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RESEARCH ARTICLE

# The New Trends in Physiological and Pathological Actions of Ghrelin (Brain-Heart Axis) on the Heart and Cardiovascular System.

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## ABSTRACT

Background: Ghrelin increased significantly the Left Ventriculus Eject Fraction and end-systolic volume after 30 minutes of intra-venous injection and without alterations heart rate and blood pressure.
Ghrelin was discovered in 1999 as an only one 28 amino acid peptides (with octanoyl serine group) located on the short arm of chromosome 3 (position 3p25-26) having six exons, two are noncoding and four introns and encodes a 511 bp mRNA.
Ghrelin is synthesized by the endocrine X/A-like cells located from the gastric fundus mucosa through the whole mucosa of the medium right vertical side of the stomach until to the 1 inch before anatomical pylorus. These cells are responsible to produced 80% of the whole ghrelin produced in the human body. Furthermore, other place of this production occurs at the hypothalamus, the pituitary, second portion of duodenum, pancreas, heart and other tissues. Bibliographic references also demonstrate the importance of ghrelin's action in the main cardiovascular activities.
Related to cardiovascular activities, ghrelin plays multitudinous beneficial and thereby help during cardiovascular diseases. Several studies demonstrated that ghrelin cause an anti-inflammatory activity by the inhibition of proinflammatory cytokines which can diminish inflammatory diseases in the heart, pericardium and specific innervations, for instance, vagus nerve and inhibited sympathetic nerves. Outcomes of this review emphasize these important actions of ghrelin.
Methods: A systematic review of ghrelin activities over the heart and cardiovascular system with the inclusion of papers in review involved the physiological and physio pathological activities of ghrelin in vivo and in vitro studies.
Results: Ghrelin is a natural tide with the growth hormone secretagogue (GHS) receptor (GHS-R) which cloned in 1996. The processes which generate this peptide and ghrelin-related peptides are transcriptional, translational and posttranslational. Homo and heterodimers of GHS-R and other yet unidentified receptors mediate the biological actions of acyl ghrelin and desacyl ghrelin. However, the main biological functions of ghrelin involve the secretion of growth hormone, stimulation of appetite and food intake at the hypothalamus, modulate acid secretion and motility, endocrine and exocrine pancreas secretion, blockaded insulin activity, heart functions and cardiovascular responses and other.
Conclusion: One of the main occurrences in acute heart infarction is an increase activation of cardiac sympathetic nerve activity (CSNA) which is one of the causes of chronic cardiac dysfunction (CCD). Ghrelin is an effective for obtain a better cardiac function and by the suppression of renal sympathetic nerve activity which also have an important benefit to the acute myocardial infarction.
Therefore, the physiological effects of ghrelin are very important to the body homeostasis even in the grave heart and cardiovascular diseases and in the immunological system.

**Keywords**: Ghrelin, growth hormone, receptors, heart failure

## Introduction:

Ghrelin is at this moment the only peptide hormone modified by a fatty acid. It is produced in great part by the gastric endocrine mucosal cells called X/A-Like cells. Ghrelin is defined as a unique 28 amino-acid (28 AA) which present an only n-octanoylation modification on the serine in position 3 modified of ghrelin O-acyl transferase (Fig.1). From the ghrelin gene (chromosome 3p25-26) to ghrelin-related peptides, transcriptional and translational mechanisms as well posttranslational acylation mechanism are necessary to processing preproghrelin into ghrelin. Preproghrelin (117 AA) contains 23 AA signal peptide and a 94 AA segment peptide named proghrelin.

