Growth hormone-releasing hormone (GHRH) is produced by the hypothalamus and stimulates growth hormone synthesis and release in the anterior pituitary gland. In addition, GHRH is an important regulator of cellular functions in many cells and organs. Expression of GHRH G-Protein Coupled Receptor (GHRHR) has been demonstrated in different peripheral tissues and cell types, including pancreatic islets. Among the peripheral activities, recent studies demonstrate a novel ability of GHRH analogs to increase and preserve insulin secretion by beta-cells in isolated pancreatic islets, which makes them potentially useful for diabetes treatment. This review considers the role of GHRHR in the beta-cell and addresses the unique engineered GHRH agonists and antagonists for treatment of type 2 diabetes mellitus. We discuss the similarity of signaling pathways activated by GHRHR in pituitary somatotrophs and in pancreatic beta-cells and possible ways as to how the GHRHR pathway can interact with glucose and other secretagogues to stimulate insulin secretion. We also consider the hypothesis that novel GHRHR agonists can improve glucose metabolism in Type 2 diabetes by preserving the function and survival of pancreatic beta-cells. Wound healing and cardioprotective action with new GHRH agonists suggest that they may prove useful in ameliorating certain diabetic complications. These findings highlight the future potential therapeutic effectiveness of modulators of GHRHR activity for the development of new therapeutic approaches in diabetes and its complications.

Keywords: diabetic complications, GLP-1, islet, insulin, pancreatic beta-cell

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is an important metabolic disease affecting almost 30 million Americans with an estimated $250 billion lost yearly, due to effects of morbidity and mortality on total medical costs and lost wages. T2DM is associated with a progressive decline in insulin secretion by pancreatic beta-cells in the face of insulin resistance (1). Despite its importance, we do not fully understand the complex interplay of molecular signals and signal transduction events.
that control beta-cell functionality and survival. This limits our ability to develop novel approaches for prevention and treatment of diabetes.

The beta-cell membrane contains a profusion of G-protein coupled receptors (GPCRs) that are critical for the regulation of insulin secretion by hormones and neurotransmitters (2–4). Growth hormone-releasing hormone (GHRH) is an important regulator not only of growth hormone secretion but also of a variety of cellular functions in many cells and organs. Expression of GHRH G-protein coupled receptor (GHRHR) has been demonstrated in different peripheral tissues and cell types, including pancreatic islets (5, 6).

Recent studies demonstrate a novel ability of GHRH analogs to increase and preserve insulin secretion by beta-cells in islets and diabetic mice (7, 8) that makes them potentially useful for treatment of T2DM. Remarkable results from the study of new GHRH agonists in wound healing and cardiovascular performance could also provide novel treatments in patients with diabetes (5, 7, 9). This review addresses the possible role of GHRHR and its unique engineered agonists and antagonists for treating diabetes and its complications.

GHRH AND ITS ANALOGS

Hypothalamic growth hormone-releasing hormone is one of the “humoral factors” that is critical for growth hormone secretion. The discovery of hypothalamic hormones, such as thyrotropin-releasing hormone, luteinizing hormone-releasing hormone (also known as gonadotropin-releasing hormone), which regulate the secretion of anterior pituitary hormones led to the awarding of the Nobel Prize (1977) to one of us (Andrew V. Schally) (10). GHRH, expressed in the arcuate nucleus of the hypothalamus and released into portal vasculature, directly stimulates growth hormone synthesis and secretion from the pituitary somatotropes by activating the corresponding GHRH receptors (5, 11). GHRHR is present in several other tissues, such as myocardium, lymphocytes, testes, ovaries, skin, and pancreas and is involved in a variety of biological processes (5). The roles of GHRHR in other cells and tissues continue to be explored. In addition, GHRHR have been detected in various tumor cells and in some stem cells (5, 6).

