillary response[40]. Based on the presence of neovascularization in patients with DR, DR can be classified into non-proliferative DR and proliferative DR (PDR). PDR is characterized by the formation of a fibrovascular membrane at the interface between the vitreous and the retina. Recently, it has been found that the levels of GHRH and GH in the vitreous humor and aqueous humor are significantly higher in patients with PDR than those in non-diabetic patients[41]. Additionally,

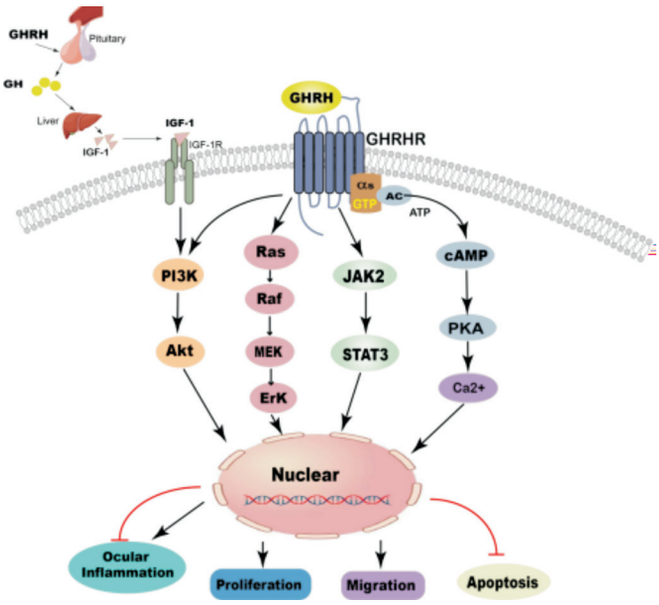

Figure 1 Cellular effects of GHRH analogues GHRH and its agonists can bind to GHRHR on the cell membrane. Signaling pathways activated by GHRH and its agonists include AC/cAMP/PKA, JAK2/STAT3, Ras/Raf/ErK, and PI3K/Akt. Through the mediation of these signaling pathways, anti-inflammatory effects, cell proliferation, cell migration, and anti-apoptosis effects are achieved. GHRH: Growth hormone-releasing hormone; GH: Growth hormone; IGF-1: Insulin-like growth factor-1; GHRHR: Growth hormone-releasing hormone receptor; AC: Adenylate cyclase; cAMP: Cyclic adenosine monophosphate; PKA: Protein kinase A; JAK2: Janus kinase 2; STAT3: Signal transducer and activator of transcription 3; Ras: Rat sarcoma viral oncogene homolog; Raf: Rapidly accelerated fibrosarcoma kinase; ErK: Extracellular signal-regulated kinase; PI3K: Phosphoinositide 3-kinase; AKt: Protein kinase B (PKB). This figure was created by Adobe Illustrator.

in fibrovascular membranes collected from patients with proliferative DR, GHRH and GHRHR were detected in vascular endothelial cells as well as in polymorphonuclear cells, whereas IGF-1 expression was not detected[41]. These findings suggest that GHRH, which has been found to be involved in the development of fibrovascular membranes in proliferative DR, may regulate the disease progression in patients with proliferative DR. However, other researchers reported that in a streptozotocin (STZ)-induced diabetic rat model, the expression of GHRH and GHRHR in the retina was reduced. Treating STZ-induced diabetic rats with the GHRH agonist MR-409 could prevent hyperglycemia-induced morphological changes in the retina, especially preserve the survival of RGCs. Subsequent research has revealed that in the early stage of DR, MR-409 reduces hyperglycemia-induced retinal vascular permeability and exerts a retinal neuroprotective effect by virtue of its antioxidant and anti-inflammatory properties, by downregulating the expression of VEGF, and by increasing the expression of pigment

epithelium-derived factor[42]. These findings imply that, as witnessed in an experimental DR model, retinal disturbances and inflammatory responses may result in the destruction of glial cells[43]. Conversely, in patients with DR, the innate immune system entails intricate individual responses and interactions among multiple systems, including receptor cells, mediators, and complement. Consequently, distinct responses are noted between patients with DR and laboratory models[44].