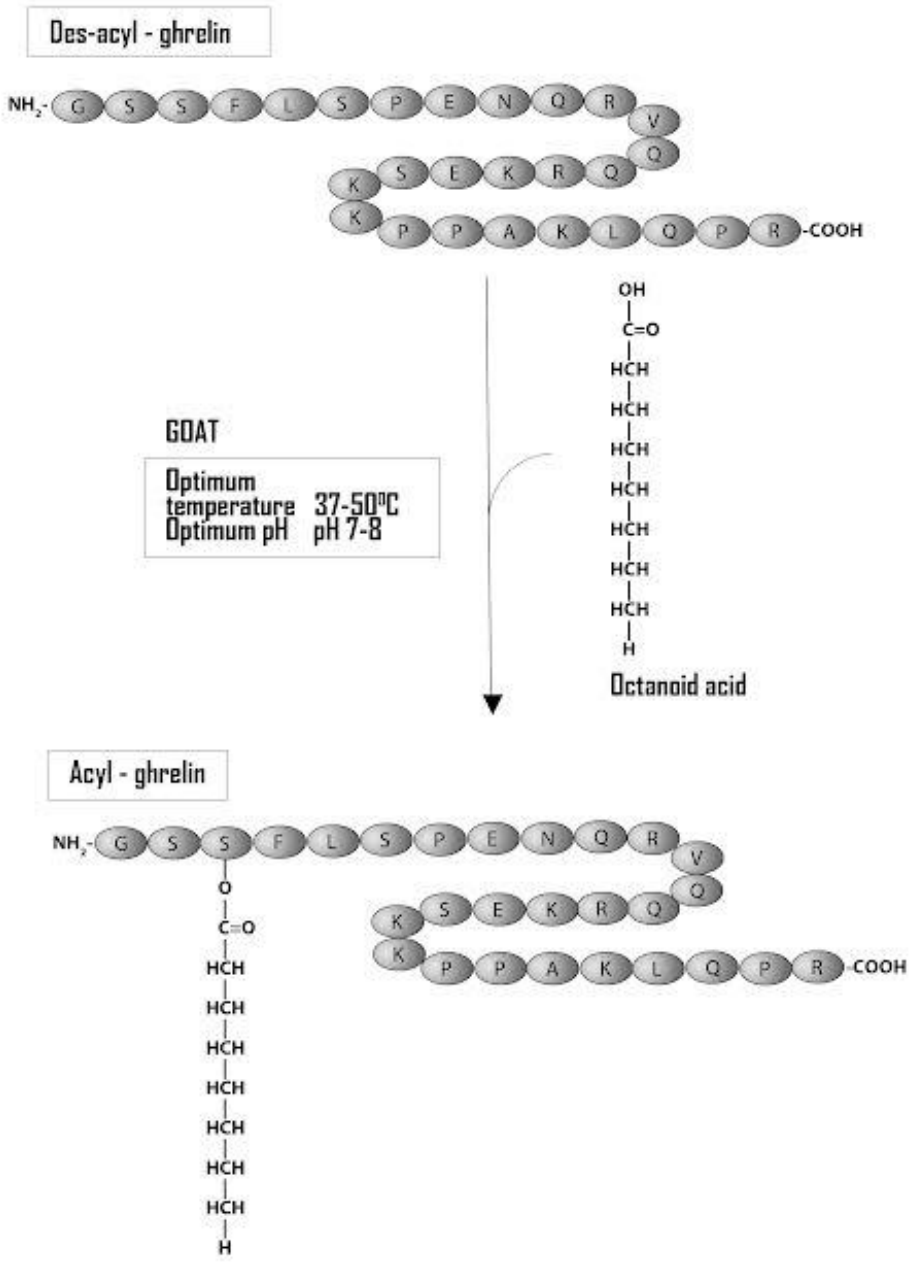


**Figure 1.** Structure of Human Ghrelin n-octanoyl group (C8:0)

Study developed in an animal model based in acute myocardial infarction (AMI) caused by coronary artery ligature, early approach treatment with ghrelin infusion can reduces a grave arrhythmia event which cause high rates of mortality. This may point to the high potential therapeutic management of this peptide in AMI[4,5,6].

Ghrelin as a gastrointestinal hormone (Ghrelin and its mRNA) is produced and secreted by X/A cells in the oxyntic mucosa of the stomach (mainly in the middle vertical line of the stomach toward to great curvature from the gastric fundus until 1 inch to surgery pylorus sphincter in the antral area. The morphology of this cell is suchlike to pancreatic alpha cells. In fact, ghrelin is produced into gastric submucosal layer and widespread by the blood stream[7,8].

Synthetic elements named growth hormone secretagogues (GHS) is the responsible to stimulation release of growth hormone from the pituitary gland[6,7].

A lot of studies defined since 1995-1999, a total regulation of the brain over the great part of hormones and they connections with hormonal glands and other organs called brain-pituitary axis, places in the anatomic region of midbrain, for instance hypothalamus (arcuate

nucleus, paraventricular nucleus, dorsomedial region, central nucleus of amygdala and the nucleus of solitary tract)[12,13].

