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Structure and Physiological Functions of Ghrelin

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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.

Abbreviations: GHSR: Growth Hormone Secretagogue Receptor; CaMKK: Calmodulin Kinase; CB1: Canna BinoidReceptor Type 1;ACC: Acetylcarboxylase; FAS: Fatty Acid Synthase; CPT1: Carnitine Palmitate Transferase;ROS: Reactive Oxygen Species; UCP2: Unconjugated Protein 2 (UCP2); NPY: Nerve Peptide Y (NPY); AgRP:Agouti Related Peptide ; POMC: Proopio Milano Curtin

Introduction

Biochemistry of Ghrelin

Ghrelin hormone composed of 28-amino acid peptide modified at its third residue, a serine (Ser3), by a middle-chain fatty acid, n-octanoicacid.The Ser3-acylation is necessary for its biological activity, especially the binding and activation of the ghrelinhormone receptor. Ghrelinhormonewas discovered in 1999 from stomach, practiced potentappetite and growth hormone releasing stimulating activities [1,2] (Figure 1).The name "ghrelin" is based on "ghre", which is the root ofthe word in the Indo-European primary languages of the word "grow", in reference to ghrelin hormone ability to induce growth hormone release. Both the precursors of rat and human ghrelin are consists of 117 amino acids. In these precursors, the active ghrelin sequence of 28 amino acids immediately follows the signal peptide. Ghrelin hormone(peptide hormone), serine 3 (Ser3) is n-octanoylated and this modification is necessary for ghrelin activity.The enzyme that catalyzes acyl adjustment in ghrelin has not yet been specified. GlobalismInclusion of n-octanoic acid has been suggested inamphibians, mammals, fish, andbirdsthat this putative enzyme is somewhat specific in its choice of medium-chain fatty acid substrates [3].

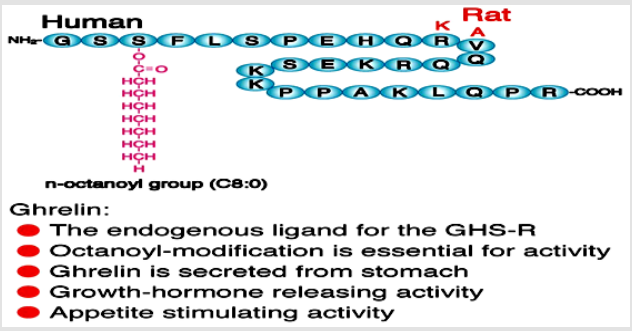

Figure 1: Structure and summary of ghrelin.

Mechanism of Action

Ghrelin emerged as the first circulating hunger hormone. Ghrelin and Synthetic ghrelin imitative (the growth hormone secretagogues) increase fat massand increase eat the food[4,5].An action is practiced at the level of the hypothalamus.They activate the cells in the arcuate nucleus which include the orexigenic neuropeptide Y (NPY) neurons[6]. Ghrelin responsiveness of these nerve cells bothinsulinsensitiveand leptin [7]. Ghrelinhormone

activates the mesolimbic cholinergic dopaminergic bonus link, a circuit that communicates the hedonic and reinforcing aspects of natural bonus, like food as well as addictive drugs like ethanol[8].

Ghrelin is Secreted in Two Forms

(Figure2)[9].

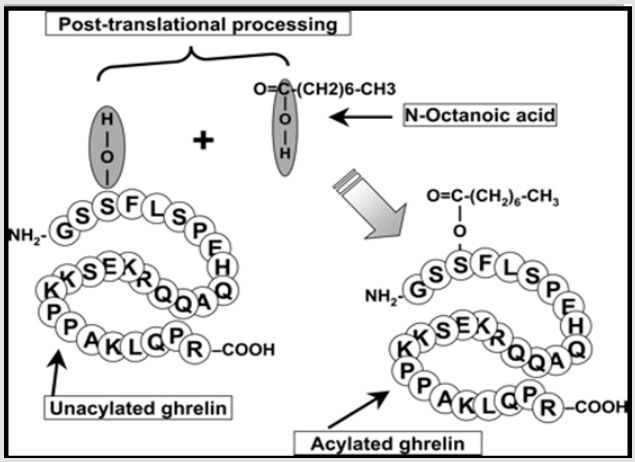

Figure 2: Ghrelin hormone in its inactive form (desacyl ghrelin) is converted to its active form (acyl ghrelin). Adapted from Sato *et* al. [9].

