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GAVIN PUBLISHERS

Journal of Pharmaceutical and Pharmacological Sciences

Mini Review

Zheng L. J Pharma Pharma Sci 03: JPPS-174.
DOI: 10.29011/2574-7711.100074

Growth Hormone-Releasing Hormone (GHRH): Its Biology and Therapeutic Aspects

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Citation: Zheng L (2018) Growth Hormone-Releasing Hormone (GHRH): Its Biology and Therapeutic Aspects. J Pharma Pharma Sci 03: 174. DOI: 10.29011/2574-7711.100074

Received Date: 01 October, 2018; **Accepted Date:** 15 August, 2018; **Published Date:** 23 August, 2018

Introduction

GHRH, (also known somatocrinin; Growth Hormone Releasing Factor (GRF); Growth hormone releasing hormone (GRH) and somatorelin) is a 44-amino acid peptide which synthesized in arcuate nucleus of the hypothalamus in Central Nervous System (CNS) and subsequently released into hypothalamic-pituitary portal vascular system. By binding with GHRH receptors at anterior pituitary gland, GHRH stimulates synthesis and release of Growth Hormone (GH). After Schally, AV et al made his discoveries concerning the peptide hormone production of the brain [1-3], in 1982, GHRH was isolated and sequenced its full length by two groups Rivier, J et al and Guillemin, R et al. from two pancreatic tumors patients beared with acromegaly [4,5], All these discoveries made GHRH knowledge more rapidly acquired by scientists in the following decades. The important roles GHRH played in different biological process, such as energetic metabolism [6], cancer initiation and progression [7], sleep process [8], pituitary hypoplasia and dwarfism [9], also gradually recognized by researchers.

Mayo KE. et al. mapped the first GHRH gene to chromosome 20 and reported it is synthesized as 108 amino-acid preproGHRH. After processed by unknown proteinases in two cleavage points (Arg-Arg and Gly-Arg in Figure 1), human pituatory GHRH1-44 was then released, whose biological activity is almost the same as its C-terminal truncated derivatives, which are due to alternative processing in its preproproteins [10,11]. Further studies revealed that removal of C terminal amino acids and its N-terminal molecules from GHRH1-29 will both result in dramatic loss of its GH releasing activity and less rapid degradation rate, suggesting the importance of these amino acids for peptide structure and stability [11]. Up to now, no mutations have been reported regarding the GHRH genes.

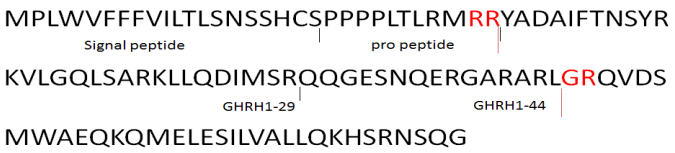

Figure 1: Amino acids sequence of human preproGHRH. Red letters represent possible cleavage sites.

Expression of GHRH has been found in various normal extra-pituitary tissues: ovary, placenta, testis, pancreas, gastrointestinal tract, prostate and immune cells (Figure 2) and biological fluids, such as CSF (human cerebrospinal fluids) and milk [12]. The content of GHRH in the human hypothalamus is vary from 10-250ng/hypothalamus and has a low level in peripheral plasma, but when ectopic GHRH-secreting tumors occurred; the content in plasma will be increased indicating a promising biomarker for diagnosis of specific tumors. The structure of GHRH from several species exhibits almost complete homology except the rats. The GHRH in rats only has 70% homology with humans and 43-amino acids in its full biological activity form. The difference mainly resides in C terminal sequence, which results in decreased biological activity and receptor binding ability.