The receptor for GHS (GHS-R) found in the brain is the target of enzymes to initiate ligand purification proving that pituitary hormones are regulated in the brain[7,8] (Fig.5).

GH release from the pituitary gland is regulated by the hypothalamus and by the gastrointestinal tract. Ghrelin includes an exclusive structural capacity which is an acylation in one of its third residue named serine, the first peptide hormone with acyl transformation. This acylation is pivotal for the ability of ghrelin to binding to GHS-R and hence the activation of its receptor. In summary, ghrelin release of GH, stimulated appetite and have been involved in the cardiovascular system, bone, gastrointestinal and immune systems[9,10,11]. Ghrelin produced by the stomach' submucosal layer reaches the brain by central and peripheral pathways also via vagus nerve. Ghrelin-conducting neurons send efferent stimuli to arcuate nucleus neurons (ARC) which producing neuropeptides Y (NPY), pro-opiomelanocortin (POMC), agouti-related peptide (AGRP) and corticotropin-releasing hormone (CRH). Through stimulating the activity of NPY and AGRP and decreasing the activity of POMC and cocaine-amphetamine-regulated transcript (CART) neurons ghrelin leads to increases appetite and food intake. The hypothalamic enzyme 5' AMP-activated protein kinase (AMPK) plays an essential role in the ghrelin' actions on appetite and food-intake[14,15,16,17].

Related a cardiovascular activities ghrelin plays multitudinous beneficial and thereby help during cardiovascular diseases. Several studies demonstrated that ghrelin cause an anti-inflammatory activity by the inhibition of proinflammatory cytokines which can diminish inflammatory diseases in the heart, pericardium and specific innervations, for instance, vagus nerve and inhibited sympathetic nerves[18,19].

## Methods

STUDY OVERVIEW

Data were analyzed retrospectively in a systematic review since 1996 to 2024 and other complementary studies. A systematic review of ghrelin activities over the heart and cardiovascular system with the inclusion of papers in review involved the physiological and physio pathological activities of ghrelin in vivo and in vitro studies.

STUDY QUESTIONS

Key Points:

1. Has Ghrelin an important benefit to the acute myocardial infarction?
2. Ghrelin activities involve heart functions and cardiovascular responses.
3. The physiological effects of ghrelin are very important to the body homeostasis even in the grave heart and cardiovascular diseases.

INCLUSION CRITERIA

Studies which main theme was an explanation with in vitro and in vivo research involved activities of Ghrelin and derivates peptides on the heart and cardiovascular system and their pathways.

## Discussion:

Actions of ghrelin in the cardiovascular system are very important to prevent and treatment of cardiovascular diseases. Cardiovascular beneficial effects are intermediated through combinations of variables actions cytokines, parasympathetic and sympathetic nerves, growth hormone level and immunologic system[6,7,8,10,18,19,20,21].

Ghrelin is one of hormones which dilates artery with endothelium-independent action in human beings.

Ghrelin (Ghr) actions also inhibits apoptosis cardiomyocytes and endothelial cells through the activation of an extracellular signal-regulated Kinase 1 and Kinase 2 also Akt serine Kinases[20,21,22,23].

In cardiovascular tissue ghrelin is important as vasodilator and inotropic positive effects. Treatment with the infusion of ghrelin or des-octanoyl ghrelin ameliorated ISO-induced (isoproterenol) myocardial injury. This protective effect of ghrelin is in part caused by its hemodynamic potency[23,24]. In myocardial infarction (MI) occurs a rise in cardiac sympathetic nerve activity (CSNA) causing a critic elevation of chronic cardiac dysfunction.

Ghrelin can have an effective treatment, for instance, by suppresses renal sympathetic nerve action (RSNA) what may have great therapeutic benefits during early period of acute MI improving early survival prognosis. Many studies demonstrated this benefit of Ghr to the cardiac function through the release of GH. However, a lot of evidences supports a direct cardioprotective actions of Ghr through the central modulation of SNA (fig. 2).