Facts of Ghrelin

Ghrelin consists of 28 amino acids that originate from 94 long precursors of amino acids (progerlin). The other products of Progrelin are; des-Gln14-ghrelin (27 ghrelin), C-ghrelin, and obestatin.

Effects of Ghrelin

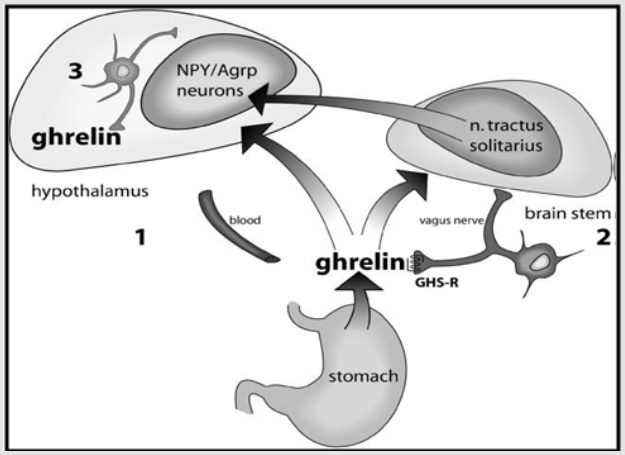

Figure 3: Ghrelin exerts its effects in the hypothalamus via threedifferent pathways.

Ghrelin stimulates CRH by stimulating NPY, which inhibits endogenous g aminobutyric acid (GABA) neurons thus releasing the ventricular CRH nucleus from inhibiting [10,11](Figure 3).Ghrelinhormonesynthesised in the stomach reaches the ARC via the bloodstream and possibly other brain areas via an active transport through the blood-brain barrier. Ghrelin hormone synthesized in the periphery stimulates the vagal connections that have been shown to express GHS-R, and the vagal connections connect to the tractussolitarius nucleus in the brainstem which then connects with the hypothalamus.Ghrelin is locally synthesized in the hypothalamus and has direct links with the NPY / agouti-bound protein and other hypothalamic cells.

Ghrelin Physiological Functions

Ghrelin receptor (GHS-R), two types of GHS-R, GHS-R1a (385 amino acids) and GHS-R1b (295 amino acids).

Ghrelin is a Potent Stimulator of GH Release(Figure 4).

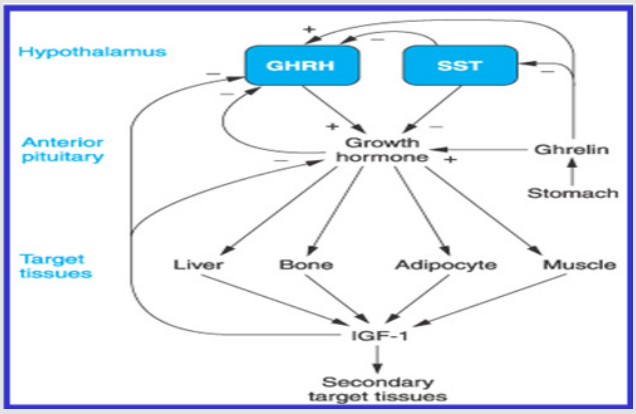

Figure 4: Schematic diagram showing two hypothalamic factors, Somatostatin (SST) and Growth Hormone-Releasing Hormone (GHRH) act on the Somatotropes in the Anterior Pituitary to regulate GH secretion. SST also inhibits GHRH release

A. Growth Hormone Secretion: Growth hormone (GH) is secreted from the somatotroph cells of the pituitary gland. The secretion is inhibited by Somatostatin (SS) and stimulated by Growth Hormone Releasing Hormone (GHRH) and ghrelin. Ghrelin stimulates the secretion of GH via binding to its receptor GHS-R1a, which activates a G-protein Ga11, and this activated G-protein then stimulates Phospholipase C. The action of this lipase increases the interacellular concentration of Inositol Triphosphate (IP3) which causes the release of Ca^{2+} from Interacellular stores, increase the Interacellular Ca^{2+} that lead to the release of GH.Binding of Somatostatin and growth hormone releasing hormone to their receptors (SS-R and GHRH-R) on the cell surface lead to Inhibit (G0 and Gi) and stimulate (Gs), stimulate (Gs) lead to stimulate adenlyatecyclase (AC), the activation of AC increases the concentration of cyclic AMP (cAMP), this in Turn stimulates protein kinase (PKA).

