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Review Article

Ghrelin and Its Role in Therapeutics

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Abstract

Ghrelin, derived from the word "ghre" referring "to grow," is a multifaceted hormone containing 28 amino acids produced from X/A cells of oxyntic glands in stomach. Pituitary gland regulates growth of various organs through hormones which, in turn, are controlled by a master switchboard, the hypothalamus. Ghrelin functions by increasing the release of growth hormone (GH) and plays a key role in endocrine system. The name ghrelin may wrongly make us think that it acts through GHRH, but it has receptor named GH secretagogue-receptor having a wide distribution and its therapeutic actions are not limited to one system. Its localization with dopamine receptor in hippocampus, hypothalamus, and striatum makes ghrelin to exert neuroprotective effect. Main physiological role of ghrelin is to regulate food intake and has orexigenic properties. Ghrelin has a short half-life due to degradation by proteases, and thus, ghrelin mimetics are employed as therapeutic agents. Ghrelin is regulated by acylation with the acylated form being active. Drugs affecting ghrelin functions are being evaluated for various conditions including cancer cachexia, diabetic gastroparesis, post-operative ileus, and fibromyalgia. This review will deal about the physiological functions of ghrelin, its possible therapeutic indications, approved drugs, and drugs in trials.

Key words: Ghrelin mimetics, Ghrelin, Growth hormone

INTRODUCTION

In the year 1976, Bowers *et al.* found that opioid peptide had no opioid activity but had mild growth hormone (GH) releasing property and they referred it as GH secretagogues which was found to act through receptor GH secretagogue receptor 1a (GHS-R1a), while GHS-R1b, the truncated form of the receptor, is found to be without any clear action. In 1999, endogenous ligand was identified from rat stomach and it was known as ghrelin taking its base from a word "ghre" meaning "to grow."[1] Ghrelin is a peptide which causes orexia by acting as regulator of food intake and since it stimulates release of GH, its use is also utilized in GH deficiency.

STRUCTURE

Human ghrelin gene is present in chromosome 3p25–26. After it undergoes transcription and translation, it yields preproghrelin precursor containing 117 Aminoacids (AA) and the final peptides formed include ghrelin with 28 AA and obestatin having 23 AA. Ghrelin is a peptide which is 28 in number and exerts its action by binding to GHS-R1a which is a seven transmembrane GPCR. It exists in 2 forms as acylated and desacylated. Acylated form is essential for ghrelin action (Figure 1). Ghrelin-O-acyl transferase is essential for the acylated form which is an unique post-transcriptional modification at 3rd position and plasma proteases have a role to degrade circulating ghrelin. Suppression of acyl ghrelin is related with acute exercise whereas increased des-acyl ghrelin results due to weight loss.[2] Recent evidence showed that desacylated ghrelin can also function as an independent hormone and can act as endogenous antagonist for acylated ghrelin at supra-physiological concentration.[3]

LOCATION

Ghrelin receptors are ubiquitously present both centrally and peripherally with its central distribution maximum in hypothalamus and peripheral tissues distribution maximum in stomach and also seen in heart, pancreas, kidney, and vasculature. Ghrelin is produced in maximal amount from X/A like cells which are present in fundus of stomach.

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REGULATION OF GHRELIN SECRETION

Ghrelin secretion is regulated by the following factors. The positive regulators include fasting, parasympathetic nervous activity whereas negatively regulated by food intake, sympathetic nervous activity, and leptin.

Physiological Functions and its Possible Indications

Central nervous system

Regulation of food intake

Ghrelin has a very important role in regulation and control of food intake. It is considered to be a signal for hunger. When hunger develops in the presence of decreased nutrients to brain, ghrelin levels gets raised and this plays as an orexigenic peptide to stimulate feeding center present in hypothalamus. After food intake, levels of ghrelin fall down and this causes a feeling of fullness. Ghrelin has opposite action of leptin and this activates NPY/AgRP neurons to stimulate food intake is shown in Figure 2.[4] The molecular mechanisms involved in regulation of food intake is shown in Figure 3. [5]

Higher brain functions

Ghrelin is found to increase dopamine release from ventral tegmental area and this has a role in reward system. Colocalization of ghrelin receptors with dopamine receptors and dimerization of them in hippocampus, striatum, and arcuate nucleus helps in learning, memory, and improves synaptical plasticity.[6]