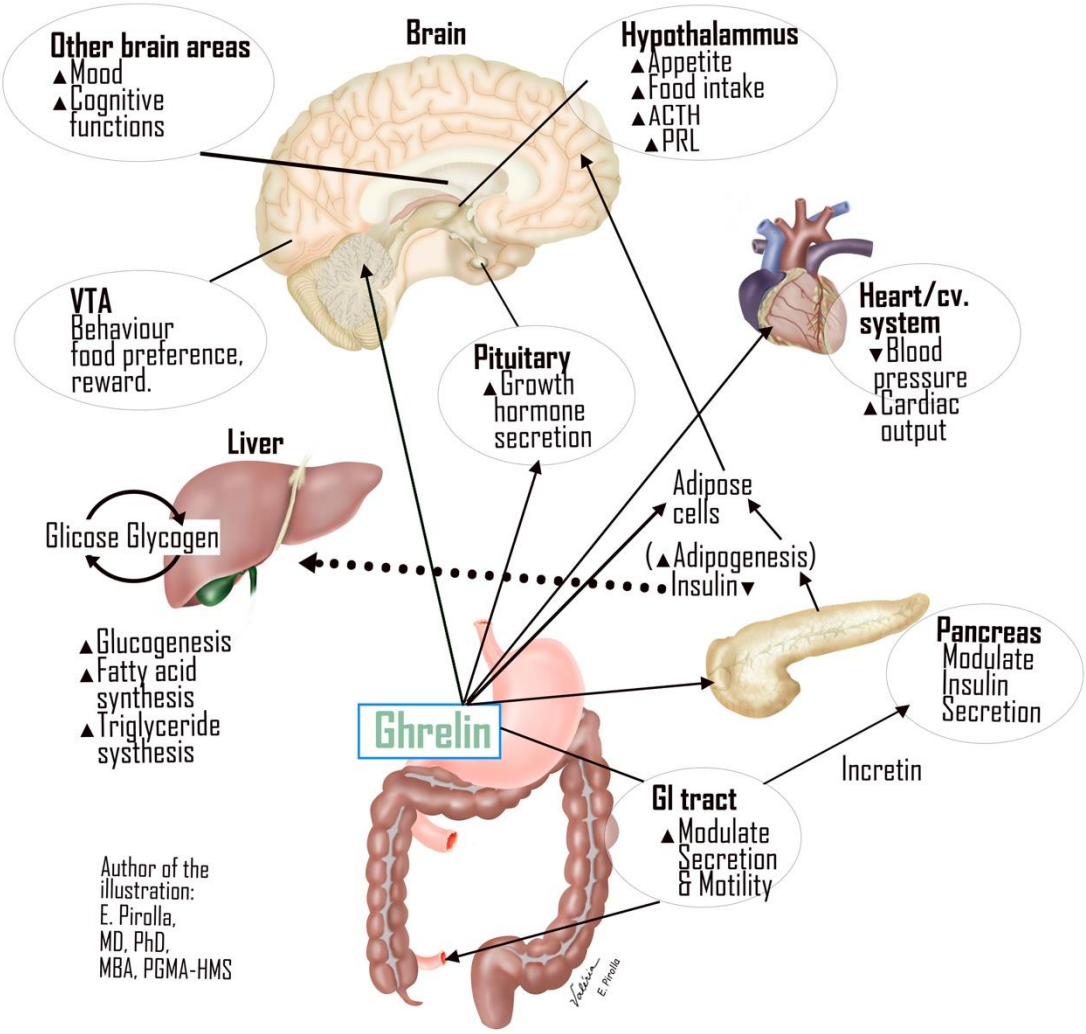


**Figure 2.** Systemic action of the Ghrelin hormone. Adrenocorticotropic hormone (ACTH); Parvocellular Red Nucleus (pRN).

Early Ghr treatment infusion prevented the adverse rise in CSNA within 1st 5 hours of monitoring and decrease the occurrence of arrhythmias. Also, studies are demonstrated that GH scretagogue receptor (GHS-R) is localized in the vagal nerve terminals in myocardial, which send afferent stimulations to the nucleus tractus solitarius (NTS). Therefore, Ghr may operate to increase vagal tone and thereby reduce SNA[25,26,27,28] (Fig. 2).

Some studies showed that in Ghr-treated patients, left ventricular enlargement which can occurs after MI was significantly attenuated compare with the patients who received placebo. This action occurs by the activity of Ghr and des-acyl Ghr which inhibit cells death in the cardiomyocytes and endothelial cardiovascular arteries through ERK1/2 and PI 3-Kinase/ATK[29,30,31].