Activated PKA leading to influx of calcium ion Ca^{2+} into the Cell, it leads to stimulate GH. Once ghrelin hormoneassociated GHSR-1a, it obtains activated which in addition to activate Phospholipase

C (PLC) bind to the inner parts of the receptors. Phospholipase C contains at least eight isoforms.Phospholipase C isoforms stimulate hydrolysis of some cell membrane phospholipids particularlyPhosphatidyl Inositol 4, 5-diphosphate (PIP2) into Inositol Triphosphate (IP3) and Diacylglycerol (DAG) which works as two different messengers. Inositol triphosphate bound to the receptor inositol triphosphate and is a Ca^{2+} channel with ligand gates to theendoplasmic reticulum and catalysts for Ca^{2+} release in the. Additional calcium enters from the extracellular medium via voltageoperated L-type channels. Then the calcium ions act as a second messengers and cause the smooth muscle to contract in the celland causes secretory changes in the cell. Calcium ions interact with the vesicular membrane and cause growth hormone-secreting vesicles to fuse with the cell membrane;it is followed by exocytosis, i.e. the extrusion of growth hormone outside the cell[12].

B. Ghrelin in Growth and Development: Ghrelin hormone catalyzes the secretion of growth hormone in the hypothalamus, a procedure that requires secretionGrowth Hormone Releasing Hormone(GHRH)[13]. Diagram of the effect of ghrelinhormoneonGrowth Hormone (GH) metabolism in adults. Ghrelin is excreted mainly by the stomach but also from the hypothalamus. Ghrelin regulates Growth Hormone Releasing Hormone. Growth Hormone Releasing Hormoneexpression in the hypothalamus in vivo. It also directly stimulates growth hormone releasing hormonefrom the pituitary, at least *in vitro*.

2-Reproductive Effects (Ghrelin Effects at the Level of the Hypothalamic-Pituitary-Gonadal Axis): Schematic representation of ghrelin hormone effects at the level of the hypothalamicpituitarygenital axis. Ghrelin hormoneon the principle produced by the stomach, can act through its functional receptor GHS-R1a in endocrine or/and local manner in all male and female reproductive tissues including hypothalamus, pituitary, ovary, and testis. It isknown that ovarian steroid production (oestradiol and progesterone) can alter the secretions of the pituitary and hypothalamus.Moreover, hypothalamusinduced GnRH controls LH, FSH secretion known to regulate gonadal functions.In mammalian species, ghrelin hormone treatment inhibits the release of GnRH, LH, and FSH at the hypothalamic and pituitary levels.Adverse effects have been described in several species of fish.In gonads, ghrelin hormone also exerts inhibitory effects by altering steroid composition and germ cell production or viability in the ovaries and testicles. On the other hand, ghrelin hormone treatment reduces proliferation of Leydig cells whereas it increases those of granulosa cells. SCF pathway: Stem Cell Factor pathway. ↓: decrease, ↑: increase, and inhibition.

Ghrelinand Apoptosis: The schematic diagram summarized the molecular mechanisms by which DOX-induced excessive autophagy, apoptosis and cell size decrease in cardiomyocytes were inhibited by ghrelin supplement. In response to DOX exposure, the increased autophagy is paralleling with the apoptotic level, and cell size is decreased, which are associating with the increase in ROS content. Ghrelin attenuates the DOX induced Cardiomyocyte apoptosis and size decrease by suppressing the excessive autophagy level through the inhibition of ROS level and activation of mTOR pathway, which depends on AMPK signaling inhibition and p38-MAPK signaling activation. DOX, doxorubicin; Reactive Oxygen Species (ROS).