Taste

Two systems are present in taste cells which have role in transduction of taste. They include Amiloride-sensitive and insensitive and this is differentiated based on their response to Amiloride (ENaC blocker). There is coexpression of ENaC with ghrelin and this has been found in animal studies. Ghrelin is found to have role in transmitting taste sensation to CNS by increasing serotonin levels in nucleus accumbens.[7]

Indication

Ghrelin agonists MK-0677 and LY444711 have found to have protective role in Alzheimer's disease (Figure 4) in animal studies by following mechanisms.[8]

Endocrine role

GH releasing function

Ghrelin being a GH release facilitator finds its use to find out, whether there is GH deficiency or not.

Indication

Macimorelin acts by increasing GH release and this is used to find out deficiency of GH after the drug is given orally.[9]

Relation with cortisol

Cortisol is considered to be involved in stress and it increases level of ghrelin to increase food intake.[10]

Reproduction

Ghrelin decreases LH and FSH levels and delays the development of puberty. Dysregulation of ghrelin secretion has been observed in Polycystic Ovarian Syndrome.[11]

Glucose homeostasis

Ghrelin and insulin are inversely related and increase in ghrelin levels leads to hyperglycemia. Ghrelin exerts this action by stimulating secretion of glucagon and inhibiting insulin secretion (Figure 5). *Ghrelin has only role in low-energy balance to maintain glucose homeostasis*.[12]

Indication

On long-term treatment with ghrelin receptor antagonist [D-Lys3]-GHRP-6 in animal studies, it worsened the diabetes most likely due to desensitization of the receptor on long term.[13] Hence, the use of ghrelin receptor antagonists for diabetes mellitus requires further research.

Heart

Ghrelin is found to have cardioprotective effect (Table 1) by the following mechanisms.[14]

- Stimulation of Akt/Mitogen-activated protein kinase pathway which is highly proliferative and exerts anti-apoptotic effects. This property is utilized in cardiac cachexia.
- Inhibits sympathetic system causing vasodilation.
- In preclinical studies, it is found to increase growth by IGF-1-mediated actions leading to hypertrophy of heart.[15]

Adipose tissue

White adipose tissue functions to store fat, whereas brown adipose tissue will release heat which will help in thermogenesis. Ghrelin promotes fat storage by activating white adipose tissue, whereas and deactivates brown adipose tissue function by inhibits sympathetic system by deactivating brown tissue function. Thus, ghrelin acts like an orexigenic peptide causing weight gain.

Indication

- An endogenous ghrelin antagonist Liver-expressed Antimicrobial peptide 2 acts as negative regulator for ghrelin and it is found to reduce food intake and GH secretion in preclinical studies, thereby becoming a potential target for regulation of energy homeostasis.[6]
- Prader–Willi syndrome: It is a congenital obesity syndrome characterized by hyperphagia, GH deficiency, and dysmorphic features. In adults, due to obesity, ghrelin levels will fall due to the progression of the disease and loss of function of ghrelin.[16]

Liver

Ghrelin exerts fat storage in liver by inhibiting expression of AMP-activated protein kinase (AMPK) leading to

lipogenesis. This activates downstream pathways mTOR and PPAR-gamma which leads to hepatic steatosis (Figure 6). The anti-inflammatory action of ghrelin in liver prevents progression of non-alcoholic fatty liver disease to non-alcoholic steatohepatitis.[17]

Intestine

Ghrelin stimulates the gastric motility mediated by parasympathetic system.[18]

Indication

This property helps ghrelin to be employed in conditions such as diabetic gastroparesis and post-operative ileus, where the motility is decreased and ghrelin mimetics are in clinical trials for those conditions.

Bone formation

GHS-R1a is also seen in osteoblasts and ghrelin by activating this is found to increase bone mineral density (BMD) in animal studies.[19]

Indication

Serum ghrelin concentration predicts BMD and this is done in patients with anorexia nervosa.

Anti-inflammatory effect

Ghrelin downregulates GHS-R present in T lymphocytes thereby inhibits pro-inflammatory mediators release. The mediators include tumor necrosis factor-alpha, IL-6, and IL-1beta. Ghrelin also enhances the expression of IL-10 which is an anti-inflammatory cytokine and it also promotes thymopoiesis.