Insulin-like growth factor-1 is mainly produced by the liver and kidneys but also in a paracrine/ autocrine pathway by endothelial of vascular smooth muscle cells and myocardial myocytes. Insulin and GH are the main factors which stimulates IGF-1 secretion and presented in ventricular myocytes and coronaries arteries promoting coronary dilation through the activation of potassium channels, cause production of nitric oxide by the cardiovascular endothelium reduced calcium intracellular and consequently substantially reduction of ischemia and infarct size[31,33,34,35]. Through the action of growth hormone which secretion in the arcuate nucleus and the nucleus tractus solitarius (NTS) is stimulated by Ghr, the increase of ACTH and parvocellular red nucleus (pRL) play a prominent role in motor and non-motor actions behavior on the myocardial activities. Ghr actions on the decrease of insulin help to maintain high levels of glucose which is better to the myocardial cells revitalization (Fig.2).

The functional action of Ghr in the control of immunologic system MHC-II or Signal 1 by the activation of naïve and innate immune cells. Ghr and GHS-R are expressed in human T cells and innate immune cells as monocytes where Ghr acts by GHS-R in the inhibition of proinflammatory cytokines 9 produced in response to damage on, for instance, the heart, IL-1beta, IL-6 and TNF-alfa[24,25].

The central Sirtuin 1/p53 and AMP-activated protein kinase (AMPK) signaling pathway is fundamental for the orexigenic actions of endogenous Ghr and the activities to decrease heart damages in acute IM[35,36,37]. This orexigenic action (basically appetite-stimulating) is important to the secretion ACTH, GH and pRL for the beneficial activities to the heart[37,38,39].

Ghr increase heart contractility and left ventricular function with better output volume in chronic heart failure and can reduce infarct size too.

The apparatus used by Ghr responsible for the hypotensive action involve the suppressive management of sympathetic activity and the direct vasodilatory approach[40,41,42]. Presence of low plasma levels of Ghr is associated with resistance of insulin control, hypertension, decrease of immunological system and Type 2 diabetes. This occurrence and their consequences is worst during treatment and prognosis of acute IM[1,2,3].

Important is the desacyl ghrelin as a potent acyl ghrelin in exerting a protective effect on the heart probably by the action on a receptor distinct from GHS-RIA[8,45]. Besides, desacyl ghrelin raise neovascularization in heart and other tissues in the body helping cardiac ischemic injuries and the vascularization in diabetes patients[47,48,49,63,64,65].