Thyroid Hormone Esmodulate the Bioactivity, Secretion and/or Metabolism of Ghrelin and Obestatin: The present study had a limitation to elucidate the mechanism(s) of effect of TSH and thyroid hormones on gut peptides and vice versa. At present, we may consider that thyroid hormone demodulate the bioactivity, secretion and/or metabolism of ghrelin hormone and obestatin. Additionally, gut-derived metabolic hormones may be involved in regulating the hypothalamus, pituitary and thyroid functions. However, effect of obestatin on the thyroid axis still remains an open question, and further examinations will be necessary.

Ghrelin Interactions in the Feeding and Sleep Circuits: Fasting Or feeding leads to changes in leptin,glucose, and ghrelin levels, which may affect the transition from sleep to waking.Acyl ghrelin appears to regulate nocturnal growth hormone secretion through a direct effect on the pituitary gland.Increased growth hormone may be necessary for glucose balance during sleep.The gastric or hypothalamic ghrelin hormone also activates the orexin neurons in LHA, which in turn activates the NPY / AgRP neurons in the ARC (ghrelin or oxygenic pathway). At the same time, this originating stimulant produces SST secretion that inhibits the action of GHRH, thus impeding the production of growth hormone in the pituitary gland. The net effect is to enhance arousal and compulsive behavior.On the other hand, Sleep disturbances lead to elevated ghrelin with decreased levels of leptin that directly increase the activity of the orexin system, affecting the animals' sleep wakefulness state and their complete behavior.

Appetite: Act in the arcuate nucleus by stimulating neurons NPY / AGRP (Y / Agouti Associated Neuropeptide) →↑ Appetite (orexigenic effect).The clinical application of ghrelin and the diverse functions of ghrelin increase its clinical applicability.Attempts at clinical use of ghrelin are now underway. Ghrelin is basically a peptide hormone that provides cells with nutrition, energy and regulates metabolic activities.The target diseases of ghrelin will not only be growth hormone deficiency but also nutritional disorder and weight loss due to various reasons.Moreover, ghrelin will be applied to the elderly to maintain an esteem of "quality of life" through the prevention and treatment of osteoporosis and the improvement of muscle strength through the direct action of ghrelin and the indirect action of the growth hormone released by ghrelin.The clinical application of ghrelin is now in its second phase to target chronic anorexia nervosa and cachexia.In the near future, we hope ghrelin will be used to treat these ailments (Figure 5).

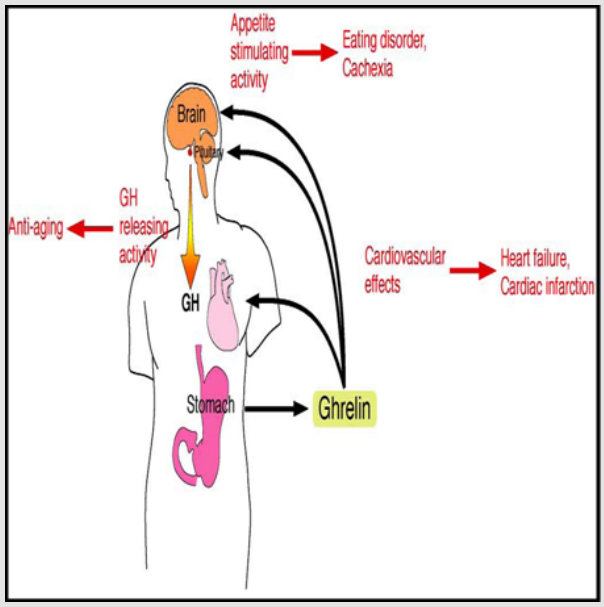

Figure 5: Multiple functions of ghrelin and its clinical application.

