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Review Article

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Discovery of Ghrelin and Its Physiological Function

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Abstract

The endogenous ligand for growth-hormone secretagogue receptor (GHS-R) was discovered in 1999 from stomach and named it "ghrelin," after a word root ("ghre") in Proto-Indo-European languages meaning "grow", since ghrelin stimulates growth hormone (GH) release from pituitary. In addition, ghrelin stimulates appetite and increases food intake by acting on the hypothalamic arcuate nucleus, a region known to control food intake. Thus, ghrelin plays important roles for maintaining growth hormone release and energy homeostasis in vertebrates. The diverse functions of ghrelin raise the possibility of its clinical application for GH deficiency, eating disorder, gastrointestinal disease, cardiovascular disease, osteoporosis and aging, etc.

Keywords: Ghrelin, acyl-modification, stomach, growth hormone releasing activity, appetite stimulation.

1. Introduction of Ghrelin

Ghrelin, purified from stomach, exerts potent growth hormone releasing and appetite stimulating activities (*Fig. 1*)[1,2]. The name "ghrelin" is based on "ghre", a word root in Proto-Indo-European languages for "grow", in reference to its ability to stimulate GH release. The rat and human ghrelin precursors are both composed of 117 amino acids. In these precursors, the 28-amino-acid active ghrelin sequence immediately follows the signal peptide. Ghrelin is a peptide hormone, in which the serine 3 (Ser3) is n-octanoylated and this modification is essential for ghrelin's activity. An enzyme that catalyzes the acyl-modification of ghrelin has not yet been identified. However, the universal incorporation of n-octanoic acid in mammals, fish, birds, and amphibians suggests that this putative enzyme is rather specific in its choice of medium-chain fatty acid substrates[3].

In all vertebrate species, ghrelin is mainly produced in the stomach. Ghrelin-containing cells in the stomach are more abundant in the fundus than in the pylorus [4]. The X/A-like cells in the oxyntic mucosa contain round, compact, electron-dense granules that are filled with ghrelin. Ghrelin producing cells are also found in the duodenum, jejunum, ileum, colon, pancreas, kidney and placenta [5]. Moreover, ghrelin content of the brain was found to be very low; ghrelin has been found in the hypothalamic arcuate nucleus, an important region for controlling appetite. In addition, a recent study has reported the presence of ghrelin in previously uncharacterized hypothalamic neurons adjacent to the third ventricle between the dorsal, ventral, paraventricular, and arcuate hypothalamic nuclei. These ghrelin-containing neurons send efferent fibers to neurons that contain neuro-peptide Y (NPY) and Agouti-related protein (AgRP) and may stimulate the release of these orexigenic peptides.

RT-PCR analyses demonstrated ghrelin receptor mRNA expression in many peripheral

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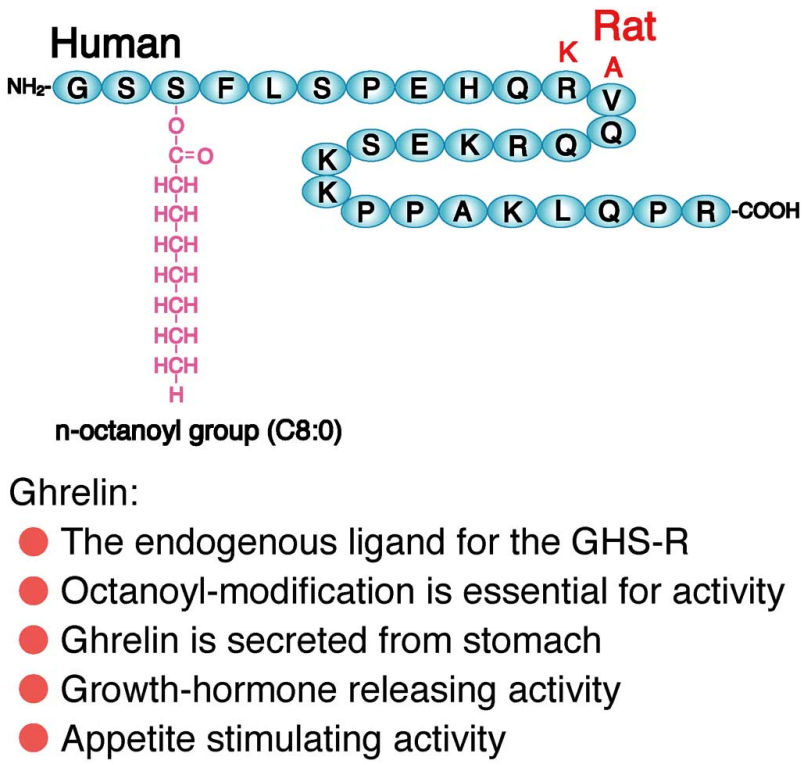

Fig. (1). Structure and summary of ghrelin.

organs, including heart, lung, liver, kidney, pancreas, stomach, small and large intestines, adipose tissue and immune cells, indicating that ghrelin has multiple functions in these tissues. In fact, ghrelin shows not only GH release and appetite stimulation but also cardiovascular effects, increase of gastric movement and secretion of gastric acid, suppression of symphathetic nerve and regulation of glucose metabolism.