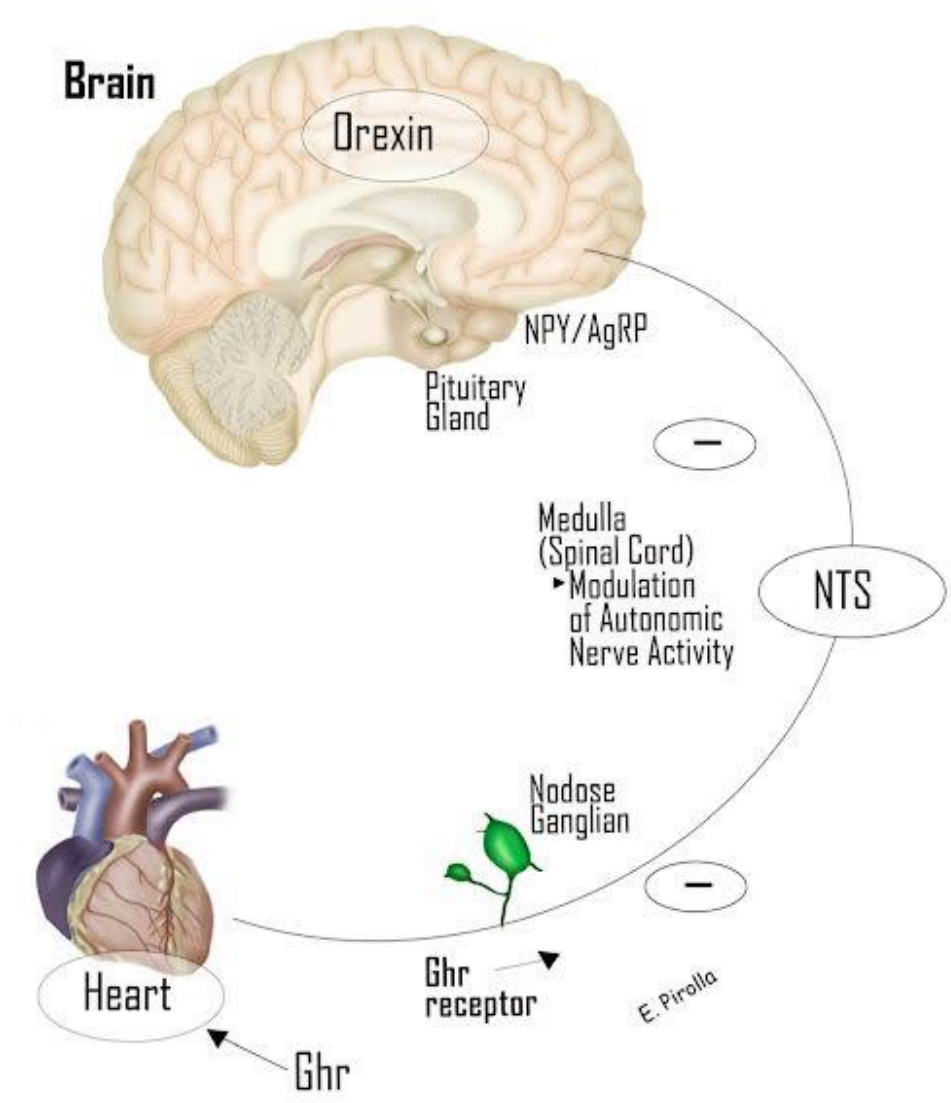


**Figure 3.** Anatomic modulatory actions pathway of Ghrelin. Ghrelin activities by vagal afferent nerves and send impulses to vasomotor center on the medulla through the autonomic nerve activity.

Ghrelin also acts on the nucleus of solitary tract to obtain a decrease of the arterial pressure and is responsible of better cardiac output in acute IM evolutive period[58,62] (Fig.3). As well, Ghrelin is a potent antagonist of endothelin-1 and provide a vasodilation of internal mammary artery helping the blood flow in an IM and in the post-operatory of cardiac coronary and internal mammary bypass[57,58,59].

Ghrelin has the capacity to blockade the rennin-angiotensin system thus reducing hypertension and other cardiovascular disorders, for instance, arrythmias, inflammatory states, dyslipidemia and glucose metabolism. Therefore, Ghrelin protects heart against ischemia, arrythmias and other reperfusion injuries[59,60,61,62] (Fig.4).