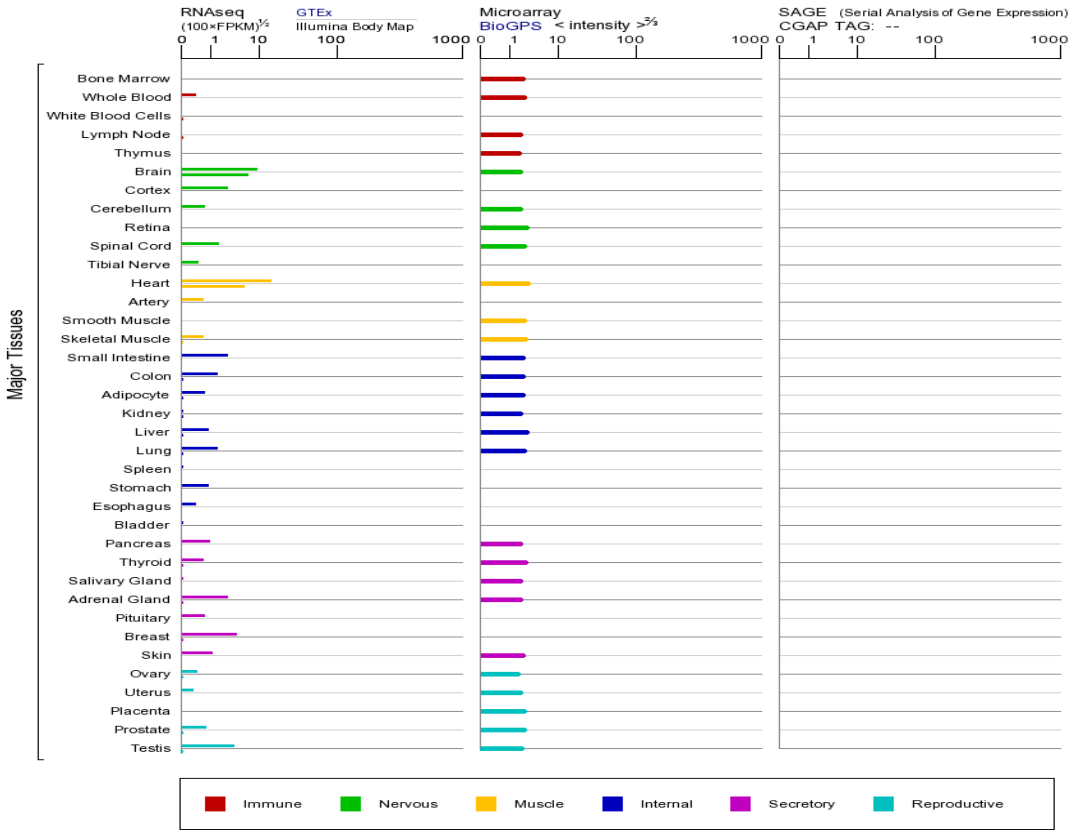

Figure 2: GHRH gene expression of different normal human tissues. (analysis from gene card) Left panel: the results from RNA seq analysis. Middle panel: the results from Microarray analysis. Right panel: the predict results from SAGE (serial analysis of gene expression) analysis.

GHRH exerts its function by binding to GHRH receptors (GHRHRs), which is belonged to the Gs-protein – couple receptors. After binding to GHRHRs, GHRH stimulates the Adenylyl Cyclase (AC) with resulting increase in cAMP levels and activation of proteinase A. Then, with the influx of calcium, GH is released from somatotrophs. It is also reported that by binding with GHRHRs, the down streaming signals are associated with MAPK pathways, STAT3-PAK1 pathways and cell cycle factors [7].

GHRH Therapeutic Aspects

Physiologically, GH deficiency is due to familial GH deficiency (5%-10%), autosomal recessive mutations; and impaired GH response to GHRH. Clinically, the patients with irreversible GH response to GHRH include patients bear with organic pituatory disease, thalassemia or sideroblastic anemia [13] and primary microcephaly [14]. The reason for this is partly due to a decreased somatotroph secretory reserve, decreased pituatory GH stores or a resistance to the action of GHRH, the decreased content iron deposition in the pituatory and mutated PLEKHG2 with impaired actin polymerization. However, the patients with hypothalamic disease and hypothyroidism represent a reversible response of GH to GHRH, and a recovery of this response will always be seen after initiation of treatment with thyroid hormone in patients [13]. Sermorelin, a functional peptide fragment of GHRH, has been used in the diagnosis of deficiencies in growth hormone secretion and measuring GHRH plasma levels therefore provides a precise and cost-effective test for the diagnosis of ectopic acromegaly. At present, it has been clearly demonstrated that GHRH and/or GHS represent reliable tools for the diagnosis of GHD [15,16].

Obesity patients showed a blunted GH response to all CNS-mediated stimuli, and it will be significantly improved by weight loss. For the diabetes patients, agonists of Growth Hormone-Releasing Hormone (GHRH) have been previously reported to promote growth, function, and engraftment of islet cells following transplantation, in 2013, Zhang et al reported that transplantation of rat islets preconditioned in vitro with GHRH agonists and its administration in vivo promoted growth, function, and engraftment of exogenous islets [6], supporting the use of GHRH agonists in type-1 diabetes.

The discovery of local autocrine/paracrine production of GHRH and other cells, directed the research to synthesis of more

potent GHRH antagonists to strongly inhibit the tumor growth with scarce endocrine action. The receptor mediated mehanisms comprise complex and still not completely understood on intracellular pathways that are strictly related to human tumorgenesis. However, it creates a new potential the rapeutic option for various neoplasms [7]. The growing knowledge of mechanisms gives us new ways to its possible applications. Tesamorelin, a GHRH analog, trade name Egrifta, received U.S. Food and Drug Administration approval in 2010 for the treatment of lipodystrophy in HIV patients under highly active antiretroviral therapy [17].

In summary, new understandings have been gained in relation to the pathogenesis with different diseases of GH deficiency and GH excess state, and the use of GHRH and its analogs as diagnostic and therapeutic agents already represents a reality.

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