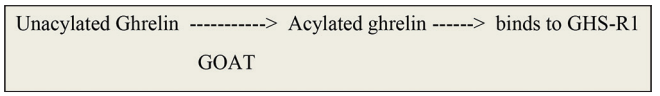

Figure 1: *Illustration of ghrelin metabolism in target tissues*: Unacylated ghrelin metabolized by Ghrelin-O acyl transferase (GOAT) forming acylated ghrelin which binds to Growth Hormone Secretagogue –Receptor 1 (GHS-R1) and exerts its actions.

Indication

- In animal studies, ghrelin has a protective role in sepsis by proliferation of CD4 T-cells. Ghrelin also exerts its action by inhibition of pro-inflammatory mediators and inhibition of High Mobility Group Box 1 protein.[20]
- Ghrelin agonist GH releasing peptide (GHRP-2) was found to decrease inflammation by inhibiting IL-6 in arthritic rats.[21]
- Parkinson's disease is characterized by degeneration of neurons and activation of microglia leading to release of inflammatory mediators. Ghrelin exerts neuroprotective effect by its anti-inflammatory property of decreasing IL-6 in animal model of Parkinson's disease.[22]
- *Whole body radiation and sepsis* induced in animals activates the sympathetic system and release norepinephrine. This stimulates Kupffer cells in liver to release inflammatory mediators which are inhibited by giving ghrelin through anti-inflammatory effect.[23]
- It inhibits nuclear factor-kappa B in endothelial cells and exerts its protective effect in atherosclerosis by decreasing inflammation.[24]

Table 1: Ghrelin as cardioprotective agent

Indications	Rationale for use
Coronary artery disease	Anti-inflammatory effect and regulate atherosclerosis
Hypertension	Vasodilation and decrease in sympathetic nervous activity
Cardiomyopathy	Inhibit myocardial apoptosis
Heart failure	Promote growth of heart and in cardiac cachexia (end-stage HF), used by acting as regulator of food intake and by its anti-oxidative effects.

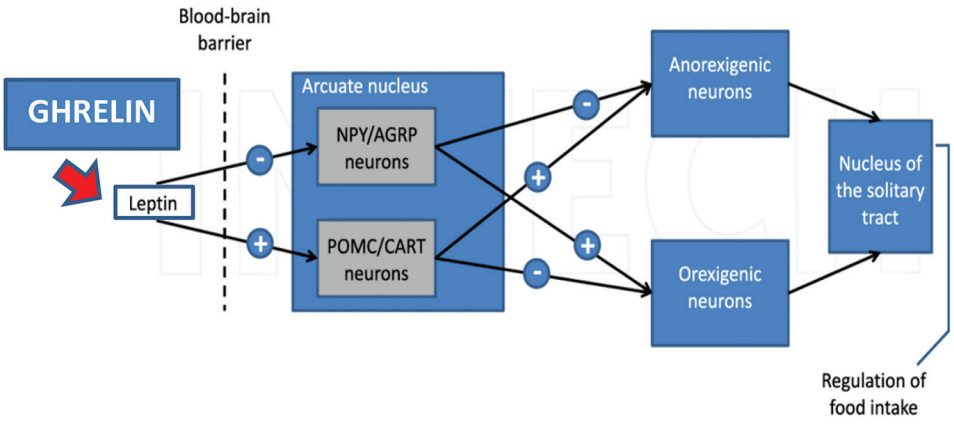

Figure 2: *Relation between leptin and ghrelin*. Ghrelin inhibits the activity of leptin and stimulates NPY/AgRP neurons to regulate food intake, leading to weight gain. NPY: Neuropeptide Y, AGRP: Agouti-related peptide, POMC: Pro-opiomelanocortin, and CART: Cocaine and amphetamine regulated peptide.[4]