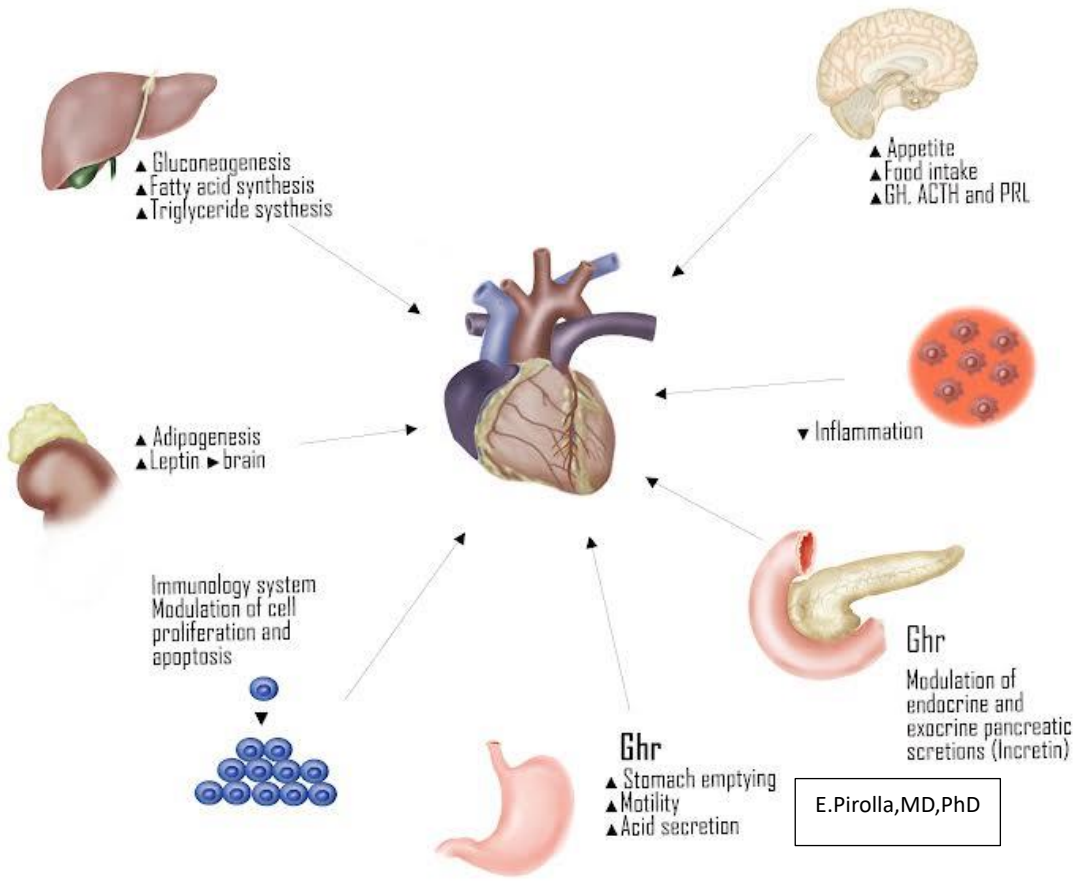


**Figure 4.** Ghrelin actions on multiple organs and systems in the human body thereby acting on the heart and cardiovascular system nucleus in the solitary tract (NTS) inhibiting the activity of sympathetic nerve, protecting heart from excessive damages.
(NPY) Neuropeptide Y; (AgRP) Peptide related to agouti; (Ghr) Ghrelin; (OREXIN) hypocretin neuropeptide regulate arousal, wakefulness and appetite.

The extracellular signal-regulated Kinase-1/2 (ERK1/2) is an important role for the mitogen-activated protein Kinase group and can be find in many organs. This activate participates in the intracellular signal transductions. Existing various stimuli which induce phosphorylation of ERK1/2Nand these processes move to the nucleus and activates a lot of transcriptions factors, regulates gene expression and also control various physiological process. It is a very important immunological and biochemical interactions in the body because is responsible for the processes of tissue repair or cells death. Because of the aging or in situations of diseases which requires the processes of ischemia-reperfusion injury (IRI), mainly in the brain, heart, kidney and other fundamental organs, this signal-regulated ERK1/2 is increasingly important and serious. Ghr is responsible to inhibits apoptosis of cardiomyocytes and even the endothelial cells, possibly by the activation of extracellular signal-regulate kinase ½ and the Akt serine kinases avoiding cells damage, for instance, in heart diseases[68-74].

Hypothalamic neural networks involving appetite-regulating peptides. Ghrelin-producing neurons in the arcuate nucleus (ARC) presynaptic induce neuropeptide Y (NPY) neurons to release NPY, a potent orexigenic neuropeptide, thus stimulating food intake. These ghrelin-producing neurons in the ARC also increase the rate of secretion of GABA, which may postsynaptic modulate the release of POMC, an anorexigenic neuropeptide. In the paraventricular nucleus (PVN), ghrelin stimulates NPY release, which in turn suppresses GABA release, resulting in the simulation of corticotropin releasing hormone (CRH)-expressing neurons, leading to ACTH and cortisol release. All this stimulation and release of NPY, AgRP, PRL, ACTH and the blockade of sympathetic nerves pathways are fundamental to protect heart of damages, cause less inflammation and better prognosis too[68,69,70,72].

Modifications in the left ventricle, for instance, dilatation and wall thinning and heart cachexia situation because of high body weight loss and muscles wasting can occurs in persons with end-stage chronic heart failure, post IM and other diseases. GH and its chemical mediator named insulin-like growth factor-1 (IGF-1) are important anabolic hormones which are fundamental for the skeletal and myocardial growth and even to metabolic homeostasis in the body[69-74]. Ghr also improved ejection fraction (EF) of the left ventricle (LV) in medium of 30%, increase LV mass and decrease LV end-systolic residual volume[74,75,76].