It should be noted that GHRH undergoes rapid enzymatic degradation in blood. Dipeptidylpeptidase IV inactivates the active form of GHRH in blood to its more stable inactive metabolite GHRH(3-44)-NH2 (12, 13). For this reason, concentration of active GHRH (that is produced in the hypothalamus) in blood may be insignificant, and so without significant influence on organs beyond the pituitary somatotropes. Interestingly, inhibitors to dipeptidylpeptidase IV are in widespread use now for type 2 diabetes treatment to increase GLP-1 concentration in blood (14). These agents should also lead to increased GHRH blood concentration. However, this interesting possibility and the effect of GHRH on various target tissues where the GHRHR is expressed have not been investigated.

Accumulating evidence also suggests that, in addition to the neuroendocrine action of GHRH, extrahypothalamic GHRH has been implicated in many peripheral actions via autocrine/paracrine mechanisms. Exogenous GHRH can regulate proliferation, survival, apoptosis, and differentiation in several tissues and cell types (5, 15).

The GHRHR is a member of the class II B GPCR family, which couples predominantly to the Gs-adenylate cyclase-cAMP signaling pathway. Peptide hormones that activate class II GPCRs include GHRH, secretin, glucagon-like peptides, gastrin-inhibitory peptide (GIP), pituitary adenylate cyclase-activating peptide, corticotropin-releasing hormone, vasoactive intestinal peptide, parathyroid hormone, and calcitonin-related peptides (16, 17).

The mechanism of the acute action of GHRH on the pituitary somatotrope to increase growth hormone synthesis and secretion has been studied (Figure 1). Binding of GHRH to its receptor activates a stimulatory G protein, which activates adenyl cyclase to produce cAMP, leading to activation of protein kinase A (PKA). This stimulates an influx of calcium, most likely through plasma membrane depolarization, and activation of voltage-sensitive Ca2+ channels. Increased Ca2+ and cAMP stimulate the growth hormone exocytosis process (18–21). For example, forskolin (adenylate cyclase activator) increases Ca2+ influx in somatotrophs, and inhibition of phosphodiesterase increases the electrical activity of somatotrophs confirming the relevance of cAMP in GHRH action (22). Regulated secretion of growth hormone involves movement of secretory vesicles along microtubules, transient “docking” in the cell membrane, and subsequent release of vesicles (21).

In pituitary somatotrophs, upon binding of the ligand GHRH to the GHRHR, the activated second messengers include not only the adenylate cyclase–cAMP–PKA and Ca2+-calmodulin but also inositol phosphate–diacylglycerol–protein kinase C (PKC), L-type calcium channels, and arachidonic acid–eicosanoic pathways as well, these ultimately result in the stimulation of growth hormone production and secretion (23–25). Increased cAMP also stimulates PKA to activate the cAMP response element-binding protein (CREB), which stimulates GHRHR gene transcription.

![](https://example.com/image1.png)

**FIGURE 1** | Mechanism of the action of GHRH on Ca2+ and K+ channels: coupling with protein kinase A (PKA) and protein kinase C (PKC) systems. This diagram illustrates the coupling of the Ca2+ and K+ channels with GHRH receptors. cAMP-PKA system mediates the action of GHRH on voltage-gated Ca2+ currents, and the PKC system is essential for the action of GHRH on voltage-gated K+ currents in somatotropes. AC, adenyl cyclase; PLC, phospholipase C. Reprinted by permission from Macmillian Publishers Ltd., from Ref (23), Figure 11.
It is also likely that GHRH function relates to the ability to stimulate somatotroph cell proliferation. The activation of MAP kinase and ERK phosphorylation has been observed in the pituitary in a cAMP/PKA/PKC-dependent manner (26, 27). Alternatively, GHRH can stimulate the Ras/MAPK via βγ-subunits, to promote cell growth (26). In the myocardium, GHRHR-mediated inhibition of apoptosis involves modulation of ERK1 and ERK2 and PI3K-Akt signaling because ERK1/2- and PI3K/Akt-specific inhibitors abolished these effects (28).

Numerous high affinity and high specificity agonists and antagonists of GHRHR have been developed (9, 29–31). There are remarkable results from studies of GHRH agonists for wound healing, cardioprotective action, and protection from multiple types of cancer cells (30, 34, 35).

