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Growth Hormone Releasing Hormone Receptors Antagonists and Cancers: Do GHRH-R Antagonists Play a Role in the Management of Prostate Cancer?

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Abstract

Growth hormone-releasing hormone (GHRH) and its receptors have been implicated in the progression of various tumors such as those of the prostate. Treatment modalities for prostate cancer in a localized stage or when it is still castration-sensitive yield good results in most patients. However, such treatments are only palliative in the advanced stage. Therefore, new therapeutic targets like growth hormone-releasing hormone receptor (GHRH-R) and its splice variants should be found in order to get effective treatments for more aggressive stages in prostate cancer. This review talks about the GHRH-R and its splice variants, the signaling pathways induced by GHRH to produce cancer, the structure activity relationship of GHRH-R antagonists and the resume of some *in vitro* and *in vivo* studies on the role of GHRH-R antagonists in the treatment of prostate cancer.

Keywords

GHRH, Receptors, Antagonists, Prostate, Cancer

1. Introduction

In spite of the impressive progress in diagnosis, surgery, and chemotherapy, prostate cancer is still the second most common cancer and the fourth leading cause of cancer death among men in China [1]. Considering the disadvantages of standard treatments for prostate cancer in their late stage, it's crucial to ex-

plore new therapeutic strategies for advanced prostate cancer with less or no side-effects and to substitute the palliative treatment. In addition to its endocrine role, the GHRH has been shown to act as a growth factor driving the progress of cancer in diverse malignancies including prostate cancer [2]. Therefore, the molecular changes in prostate carcinogenesis induced by GHRH make GHRH-R and its splice variants (**Figure 1**) therapeutic targets for patients with advanced prostate cancer.

2. GHRH-R and Its Splices Variants in Human Prostate Cancers

Besides the pituitary type of GHRH-R, some studies have described GHRH-R splice variants (SVs) in human prostate cancers [3] [4]. From these studies we noted that SV1 is present in 65% of the human prostate cancers. A major part of the nucleotide sequence of SV1 has more than 99% identity with the corresponding sequence of pituitary GHRH-R cDNA [5]. SV2 is shown in 60% of prostate cancer specimens. SV2 most likely encodes a GHRH receptor isoform truncated after the second transmembrane domain [5]. The deduced protein sequences of SV1 and SV2 suggest that they possess a distinct 25-amino acid sequence at the N-terminal extracellular domain, which could serve as a signal peptide. The expression of SV4 is about 15%. The short protein sequence corresponding to SV4 lacks all transmembrane domains, implying that it is not expressed on the cell surface. After PCR amplification, it has been detected a novel SV of GHRH receptor in prostate cancer in which exons 5 and 6 are missing, whereas exon 7 is retained [5].

GHRH receptor isoform encoded by SV1 could mediate the effect of GHRH and its antagonists on extrapituitary cells and various tumors [4]. These SVs forms have demonstrated both ligand-dependent and independent activities [2] [6].

3. Physiological Action of GHRH as a Protumoral Agent

Pituitary type GHRH receptor (pGHRH-R), is a class II G-protein-coupled receptor with seven transmembrane domains and is homologous with the receptors for vasoactive intestinal peptide (VIP), pituitary adenylate cyclase activating peptide (PACAP) and calcitonin [7]. Activation of the G-protein complex stimulates adenyl cyclase, which results in the conversion of ATP to cAMP. cAMP, functioning as second messenger in the GHRH signal transduction, induces phosphorylation of intracellular and membrane-associated proteins and leads to IGF-I secretion (a known mitogen) from the liver [8]. At the level of the mechanism of GHRH action, it is important to identify the specific receptors in which the local effects of GHRH are mediated and to define the network of the proliferative and non-proliferative consequences of GHRH action. The elucidation of the downstream targets that follow receptor binding and activation will shed light on how GHRH exerts its mitogenic effects. The stage of tumorigenesis with which GHRH production is associated, being briefly the initiation, promotion and maintenance of cancer, also remain an open question.