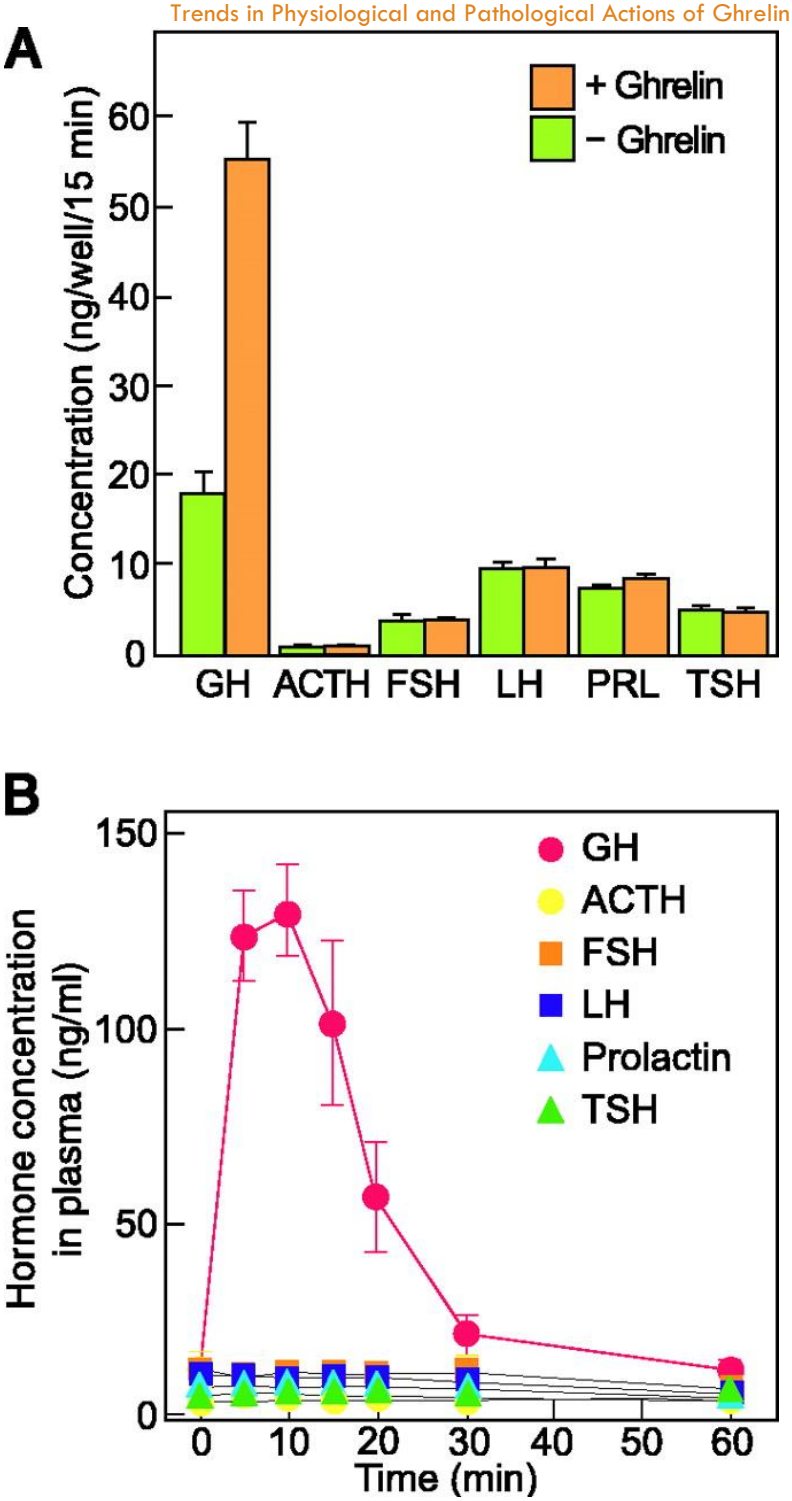


**Figure 5.** Ghrelin actions on Pituitary hormones.
(Kojima M, Kangawa K.; Physiol Rev 2005;85:495-522)

## Conclusion

According to inotropic activities of GHS in physiological situations the possibility of effects as vasodilatory secondary an action to increase secretion and activities of GH. Some studies demonstrated: An increase of left ventricular ejection fraction (LVEF) in healthy volunteer's subjects and even in patients with deficiency of GH (GHD) which occurs with none concomitant lower blood pressure after half an hour of intra-venous infusion of hexarelin. Ghrelin increased significantly the LVEF and end-systolic volume after 30 minutes of intra-venous injection and without alterations heart rate and blood pressure. The effectivity actions on heart muscle contractility occurs during high GH secretion demonstrated in experimental models and related to alterations in $Ca^{2+}$ transmitter. A lot of other studies still be doing about this impressive and important theme and new discoveries are find every time.

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