### EFFECTS OF GHRH AND RELEVANT GHRHR AGONISTS IN PANCREATIC β-CELL AND ISLETS

Insulin is produced by pancreatic β-cells in the islets of Langerhans. GHRH receptors have been described in primary as well as clonal pancreatic β-cells (insulinoma cells) and isolated islets (7, 8, 36, 37). Human GHRH can acutely stimulate insulin secretion from isolated rodent islets and dispersed β-cells (38, 39) and from perfused dog pancreas (40). Intravenous injection of human GHRH to rats increased plasma concentration of insulin being released into the hepatic portal vein (39). In another functional assay, pretreatment with synthetic GHRH analogs improved the engraftment and the metabolic function of islets, following transplantation to streptozotocin (STZ)-induced diabetic mice (36). Pretreatment of rat islets with the GHRH agonist, JI-36, significantly enhanced graft function by improving glucose tolerance and increasing beta-cell insulin reserve in rats (41). Novel high affinity and high specificity agonists of GHRHR improve insulin secretion and preserve β-cells and islets in lethality assays (7, 8). Based on these findings, GHRH and its corresponding receptor hold promising therapeutic potential for improving β-cell function and possibly treating T2DM.

Interestingly, the discovery of GHRH was due in part to the recognition of ectopic GHRH secretion from human pancreatic islet tumors causing ectopic acromegaly (42–45). GHRH was, thus, found in human pancreatic tumor tissue extracts, leading to its structural elucidation (44). These data suggest that perhaps GHRH is expressed at low levels by pancreatic islet cells and possibly during development also at low levels. This suggests that GHRH may be part of a paracrine system in islets, but this possibility has not yet been investigated. It is also possible that the GHRHR exerts an influence on cell function even without receptor activation through some tonic receptor function.

Despite these advances, the details of GHRHR expression, signaling pathways, and function in pancreatic islet cells have not been fully elucidated. We will consider the possible mechanisms of regulation of insulin secretion as well as mechanisms relating to beta-cell proliferation to evaluate the possible roles of GHRHR activation.

The primary role of pancreatic β-cells is to regulate metabolism by sensing changes in blood glucose concentration and responding by secreting precisely regulated amounts of insulin. The action of hormones and neurotransmitters contribute to such signaling and amplify the glucose-stimulated insulin secretion (GSIS) (46) (Figure 2). GSIS is Ca2+-dependent and is regulated by metabolic signals generated by glucose catabolism. Glucose-dependent signal transduction begins with uptake of glucose into beta-cells via the GLUT2 transporter. Cytoplasmic glucose molecules are rapidly phosphorylated by glucokinase and converted to pyruvate in the cytosol via the glycolytic pathway, then oxidized within the mitochondria via the tricarboxylic acid cycle and oxidative phosphorylation pathways, respectively. Glucose catabolism generates ATP. The membrane potential of beta-cells is controlled by KATP channels. Under basal conditions, sufficient KATP channels are open so that the plasma membrane is hyperpolarized. Blocking KATP channels by an ATP-dependent mechanism initiates plasma membrane depolarization that opens voltage-gated Ca2+ channels; Ca2+ enters the beta-cell from the extracellular milieu through of these channels and increases cytoplasmic Ca2+. Glucose-induced increases in cytoplasmic Ca2+ and insulin secretion are directly correlated (46, 47).
The beta-cell membrane contains a profusion of GPCRs that are implicated in regulation of insulin secretion by hormones and neurotransmitters. GPCRs may have complimentary or antagonistic actions on insulin secretion (2–4). For example, a stimulation of insulin secretion by food begins with a “cephalic” phase due to sensory stimulation by sight and taste of food. This is largely mediated by the release of acetylcholine from nerves innervating pancreatic islets. The subsequent cholinergic stimulation via the muscarinic (acetylcholine) GPCR leads to an activation of the phospholipase C (PLC) pathway (48, 49).