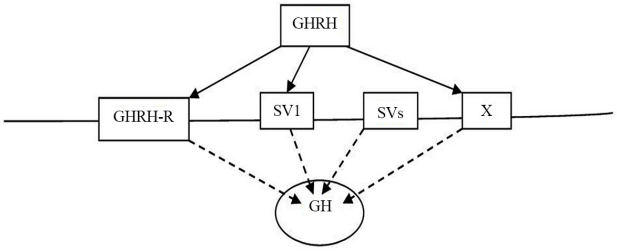

Figure 1. Representation of the action of GHRH. The effects of GHRH are mediated by GHRH-R, SV1, and probably others receptors (X), which may include the receptors of VIP and PACAP.

4. Pathological Action of GHRH: Signaling Pathways Involved in Tumoral Process

As a ligand-bound G-protein coupled receptors, GHRH can activate cytoplasmic heterotrimeric G-proteins whose α subunit responds by exchanging its GDP for GTP. The Gα subunit activates its own effectors, including the *Ras-Raf-MEK-ERK* pathway also called *MAPKs* pathway, the *Ras-PI3K-Akt* pathway, the *Jak/STATs* pathway. All these pathways are linked to cell differentiation, proliferation, metabolic changes and cell migration [9]. It is known that G-protein coupled receptors are able to activate tyrosine kinase receptors [10]. So GHRH is also involved in the transactivation of the signaling of epidermal growth factor receptor (EGFR/HER1/ErbB1) and human epidermal growth factor receptor-2 (HER2) in prostate cancer [11].

In the figure (**Figure 2**), GHRH can bind directly to GHRH-Rs on multiple cell types of endocrine and nonendocrine origin. Signaling pathways that are activated by GHRH and its agonists include AC/cAMP/PKA, Ras/Raf/ERK, PI3K/Akt, and STAT3. Mediation through these signaling pathways leads to enhanced cell survival, proliferation, and secretion of cytokines. GHRH antagonists inhibit these pathways by competitively binding to the GHRH-R.

5. GHRH-R Antagonists

GHRH-R has been considered as a potential therapeutic target for cancer in recent years. Several GHRH-R antagonists have been used experimentally against cancers; the theory of using GHRH-R antagonists is suggested to be discussed. We can enumerate some GHRH-R antagonists: earlier GHRH-R antagonists (MZ-4-71 and MZ-5-156), JV-1-series (38, 63, 65, 68, 80), MZ-J-7-series (114, 118, 138 and 132) and the MIAMI-series (602, 604, 606, 610, 640 and 690). JV-1-63 is one of the more potent endocrine antagonist of GHRH reported to date again human prostatic growth [12]. The theory of using GHRH-R antagonists is suggested to be discussed.

5.1. Structure Activity Relationship of GHRH-R Antagonists

Early studies revealed that replacement of Ala^2 in GHRH by $D\text{-}Ala^2$ or $N\text{-}methyl\text{-}D\text{-}Ala^2$ lad to superpotent agonist while the replacement by $D\text{-}Arg^2$

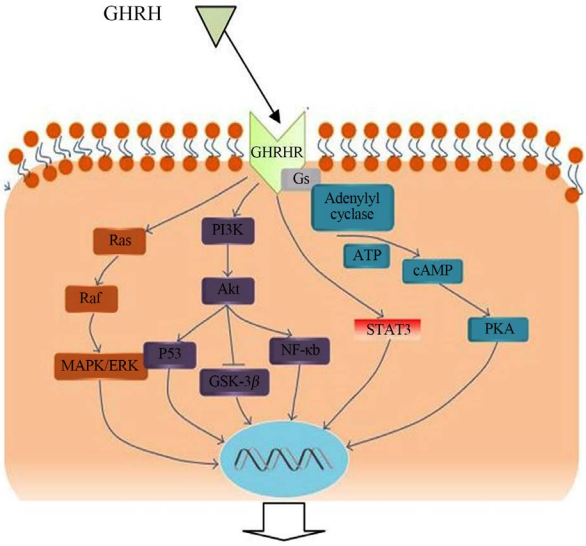

Figure 2. Schematic illustration of pathological activity of GHRH.

produce antagonists [13]. Chemical modifications tend to increase the selectivity of new series of GHRH-R antagonists because they exhibit increased antitumor effects *in vivo* on human experimental prostatic cancer but weaker endocrine effects on the inhibition of hepatic IGF-1 in serum as compared to earlier antagonists such as MZ-4-71 or MZ-5-156 [14] [15] [16] [17].