GHRH and Uveitis GHRH also exerts a regulatory function in uveitis. Uveitis, which is responsible for 10%-15% of blindness cases in developed countries, stands as a major global cause of blindness. It predominantly affects individuals aged between 3 and 60y, with anterior uveitis being the most commonly affected anatomical site[45-46]. Symptomatic patients usually manifest symptoms such as pain, redness, photophobia, and blurred vision, accompanied by conditions like cyclitis, retinal edema, and necrosis[47]. Research on endotoxin-induced anterior uveitis in rat models has demonstrated that GHRHR expression is significantly up-regulated in macrophages, ciliary bodies, and leukocytes[48]. In addition, in ciliary epithelial cells, GHRHR interacts with JAK2 to phosphorylate STAT3, which can generate pro-inflammatory factors that lead to the development of anterior uveitis. It has been suggested that ciliary epithelial cells in anterior uveitis play an immunosurveillance role, which provides a new direction for investigations into anterior uveitis treatment[48]. Therefore, GHRH antagonist, MIA-602, can exert anti-inflammatory effects by inhibiting the GHRHR/JAK2/STAT3 signaling pathway and is considered a potential therapeutic agent for uveitis. Additionally, leukocytes can also play a pro-inflammatory role by increasing the GHRHR expression in the ciliary body and iris. The GHRH antagonist MIA-602 can reduce endotoxin-induced leukocyte infiltration in aqueous humor by inhibiting the secretion of inflammatory cells; thus, it can be speculated that the GHRH signaling pathway may be involved in inflammatory response regulation in anterior uveitis[49]. It has also been shown that the inflammatory response in both the iris and ciliary body involves activating the GHRH signaling pathway, which affects the recruitment of immune cells and the production of pro-inflammatory cytokines and may also be involved in the development of uveitis[21]. Thus, GHRHR modulators have a potential therapeutic role in the treatment of diseases that damage the innate immune system of the retina; however, further in-depth studies are needed to explore their full potential.

GHRH and Glaucoma Glaucoma is also an important disease leading to irreversible blindness, with a prevalence of 3.5% among the global population aged 40–80y[50]. Progressive and irreversible damage to RGCs is a common outcome in all types of glaucoma, where elevated intraocular pressure (IOP) stands as the primary risk factor for the death of RGCs[51]. Moreover, progressive optic nerve damage can still occur even in the absence of abnormal IOP elevation[52]. There have been a few investigations into the role of GHRH in glaucoma. Cen *et al*[9] found that GHRH agonists promoted the survival of RGCs after retinal injury and enhanced retinal nerve cell protection induced by macrophage activation. It has also been suggested that the GHRHR signaling pathway is involved in inflammation-mediated RGC modulation in optic neuropathy. Notably, the GHRH agonist MR-409 protects RGCs from degeneration, which is considered to be a pathogenetic mechanism of glaucoma, and MR-409 is believed to have potential therapeutic value in the treatment of glaucoma[9,42]. Currently, there are not many reports on GHRH in glaucoma. In the future, further exploration should be carried out regarding its effects on IOP regulation, aqueous humor dynamics, optic nerve protection, and hemodynamics.

GHRH and Traumatic Optic Nerve Injury Traumatic optic nerve injury refers to the pathological changes caused by damage to the optic nerve from various reasons. Due to the massive loss of RGCs and their axonal fibers, it usually leads to partial or permanent visual impairment[53]. Its pathological manifestations mainly include optic nerve axon rupture, edema, hemorrhage, microglial activation, and inflammatory response[54]. In the chronic stage, apoptosis of RGCs and optic nerve atrophy occur, accompanied by glial scar formation, resulting in irreversible vision loss[55]. At present, research has been conducted to investigate the mechanisms of nerve repair, inflammatory responses, optic ganglion cell survival, and axonal regeneration after optic nerve injury[56]. It was found that the subcutaneous application of the GHRH agonist MR-409 or antagonist MIA-602 promoted ganglion cell survival. Both MR-409 and MIA-602 activated the PI3K/Akt pathway in the retina after optic nerve crush injury, which may be related to their role in elevating cAMP levels to promote optic nerve repair and optic ganglion cell survival[9]. In studies on human nonpigmented ciliary epithelial cells, GHRHR antagonists reduced lipopolysaccharide (LPS)-induced acute ocular inflammatory responses *via* the STAT3 pathway[48], whereas in the optic nerve injury study, neither the GHRH agonist MR-409 nor antagonist MIA-602 affected the STAT3 pathway in RGCs[9]. In contrast, in mild ocular inflammation caused by lens injury, MR-409 enhanced lens injury-induced macrophage activation, resulting in a protective effect on RGCs, while MIA-602 reduced macrophage activation, resulting in decreased RGCs' survival[9]. Due to the different effects of GHRH on RGCs in various disease models, the role of GHRH in optic nerve injury needs to be further investigated. Table 1 summarizes the effects and potential therapeutic applications of GHRH agonists.