2. Physiological Functions of Ghrelin

2.1. Growth Hormone Releasing Activity

Ghrelin acts on the ghrelin receptor (GHS-R), increasing intracellular Ca^{2+} concentration *via* IP_3 to stimulate GH release from pituitary. Ghrelin stimulates growth-hormone release both *in vitro* and *in vivo* in a dose-dependent manner [1]. Intravenous injection of ghrelin induces potent GH release both in mammalian and non-mammalian vertebrates. In term of both the area under the curve and mean peak GH levels, the GH-releasing activity of ghrelin is similar to that of GHRH when injected intravenously into rats. However, the maximal stimulation effected by ghrelin is 2 to 3 times greater than that of GHRH.

Ghrelin stimulates GH release from cultured primary pituitary cells, which indicates that ghrelin can act directly on the pituitary. However, the involvement of the hypothalamus in ghrelin-mediated stimulation of GH release has been strongly suggested. Patients with organic lesions in the hypothalamic region showed insufficiency of GH release even when stimulated by ghrelin. Moreover, when using primary pituitary cells, the ghrelin treatment only increased GH release by 2-3 times above the basal level, which is lower than the level of induction seen when ghrelin is administered to rats *in vivo*. These facts suggest that other factors are involved *in vivo* in order for the maximal level of GH release to be achieved by ghrelin administration. One possibility is transmission *via* the vagus nerve. When the vagus nerve is cut, GH release after ghrelin injection is dramatically decreased, indicating that the vagus nerve is needed for the maximal stimulatory effects of of ghrelin. Another possibility is the lack of GHRH in primary pituitary cells. Co-administration of ghrelin and GHRH had a synergistic effect on GH secretion; that is, co-administration results

in more GH release than does either GHRH or ghrelin alone. Synergistic effect on GH release was also observed by co-administration of GHSs, synthetic ghrelin agonists, and GHRH. This finding implies that GHRH is necessary for GH release to be maximally effective in inducing GH release by ghrelin.

2.2. Appetite Regulation

Recent identification of appetite-regulating humoral factors reveal regulatory mechanisms not only in the central nervous system, but also in the peripheral system mediated by factors secreted from peripheral tissues. Leptin, produced in adipose tissues, is an appetite-suppressing factor that transmits satiety signals to the brain. Hunger signals from peripheral tissues, however, had remained unidentified until the recent discovery of ghrelin. Ghrelin is produced primarily in gastrointestinal organs in response to hunger and starvation, and circulates in the blood, serving as a peripheral signal telling the central nervous system to stimulate feeding. When ghrelin is injected into the cerebral ventricles of rats, their food intake is potently stimulated [6]. Moreover, not only ICV injection, but also IV and subcutaneous injection of ghrelin have been shown to increase food intake.

In the brain, the hypothalamic arcuate nucleus is the main site of ghrelin's appetite stimulating activity [6]. At least a part of the orexigenic effect of ghrelin is mediated by upregulating the genes encoding potent appetite stimulants, such as NPY and AgRP, since ICV injection of ghrelin induces Fos expression in NPY/AgRP-expressing neurons and increases the amount of NPY/AgRP mRNAs in the arcuate nucleus. In contrast, the appetite-stimulating effects of ghrelin are blocked by ICV injection of a NPY receptor 1 antagonist, an AgRP inhibitor, anti-NPY IgG, and anti-AgRP IgG. Immunohistochemical analysis indicated that ghrelin neuron fibers directly contact NPY/AgRP neurons. These results indicate that ghrelin exerts its feeding activity by stimulating NPY/AgRP neurons in the hypothalamus to promote the production and secretion of NPY and AgRP peptides. Intravenous injection of ghrelin also stimulates NPY/AgRP neurons in the hypothalamus. Studies with knockout mice of NPY, AgRP or both confirms these results. Although deletion of either NPY or AgRP caused a modest or no effect on the orexigenic action of ghrelin, the double knockout mice lacked the action of ghrelin completely.