Incretin hormones also play a critical role in insulin secretory response following meal ingestion. These hormones have significant influence on GSIS primarily through activation of the cAMP pathway that also leads to plasma membrane depolarization and an increase in cytoplasmic Ca^{2+} (50, 51). For example, glucagon-like peptide I (GLP-1) is one such potent incretin hormone activating the Gs-adenylate cyclase-cAMP signaling pathway, that is, this mechanism can be identical to that of GHRHR in somatotroph cells (see Figures 1 and 2). Interestingly, GHRHR agonists significantly increased the levels of cellular cAMP in rat beta-cell line (INS-1) (7). For this reason, it is reasonable to conclude that GHRHR agonists also employ a cAMP-based signaling mechanism and, therefore, they would have beneficial effects on insulin secretion and beta-cell survival (7). There is also a possibility that activation of cAMP pathway can lead to an increase in cytoplasmic Ca^{2+} concentration that can activate PLC and correspondingly activate this pathway [see, for example, Ref. (4)].

Interestingly, activation of the cAMP pathway in beta-cells by the incretin hormones leads to increased insulin secretion in part due to plasma membrane depolarization and an increase in cytoplasmic Ca^{2+} [for review see Ref. (4, 52)]. Mechanisms by which GHRHR increases growth hormone-release also include plasma membrane depolarization and an increase in cytoplasmic Ca^{2+} (see above) that also point to significant similarities between the mechanisms of GLP-1 in beta-cells and the mechanisms of GHRHR in the pituitary somatotropes.

Activation of GHRH receptors may also lead to activation of gene transcription, proliferation, and survival in beta-cells. For example, the mechanisms of beta-cell proliferation and survival include ERK and Akt signaling pathways (53). GHRHR agonists activate these pathways in various cell types (see above). Experiments in rat insulinoma cells (INS-1) showed that the GHRH agonist MR-409 significantly increased cell proliferation and induced activation of ERK and Akt pathways (7).

GHRH G-protein coupled receptor agonists significantly increased the levels of the phosphorylation of CREB in rat beta-cell line (INS-1) (7) as well as in somatotrophs, where GHRH agonists can stimulate growth hormone gene transcription (see above). This may also be similar to one of the mechanisms of GLP-1. GLP-1 has also been shown to promote beta-cell proliferation and survival in rodents by activating ERK and Akt pathways (50). CAMP induced by GLP-1 caused elevated phosphorylation of CREB/activating-transcription-factor-1 in insulin-secreting beta-cells (54). However, the exact mode(s) of GHRHR signaling in the pancreatic islets and the most important mechanisms of stimulation of insulin secretion and/or beta-cell survival are unknown.

Causal interrelationships between GHRHR agonists and the variety of GPCRs in beta-cells and the role of such networks in insulin secretion are unknown. We have recently employed our general beta-cell mathematical modeling approach for beta-cell GPCRs for a comparison of action of GPCRs for GLP-1 and GIP (4). Both of them couple predominantly to the Gs-adenylate cyclase-cAMP signaling pathway. Based on those models, we suggest that GHRHR agonists can have a similar role as GIP in its interaction with GLP-1. In this case, GHRHR agonists can act in a competitive manner with GLP-1 in their mechanisms of stimulating insulin secretion. This testable hypothesis remains to be directly demonstrated.

There are several possible ways as to how pancreatic beta-cell GHRH signaling can have implications in T2DM treatment. One of the root causes of T2DM is the altered signaling system in beta-cells, which leads to decreased insulin production and exocytosis. Our previous published data and that of several other groups suggest that some signaling systems in insulin-secreting cells are damaged or attenuated in diabetic states. “Diabetic conditions” – such as hyperglycemia and hyperlipidemia – can lead to the loss of the GLP-1 receptor (GLP-1R) from the cell surface and, thereby, impair GLP-1 signaling, which may underlie the reduced clinical efficacy of GLP-1R activators (50, 51). GHRHR agonists can have beneficial effects under these conditions since these agonists activate the same cAMP pathway as GLP-1R, assuming the GHRHR is not also downregulated. Therefore, we can hypothesize that glycemic insensitivity to GLP-1R agonists in T2DM can be improved by simultaneous or sequential application of GHRHR agonists, thus replacing a possible deficit of GLP-1R.