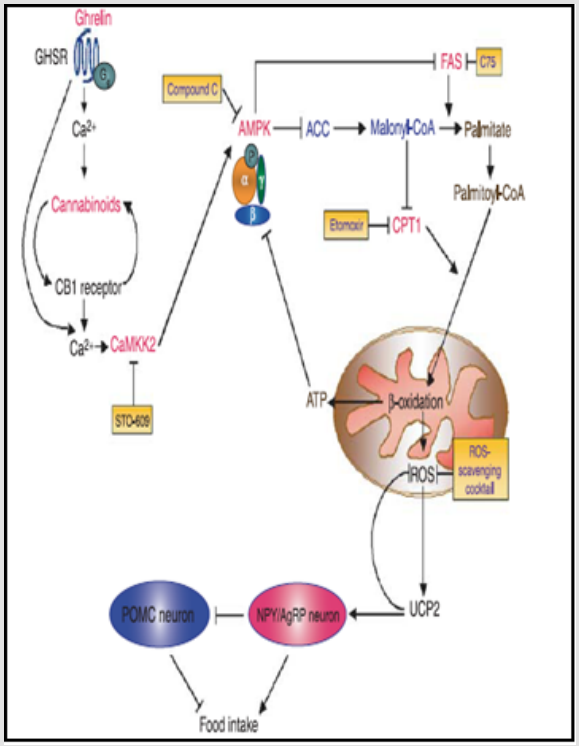

Figure 6: Schematic diagram showing the proposed molecules involved in the appetite-inducing effect of ghrelin.

A. Mechanisms of the Appetite: Activating the particles highlighted in red increases food intake, whereas the activation of molecules highlighted in purple leads to inhibition of food intake.In this figure, we depicted a simplified linear relationship between the elements that make up the ghrelin signal chain. Clearly, the different components of this cascade can also interact within and outside this pathway, activating other distinct downstream signaling components, here not reported, either sequentially or simultaneously, suggesting a much more complex regulation.Growth Hormone Secretagogue Receptor(GHSR); Calmodulin kinase (CaMKK); Canna Binoid receptor type 1 (CB1); AMPK, AMP Activated Protein Kinase; Acetylcarboxylase (ACC); Malonyl coenzyme A; Fatty Acid Synthase (FAS); Carnitine palmitate transferase 1 (CPT1); Reactive oxygen species (ROS); Unconjugated protein 2 (UCP2); Nerve peptide Y (NPY);Agouti Related Peptide (AgRP); (POMC) Proopio Milano Curtin. The effects of ghrelin hormone on appetite are mainly mediated in the hypothalamus through stimulation of neuropeptide Y (NPY), a potent orexigenic agent, and of agouti related protein (AgRP), a melanocortin receptor inverse agonist [14](Figure 6).

Diagram of ghrelin effect on energy metabolism in adults. Ghrelin is excreted mainly by the stomach but also from the hypothalamus. Ghrelin stimulates the appetite in the hypothalamus by stimulating the neuropeptide Y (NPY), which is a powerful originating factor, and agouti-binding protein (AgRP), which is a melanocortin receptor reverse agonist. These actions are mediated through (GHS-R). Ghrelin is also thought to induce adipogenesis through independent GHS-R mechanisms.

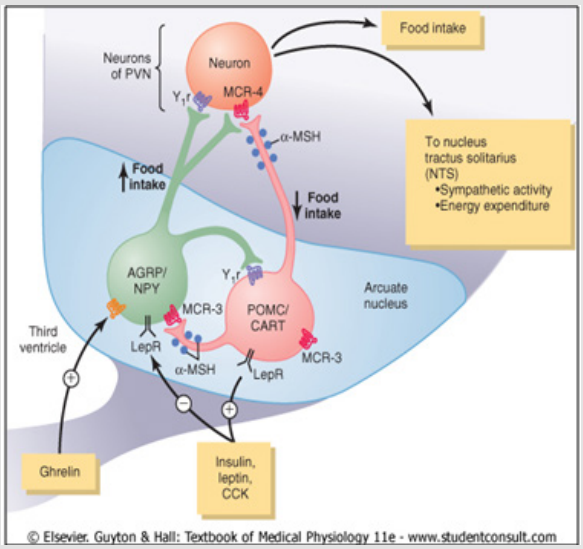

Figure 7: Hypothalamic neurons involved in energy balance regulation.