Table 1 The effects and potential therapeutic applications of GHRH agonists

Analog	Code No.	Experimental model	Experimental effects demonstrated	Potential application	References
GHRH agonist	MR-409	Streptozotocin-induced diabetic rat model	1 Maintain the survival of RGCs; 2 Have antioxidant and anti-inflammatory properties; 3 Down-regulate the expression of vascular endothelial growth factor; 4 Increase the expression of pigment epithelium-derived factor; 5 Reduce the retinal vascular permeability induced by hyperglycemia	Treatment of diabetic retinopathy	42
GHRH antagonist	MIA-602	Endotoxin-induced anterior uveitis model in rats.	Inhibit the GHRHR/JAK2/STAT3 signaling pathway to exert anti-inflammatory effects	Treatment of uveitis	48
GHRH antagonist	MIA-602	Lipopolysaccharide-induced ciliary and iris epithelial cell models	Inhibit the inflammation level of epithelial cells	Treatment of uveitis	49
GHRH antagonist	MIA-602	Lipopolysaccharide-induced uveitis rat model	Reduce macrophage/leukocyte infiltration and pro-inflammatory factor secretion in aqueous humor	Treatment of uveitis	21
GHRH agonist	MR-409	Optic nerve crush injury rat model	1 Activate the retinal PI3K/Akt pathway to promote optic nerve repair and the survival of retinal RGCs; 2 Enhance the activation of lens macrophages to produce a protective effect on retinal RGCs	Treatment of glaucoma and optic nerve injury	9

GHRH: Growth hormone-releasing hormone; RGCs: Retinal ganglion cells; PI3K: Phosphoinositide 3-kinase; AKt: Protein kinase B (PKB).

CONCLUSION AND OUTLOOK

This article reviews the latest research progress of GHRH in ophthalmic diseases. Previous studies have shown that GHRH has anti-inflammatory and antioxidant properties. Specifically, it is involved in the occurrence and development of ophthalmic diseases by modulating the inflammatory response and mediating the immune response. In detail, in uveitis, it inhibits the inflammatory response; in DR, it maintains the survival of RGCs and reduces retinal vascular permeability; in glaucoma and optic nerve injury, it promotes optic nerve repair and inhibits the development of RGC damage.

Although basic research shows that GHRH has multiple potential therapeutic effects, there is still a lack of data on its clinical application. For example, the use of GHRH may affect the human endocrine system, disrupt the normal GH secretion rhythm, and further influence metabolism. Its potential regulatory effects on certain signaling pathways may also cause unexpected effects on other physiological processes. Therefore, further research on its safety is necessary. In addition, challenges also arise from the route of administration and dosage. Different administration routes may affect the bioavailability and efficacy of the drug. Moreover, the dosage used in basic research does not necessarily represent the appropriate dosage for clinical treatment. Numerous clinical trials are required to determine these parameters. Moreover, as a potential therapeutic drug, GHRH not only needs to comply with relevant regulatory requirements but also adheres to ethical principles to ensure the rights and safety of patients. Specifically, in terms of clinical efficacy, individual differences should be taken into account. Various factors such as the patient's condition, genetic background, and lifestyle may affect the efficacy of GHRH. These challenges prompt us to conduct further exploration in the future. In basic research, there is a scarcity of studies on the effects of GHRH on cell proliferation and migration in ophthalmic diseases as well as on optic nerve protection, especially research related to optic nerve regeneration. Further in-depth investigations into other signaling pathways that GHRH may regulate and its possible impacts on the interactions between different cell types are required to provide a necessary theoretical basis for exploring new treatment strategies. Clinically, large-scale, multi-center, randomized controlled clinical trials should be carried out. Safety monitoring should be conducted during the trials, and long-term follow-up should be used to evaluate the efficacy. Given that the occurrence and development of ophthalmic diseases involve multiple factors, GHRH may only be one of the therapeutic targets. Exploring the synergistic application of GHRH with other drugs (such as antioxidants and anti-inflammatory drugs) is anticipated to improve the treatment effect. Therefore, studying the interactions between different drugs and the optimal combination regimens can provide more options for clinical treatment.

In conclusion, GHRH agonists or antagonists may serve as potential therapeutic strategies for patients with ophthalmic diseases, including DR, uveitis, glaucoma, and traumatic optic nerve injury. This can offer new treatment alternatives for patients and enhance their quality of life.

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