Peripherally injected ghrelin activates hypothalamic neurons and stimulates food intake. In general, peptides injected peripherally do not pass the blood-brain barrier. Indeed, the rate at which peripheral ghrelin passes the barrier has shown to be very low. Thus, peripheral ghrelin must activate the appropriate hypothalamic regions via an indirect pathway. The detection of ghrelin receptor mRNA on vagal afferent neurons in the rat nodose ganglion suggests that ghrelin signals from the stomach are transmitted to the brain *via* the vagus nerve. Moreover, the observation that ICV administration of ghrelin induces c-Fos in the dorsomotor nucleus of the vagus and stimulates gastric-acid secretion indicates that ghrelin activates the vagus system.

In contrast, vagotomy inhibits the ability of ghrelin to stimulate food intake and GH release. A similar effect was also observed when capsaicin, a specific afferent neurotoxin, was applied to vagus nerve fibers to induce sensory denervation. On the other hand, fasting-induced elevation of plasma ghrelin levels is completely abolished by subdiaphragmatic vagotomy or atropine treatment. These results indicate that the response of ghrelin to fasting is transmitted through vagal afferent transmission.

3. Clinical Application of Ghrelin

The diverse functions of ghrelin raise the possibility of its clinical application (*Fig. 2*). Attempts for clinical use of ghrelin are now in progress. Basically ghrelin is a peptide hormone that endows cells with nutrition and energy and regulates the metabolic activities. The target diseases of ghrelin will be not only GH deficiency but also feeding disorder and weight loss due to variable causes. Moreover, ghrelin will be applied to elder peoples to

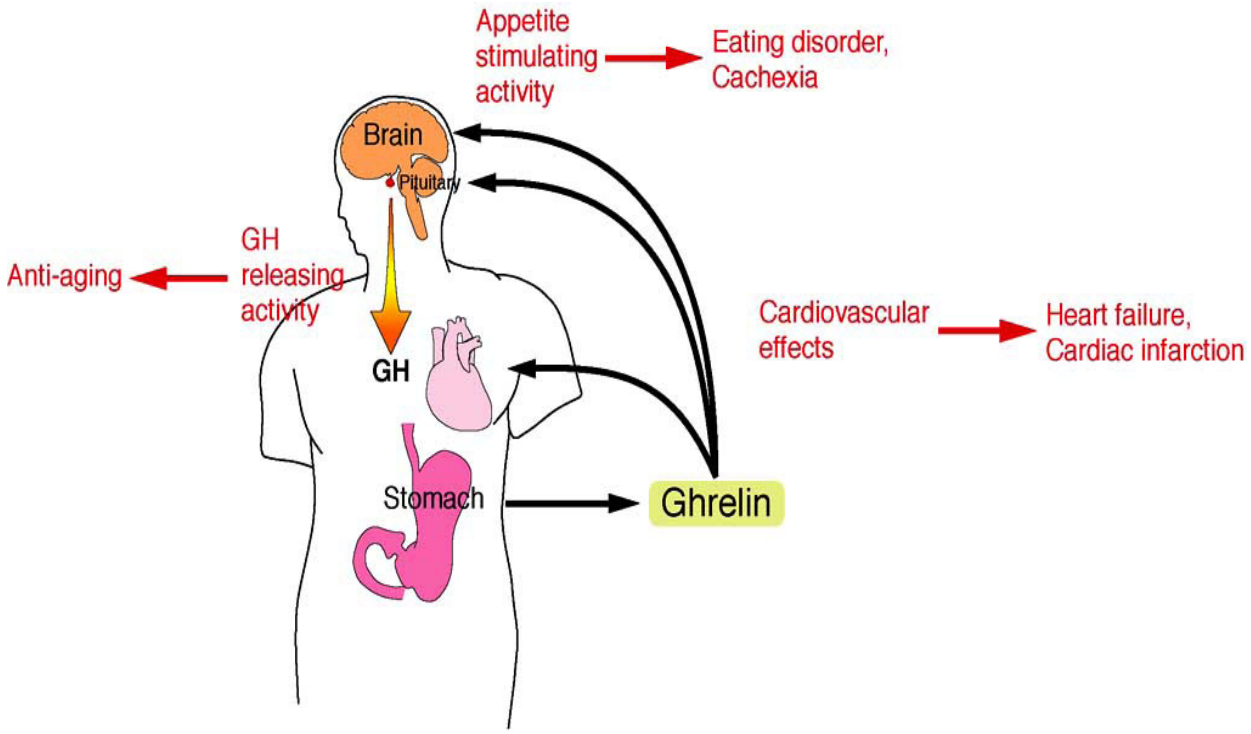

Fig. (2). Multiple functions of ghrelin and its clinical application.

keep appreciate "quality of life" by prevention and treatment of osteoporosis and improvement of muscle strength both through direct action of ghrelin and indirect action of GH released by ghrelin.

Clinical application of ghrelin is now in phase II to target the diseases anorexia nervosa and cachexia due to chronic diseases. In the near future, ghrelin can hopefully be used for treatment of these diseases.

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