B. Ghrelin and Regulate Appetite: The arcuate nucleus (ARC) of the hypothalamus and brainstem is an important area involved in the regulation of appetite, body weight and energy balance [15]. The variety of hypothalamic appetite regulators divided into two groups: The orexigenic types

(appetite stimulators) which include the Neuropeptide Y (NPY), the Agouti Related Peptide (AgRP), ghrelin, orexin and cannabinoids, while the anorectics (appetite suppressants) which include Proopiomelanocortin (POMC), and Cocaine and Amphetamine Regulated Transcript (CART), Thyrotropin Releasing Hormone (TRH), Corticotropin Releasing Hormone (CRH), Peptide YY (PYY), Cholecystokinin (CCK) and Glucagon Like Peptide (GLP 1) [16](Figure 7).

Ghrelin is a peptide made of 28 amino acids, synthesized mainly by Oxidizing glands in thestomach (Hebebr and Remschmidt, 1995). Ghrelin is acylated in the third residue which is a serine, introducing fatty acids (n-octanoyl) is essential for its activity[17]. It is one of the major signaling mechanisms the start of the meal [18].

Ghrelin and Control of Energy Balance

Control of energy balance through two types of neurons of the arcuate nuclei: (1) Proopiomelanocortin (POMC) neurons that release amelanocyte- stimulating hormone (α-MSH) and Cocaine- and Amphetamine Regulated Transcript (CART), reducing food intake and increasing energy expenditure; and (2) neurons that produce Agouti Related Protein (AGRP) and Neuropeptide Y (NPY), increasing food intake and decreased energy expenditure. α MSH released by POMC neurons stimulates melanocortin receptors (MCR-3 and MCR-4) in the Paraventricular nuclei (PVN), Which are then activated neuronal pathways that project to the Nucleus Tractussolitarius (NTS) and increase sympathetic activity and energy expenditure. AGRP act like an antagonist of MCR-4. leptin ,Insulin, and Cholecystokinin (CCK) are hormones that inhibit AGRP-NPY neurons and stimulate adjacent POMC-CART neurons, thereby decreased food intake. Ghrelin, a hormone secreted from the stomach, activates AGRP-NPY neurons and motivate food intake. leptin receptor (LepR); neuropeptide receptor (Y1R) [19].

Two groups of neurons in the arcuate nucleus are known by the neuropeptides that they coexpress, the Neuropeptide Y (NPY) and Agouti Related Protein (AgRP) Orexigenic Neurons as well as the Proopiomelanocortin (POMC) and Cocaine and Amphetamine Related Transcript (CART) Anorexigenic Neurons. These co expressing neurons they are differentially regulated by circulating adiposity signals, satiety signals, differentially activate second order neurons that control food intake and energy expenditure [19]. It stores (long term energy availability),orchestrate hormonal, autonomic responses via differential regulation of downstream neurons in the hypothalamus and other brain regions.

The Role of Ghrelin's Proautophagic Properties in Cellular Homeostasis

Ghrelin role Proautophagic Properties in Cellular Homeostasis (A) Ghrelin enhances autophagy in a GHS-R1a-dependent manner. Activated AMPK inhibits mTOR via activation of TSC and inactivation of Raptor. RaptorinducedInhibitory Phosphorylation of ULK1 is decreased, leading to activation of ULK1 Kinase activity, and activated ULK1 triggers autophagy [20].Ghrelin exerts a cytoprotective effect by inducing autophagy in neurons, Intestinal Epithelial Cells (IECs), and Vascular Smooth Muscle Cells (VSMCs). Ghrelin's proautophagic property improves hepatosteatosis by increasing the abundance of mtDNA and inducing mitochondrial FFA B oxidation. CaMKKb and the SIRT1 p53 axis also mediate signaling to AMPK in the setting of autophagy, as in the case of hypothalamic ghrelin signaling. (B) Under fasting, fat depleted conditions, Growth hormone maintains blood sugar levels by stimulating hepatic autophagy and subsequent gluconeogenesis. Ghrelin is necessary to maintain growth hormone levels under hunger, fat depleted conditions. Growth hormone signaling induces autophagy via pSTAT. The molecule that connects the growth hormonepSTAT axis and autophagy is currently unknown. (C) Desacyl ghrelin stimulates AMPK activity, induces autophagy, and reduced apoptosis andROS accumulation, thereby protecting Cardiomyocytes from ischemic injury.