More than 20% of pharmaceuticals now contain one or more fluorine atoms [18]. The novel analogs designated "MIA" have been designed by incorporating *pentafluoro-Phe* at different positions into the previous MZ-J-7-series and the JMR-132 antagonist. This resulted to an increased anti-cancer activity compared to earlier JV-series. It has been recognized that the presence of fluorine in compounds results in metabolic stability [19] leading to improved bioactivity and bioavailability [20].

5.2. GHRH-R Antagonists Effects in Prostate Cancer

The anti-tumor effects of GHRH antagonists can be mediated through direct mechanisms. One of these mechanisms is based upon the inhibition of the secretion of autocrine/paracrine IGF-I or IGF-II from the tumors; the most important pathway involves the blockade of action of autocrine GHRH in tumors. The anti-tumor activity of GHRH antagonists is especially important oncologically because of the wide expression of the intrinsic GHRH and SVs of GHRH-R in various cancers. We can share some results of recent studies:

1) In a study carried by Nektarios Barabutis and Andrew Schally (2008) on the inhibition of human cancer cell line by knocking down gene expression for GHRH, they found that of In this study, the proliferation rate of prostate cancer cell lines (LNCap) were decreased by 26% - 37% and 31 - 42% after exposure to GHRH-R antagonists MZ-4-71, MZ-5-156 and JMR-132 at concentration of 0.1 and 1 μM respectively [21];

2) In a study carried on nude mice with objective the inhibition of the orthotopic and metastatic growth of PC-3 human androgen-independent prostate cancers by GHRH-R antagonists (MZ-4-71 and MZ-5-156), bombesin and gastrin releasing peptide; Anton Stangelberger *et al.* (2005) found that the growth of subcutaneous xenografts of human androgen independent PC-3 prostate cancers was inhibited by high dose (20 μg b.i.d.) of MZ-4-71 and MZ-5-156 or much lower dose (2.5 - 5 μg/day) of new and more potent antagonists MZ-J-7-118 and MZ-J-7-138 [14] [17]. GHRH-R antagonists also inhibited the orthotopic growth of PC3 tumors [17];

3) Andrew Schally *et al.* in these studies found that, given alone, GHRH antagonists JV-1-38 (20 μg/day) or MZ-J-7-118 (5 μg/day) were ineffective for the treatment of prostate cancers LNCaP and MDA-PCa-2b, but they greatly enhanced the inhibitory effects of androgen deprivation therapies such as surgical castration and LHRH agonists or antagonists on the growth of subcutaneous and orthotopic prostate tumor [22] [23] [24];

4) Kanashiro *et al.* in three studies demonstrated that GHRH-R antagonists inhibit the *PKC-MAPKs* and *PI3K-Akt* signaling pathways, decrease the expression of *cjun* and *c-fos* oncogenes, and mutant *p*53 protein levels in human prostate cancer models [25] [26] [27]. In addition GHRH-R antagonists decrease anti apoptotic *Bcl*-2 and increase pro apoptotic *Bax* protein in the prostate cancer line LNCaP. They trigger a Ca^{2+} dependent apoptotic mechanism;

5) Laura Muñoz-Moreno *et al.* (2016) found in this study that, GHRH-R antagonists JMR-132 and JV-1-38 suppressed cell proliferation and decreased the levels of the proliferation marker, PCNA, in the three cell lines (non-tumoral RWPE-1 and tumoral LNCaP and PC3 human prostatic epithelial cells) and in PC3 tumor. They led to an increase of cells in S-phase and a decrease in G1 and G2/M phases, and induced S-phase arrest and significant increase ($p < 0.001$ vs. control) of apoptotic cells like p53, p21 and bax [28];