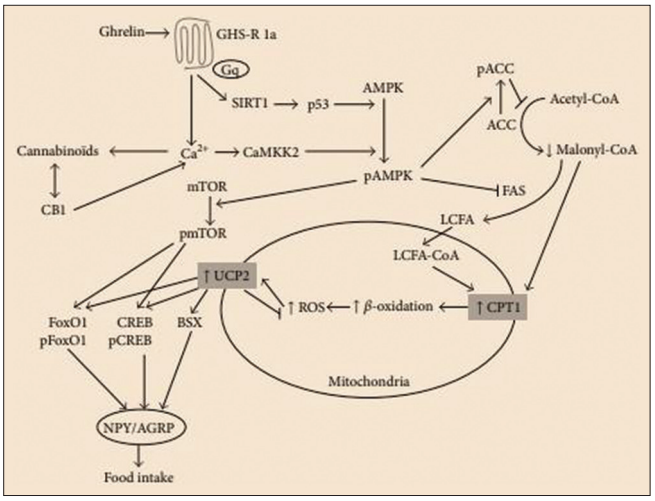

Figure 3: Molecular mechanisms involved in regulation of food intake. Ghrelin triggers a central SIRT1/p53 pathway and this leads to phosphorylation of AMP activated protein kinase (AMPK) leading to increased beta-oxidation and reactive oxygen species (ROS) production which stimulate UCP-2 to regulate food intake by stimulating NPY/AgRP neurons in arcuate nucleus of hypothalamus. SIRT1-sirtuin 1, AMPK-5' adenosine monophosphate activated protein kinase, CaMKK2-calmodulin kinase-kinase 2, CB1-cannabinoid receptor 1, ACC-Acetyl CoA carboxylase, FAS-fatty acid synthase, UCP2-Uncoupling Protein 2, CREB- cAMP response element binding protein, CPT1-carnitine palmitoyl transferase, BSX- Brain specific homeobox transcription factor, and FoxO1-factor forkhead box O.5

Muscle

It is found that ghrelin increases muscle growth by activation of insulin-like growth factor 1 in animal studies.

Indication

By this mechanism, it is used in cancer cachexia, where there are decreased muscle mass and impaired function of muscle thereby preventing muscle atrophy.[25]

Kidney

Degradation of ghrelin occurs through kidney and any dysfunction in kidney contributes for the increased plasma ghrelin concentration. Inflammation, energy homeostasis, and CVS factors play a key role in pathogenesis of chronic kidney disease.

Indication

Since ghrelin has protective role in all three pathways, it can be considered as a biomarker in end-stage kidney disease.[26]

Vasculature

The vasodilating property of ghrelin (Figure 7) is found in animal studies.[27]

Gastrointestinal Stromal tumor (GIST)

Ghrelin has a proliferative activity and this increases risk of GIST by PI3K/AKT/mTOR pathway which controls cell growth, proliferation, and differentiation.[28]

Table 2: Macimorelin[29]

Mechanism of action	Pharmacokinetic property	Dose	Interpretation	Precautions
Stimulates release of growth hormone by acting as a GHS-R agonist	Absorbed between 0.5 and 1.5 h. Metabolized by CYP3A4 Excreted in urine with half-life of 4 h.	Given as an oral solution at dose of 0.5 mg/kg body weight.	Serum GH levels of less than 2.8 ng/ml at time points 30, 45, 60, 90 min is considered GH deficient	Avoid giving drugs metabolized by CYP3A4, drugs increasing GH secretion. Oral solution to be given in *fasting of 8 h.*

Table 3: Drugs in pipeline

Drugs	Clinical indication	Phase of clinical trial*	Rationale of use
Anamorelin[31]	Non-small cell lung cancer-Cachexia (NSCLC-C)	Phase 3	To regulate appetite and increase lean body mass
	Osteopenia and Sarcopenia	Phase 1	To improve muscle mass and bone growth
Relamorelin[32]	Diabetic gastroparesis	Phase 3	To stimulate motility
	Anorexia nervosa	Phase 2	To improve appetite
	Chronic constipation	Phase 2	To stimulate motility
Ulimorelin[33]	Enteral Feeding Intolerance	Phase 2	To regulate appetite
	Post-operative ileus	Phase 3	To stimulate motility
Ipamorelin	Gastrointestinal dysmotility	Phase 2	Reduce time to recovery of GI function after partial small or large bowel resection
Ibutamoren (MK-0677)	Fibromyalgia	Phase 2	To stimulate growth hormone as patients with fibromyalgia are GH deficient.