Ghrelin activates AMPK in hepatocytes, promotes autophagy, motivate mitochondrial biogenesis, and induces mitochondrial FFA b-oxidation, and so on ameliorates hepatic triglyceride over accumulation[21].(A)ghrelin attenuates hepatic lipotoxicity by enhancing autophagy via restoration of the AMPK/mTOR signaling pathway [22]. The ghrelin autophagy axis is essential for survival in famine. Under fasting, fat depleted conditions, organismsactivate hepatic autophagy to perform gluconeogenesis andmaintain blood glucose levels. This process is mainly orchestrated by the action of GH [23].Under hunger,fat depleted conditions, GOAT knockout mice exhibit insufficientGHup regulation, a decline in hepatic autophagy, and lethal hypoglycemia[24] (B).A comprehensive screen based on in vivo delivery of arrayed cDNA libraries aimed at identifying tissue protective factors revealedStrong and specific expression of the ghrelin gene in cardiac and skeletal muscles after acute ischemia[25]. Transduction of the ghrelin gene into the heart rescues Cardiomyocytes from ROS accumulation and apoptosis, Restores heart function after myocardial infarction in an autophagy manner (C).Desacyl ghrelin also reduce ROS production, lowers tissue inflammation and reinforces insulin stimulated glucose uptake in skeletal muscle in an autophagy dependent manner[26].

4.6.9.Ghrelin is Anti-Inflammatory[27-30]: It has been shown that ghrelin is able to exert anti-inflammatory actions by inhibiting the production of inflammatory cytokines.Ghrelin practice anti-inflammatory actions in inflammatory bowel disease, sepsis,pancreatitis, arthritis, and diabetic nephropathy[31-39]. Administration of ghrelin before the development of experimental pancreatitis improved pancreatic blood flow, Lower IL1 levels, and stimulated pancreatic cell proliferation[33]. In sepsis, ghrelin, via an upregulation of MAPK phosphatase 1, lowerNorepinephrine

and TNF levels known to cause hepatocellular dysfunction and upregulation of Proinflammatory Cytokines[40]. Furthermore, organ blood flow is improved by ghrelin via an inhibition of NF-kB(Wu, et al.) and HMGB1 production by activated macrophages is inhibited by ghrelin [32].

Ghrelin decreased IL6 levels and symptoms of arthritis in an animal model [31-55]. IL8 and IL6levels induced by insoluble fibrillary amyloid protein deposition in mouse microglia are lower by desacyl ghrelin but not by acyl ghrelin probably by amechanisminvolving, as already eluded to, an unidentified receptor distinct from GHS-R1A [41].Anti-inflammatory and antihyperalgesic effects of both desacyl ghrelin and acyl ghrelin have been shown in rats [38]. The development of experimental diabetic nephropathy in mice can be prevented by acyl ghrelin acting on GHS-R1A[39]. Inflammatory bowel disease, especially Crohn's disease, is improved by administering ghrelin [36,41-55].

Conclusion

Ghrelin is a peptide hormone that the stomach secretes primarily into the bloodstream, but other tissues have been shown to also synthesize it. Ghrelin can exert its effects through systemic or atomicin/ paracrine actions. The GHS-R1A receptor binds to acyl ghrelin and presumably mediates its biological effects. None the less, it is I realized that either GHSR1A homo- or heterodimmers could be participate in the ghrelinmediated actions. The formation of homo and heterodimmers is adding another level of complexity in the understanding of the actions of ghrelinGrowing sets of evidence support an increasing number of functions for desacyl ghrelin. So far, the exact mechanisms and a potential specific receptor have eluded determination. Much work remains to be done to determine if this additional level of complexity is indeed accounting for the biological effects of ghrelin.Varied physiological andnumerouseffectsof ghrelin, It has also been reviewed in this paper, have been reported. And so on, it appears important to perform further studies to better understand the fine underlying mechanisms accounting for these pleiotropic ghrelin actions. Current understanding of ghrelin biology and biological functions has led to the development of pharmacological tools modulating ghrelin actions and the evaluation of their clinical applications.

Conflicts of Interest

The authors report no conflicts of interest in this work.

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