6) In a study carried by Nektarios Barabutis and Andrew Schally (2008) on the antioxidant activity of growth hormone-releasing hormone antagonists in LNCaP human prostate cancer line, they found that GHRH antagonist, JMR-132, inhibited the expression of the major antioxidant enzymes (GPx1, SOD1, NQO1, and Trx1), as well as the expression of COX 2 and cytochrome c oxidase IV, which are enzymes involved in the generation of ROS. It also suppressed lipid and protein oxidative stress markers, as well as the intracellular generation of ROS. They also noted that the activation of the NF-ƙB p50, which promotes carcinogenesis, is enhanced by oxidative stress and cells exposed to JMR-132 expressed lower levels of pNF-ƙB [29];

7) This study carried by Laura Muñoz-Moreno *et al.* (2018) was performed in three human prostate cell lines (RWPE-1, LNCaP and PC3). In this study, GHRH-R antagonists (MIA-602, MIA-606, and MIA-690) decreased cell viability and provoked a reduction in proliferation in LNCaP and PC3 cells. They reduced *β*-catenin levels in the nucleus preventing the activation of transcription

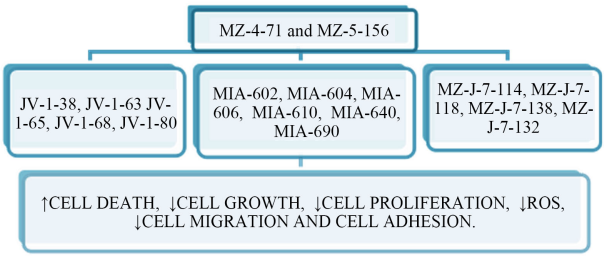

Figure 3. Pictorial representation of GHRH-R antagonist's activities.

of target genes, *c-myc*, *cyclin D*1, and *CD*44 with the highest value with MIA-690 in PC3 cells. VEGF (vascular endothelial growth factor) which is related to molecules involved in migration and adhesion as β-catenin or MMPs 9 and 2 (matrix metallopeptidase) protein levels were decreased by 31% after treatment with MIA-602, MIA-606, and MIA-690 as compared to control (β-actin antibody) [30].

Figure 3 summarizes the effects of GHRH receptor antagonists. The synthesis of the new series of GHRH receptor antagonists comes from chemical modifications of the first two molecules (MZ-4-71 and MZ-5-156). The new series thus present a more pronounced anticancer activity.

6. Conclusion

According to current existing literature, GHRH-R antagonists could be defined as inhibitors of tumor progression in prostate cancer and should be considered for use in future therapeutic strategies. Our review supports the merit of development of GHRH-R antagonists for the clinical therapy of prostate cancer. We think that other signal transduction mechanisms arise from those mediated by cAMP may also mediate the effect of GHRH, so combination therapies that target all the pathways involved in the pathogenesis of prostate cancer should increase the efficacy of future. An example could be the use of GHRH-R antagonists in association with a monoclonal antibody that target the EGFR.

Authors' Contributions

All the authors read and approved the final version of the manuscript.

Funding

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Availability of Data and Materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

GHRH-R: Growth hormone releasing hormone receptors;
cAMP: cyclic Adenosine monophosphate;
VIP: Vasoactive intestinal peptide;
PACAP: Pituitary adenylate cyclase activating peptide;
IGF-1: Insulin-like growth factor 1;
CDKN2: Cyclin dependent kinase inhibitor 2;
ERK: Extracellular signal-regulated kinase;
MAPKs: Mitogen-activated protein kinases;
Jak: Janus activated kinase;
STATs: Signal transducers and activators of transcription;
EGFR: Epidermal growth factor receptor;
HER: Human epidermal growth factor receptor;
PCR: Polymerase chain reaction;
ROS: Oxygen reactive species