*as reported in the http://www.clinicaltrials.gov

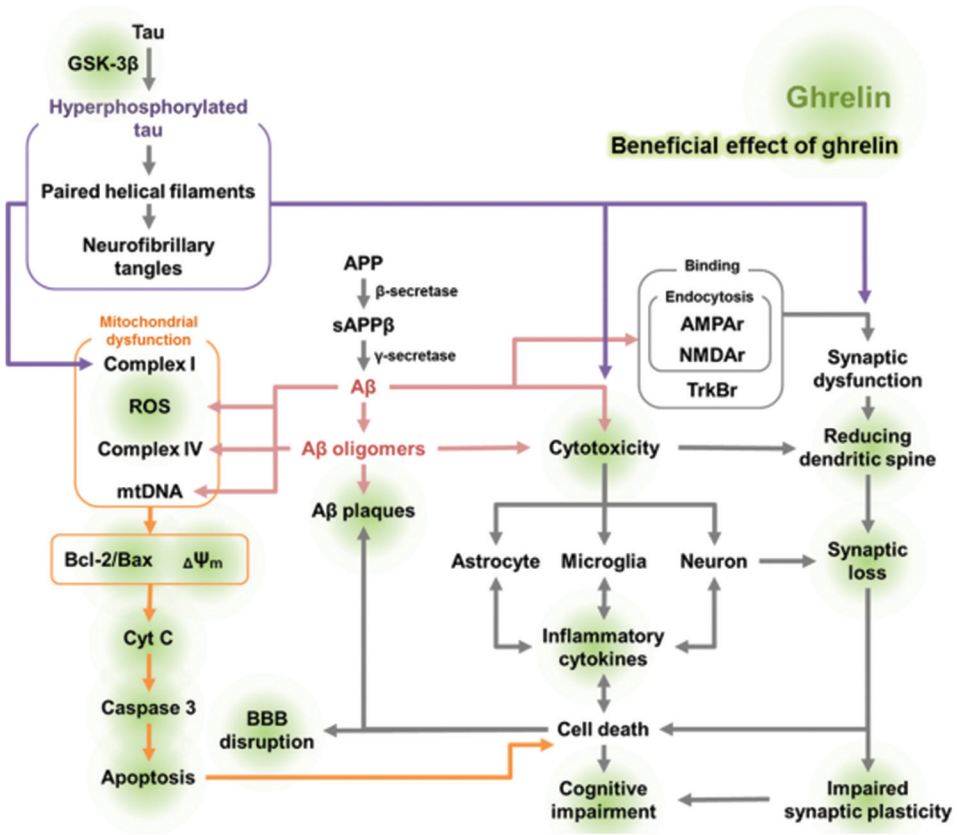

Figure 4: ***Therapeutic Use of ghrelin in Alzheimer's disease.*** **Ghrelin inhibits tau hyperphosphorylation by inactivating glycogen synthase kinase-3 β (GSK-3β) and reduces Aβ. It also reduces ROS by its anti-apoptotic effect and improves synaptic plasticity and cognition. APP-amyloid precursor protein, NMDAr-N-methyl D-aspartate receptor, TrkBr-Tropomysin receptor kinase B, and AMPAr-Alpha amino-3 hydroxy-5methyl-4isoxazolepropionic acid receptor[8]**

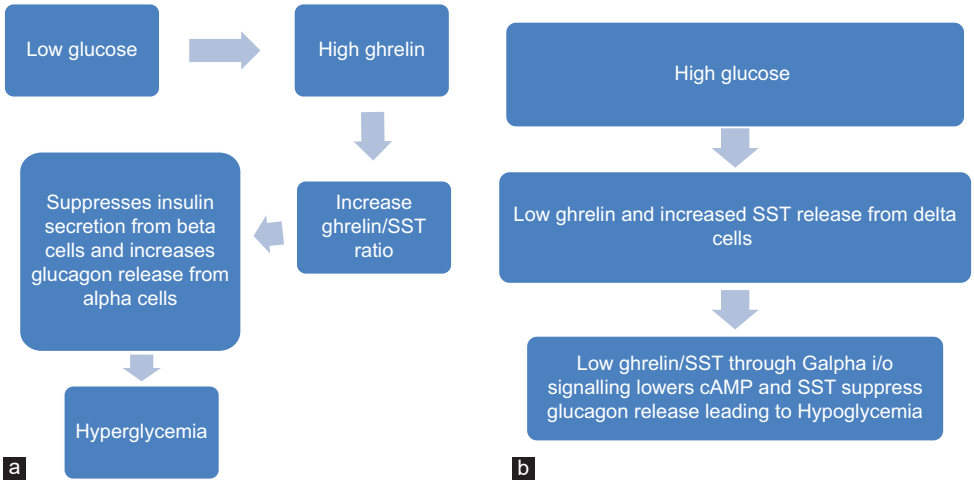

Figure 5: (a) In the setting of low glucose and (b) in the setting of high glucose[12]