Ex vivo treatment of isolated islets with GHRHR agonists may also improve results of islet transplantation in animal models. Preconditioning of encapsulated pancreatic islets with GHRHR agonists significantly enhanced graft function by improving glucose tolerance and increasing beta-cell insulin reserve in diabetic rats (41). This effect is of sufficient interest to further examine it in human islet transplantation.

Interestingly, GHRH stimulated and GHRH antagonist inhibited the expression of the major antioxidant enzymes in the LNCaP human prostate cancer line (55). Additional expression of the major antioxidant enzymes may have additional benefits in T2DM (56) as well as T1D (57), and this may be another potentially beneficial effect of GHRHR agonists in both major types of diabetes.

Based on these studies, we suggest that GHRHR analogs have the potential to enhance beta-cell function, proliferation, and survival in vivo. Further studies with human islets and beta-cells will help determine if the GHRHR expression levels and signaling systems are similar in human and rodent models.
DIABETES AND ACTIVITY OF GHRH BEYOND BETA-CELLS

Remarkable results from the study of new GHRH agonists in wound healing and cardiovascular performance could also suggest novel treatments in patients with diabetes or perhaps help understand the pathways involved (5, 7, 9). GHRHR antagonists may target certain complications of diabetes, especially in Type 1 diabetes and insulin-dependent T2DM, where insulin production by the beta-cell is at least clinically insignificant. For example, GHRH antagonism may improve some of the lipid, renal, and vascular complications of low insulin-associated diabetes (58). Another potential target for GHRH antagonists could be diabetic retinopathy, which is the main cause of blindness in patients with diabetes and diabetic nephropathy (glomerulosclerosis) (30). Despite remarkable advances in treatment and prevention of these complications, they are still dramatic components of the long-term costs of diabetes.

Gastrointestinal effects are also complications of diabetes. There was upregulation of GHRHR expression in intestinal cells in a mouse model of type 2 diabetes (58). Treatment with the GHRHR antagonist, MIA-602, interfered with GLP-1-dependent diabetes-related dyslipidemia in mice. It also decreased the plasma levels of GLP-1, glucagon, and TRL in these mice (58), which might lead to worsening of diabetes rather than improvement. Cross-talk between the GHRHR antagonist and acetylcholine signaling (M3 receptor) was observed in the aorta, where MIA-602 prevented the diabetes-related block of carbachol-mediated vasodilation (58).

Interestingly, human GHRH can reduce glucagon release from isolated mouse islets (39). We can explain this by the increased insulin secretion that suppresses glucagon secretion in this case [see, for example, Ref. (60)]. However, enhanced glucagon secretion by islet cells in diabetes was also lowered by application of antagonist MIA-602 (58). The decreased glucagon secretion in this case can be explained by cAMP decrease in alpha cells [see, for example, Ref. (60)] through blocking the corresponding GHRH receptor when insulin secretion is insignificant in islets from diabetic animals or humans. Decreased glucagon release by GHRHR antagonists could have a beneficial effect in diabetes through decreasing hepatic glucose production and perhaps decreasing ketogenesis (59, 61).

CONCLUSION

This review of recent data with GHRH agonists shows them to be capable of acutely increasing insulin secretion and enhancing rodent beta-cell proliferation and survival, when administered systemically. On the other hand, the modulators of GHRHR activity may be useful in ameliorating certain complications of diabetes. Studies are currently ongoing to determine the dose and treatment regimes of GHRHR modulators for the treatment of other diseases. The results demonstrate a clear connection of GHRH and its receptor with glucose metabolism and pancreatic beta-cell function. We believe that there is a sound basis for further studies evaluating GHRH agonists and/or antagonists as promising therapeutic agents for diabetes and its complications.

AUTHOR CONTRIBUTIONS

LF, NT, AS, and LP reviewed the literature, designed the work, and, together, wrote and edited the paper.

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