APPROVED DRUGS

- Macimorelin is a non-peptide (Table 2) and got approved in the year 2017 by FDA.[29]
- The use of the drug is to find out whether the deficiency of GH is present or not. The test done is a provocation test.
- To measure GH levels, blood sample is drawn to determine levels at time points 30, 45, 60, and 90 min after giving the oral solution.
- Final concentration of the solution is made to 0.5 mg/ml after reconstitution of macimorelin granules in water.

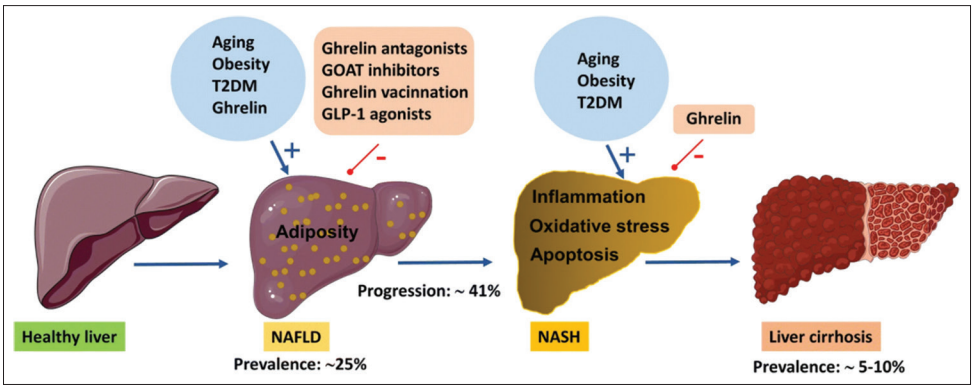

Figure 6: ***Ghrelin have a dual action on liver.*** **Metabolic factors such as aging, obesity, and Type 2 DM are risk factors for NAFLD and NASH. Ghrelin promotes hepatic steatosis and by its anti-inflammatory and anti-apoptotic effect, which prevents the progression of NAFLD to NASH. NAFLD-Non-alcoholic fatty liver disease, NASH-Non-alcoholic steatohepatitis. GOAT-Ghrelin-O acyl transferase[17]**

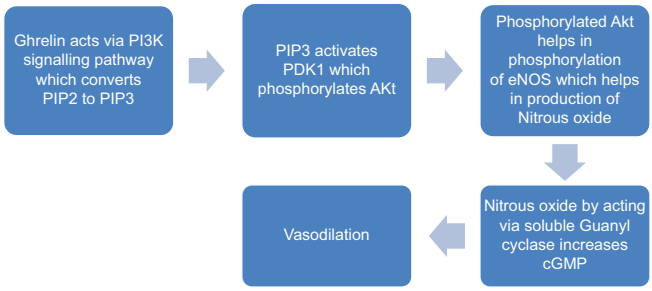

Figure 7: Vasodilator mechanisms of ghrelin

- The cutoff level of GH as 2.8 ng/ml is made from the phase 3 trials, where macimorelin is compared with insulin.
- Drugs affecting GH secretion should be avoided before doing the test as it may give false positive results.
- Drugs in pipeline for various conditions are shown in Table 3.

CAPROMORELIN

- It is a selective ghrelin receptor agonist approved by FDA in *dogs* in 2016.
- It is given orally at a dose of 3 mg/kg OD to stimulate appetite.[30]

CONCLUSION

Ghrelin has many protective effects as its release will be increased in different conditions such as restriction of calories, psychological stress and cachexia. Ghrelin mimetics show promising results in conditions involving gastrointestinal motility such as diabetic gastroparesis, post-operative ileus, and chronic constipation. It also shows promise in conditions to regulate food intake in cancer cachexia and anorexia nervosa, and hence, it is rightly called as a "Survival Hormone."

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