One must be careful when targeting GHRELIN in therapeutics

The multitude of effects associated with Ghrelin ....

- protection of neuronal and cardiovascular cells
- stimulation of growth hormone release
- increase of food intake and body weight
- modulation of glucose and lipid metabolism
- regulation of immune function
- regulation of gastrointestinal motility and secretion

Yin, et al 2014
Belly to Brain: Pathways of ghrelin and ghrelin ligands.
Three components of the ghrelin system:

- **Activated Ghrelin**
  - Ghrelin Active esterified form (acylated ghrelin)

- **The activating enzyme**
  - GOAT (Ghrelin O-acyltransferase) (the enzyme that acylates ghrelin)

- **Activated ghrelin receptor**
  - Ghrelin Receptor: GHSR1a
ghrelin receptor = growth hormone secretagogue receptor (GHSR)

GHSR response is dependent on the type of tissue and cells

Transcription
Receptor interaction
Internalization

Yin, et al 2014
Growth hormone secretagogue receptor (GHSR)

ghrelin requires acylation by the enzyme GOAT in order for the peptide to bind to GHSR1a

GHSR:
- (GPCR)
- heterotrimeric G protein-coupled receptor
- contains 366 amino acids
- seven transmembrane domains (TMI-VII)
Physiological functions of GHSR1a

- Release of hormones (adrenocorticotropic hormone, cortisol, prolactin)
- Modulation of food intake and energy metabolism
- Regulation of gastrointestinal motility and secretion
- Pancreatic function
- Cell proliferation and survival
- Attenuation of proinflammatory cascades
- Aging
- Gastrointestinal homeostasis
- Cell protection: nervous and cardiovascular systems

Note:
There are two isoforms of GHSR: 1a and 1b
GHSR1a is the active form of GHSR

Yin, et al 2014
- Human GHSR1a consists of 366 amino acids
- Molecular mass of approximate 41 kDa
- G-Protein Coupled Receptor (GPCR)
- The N-terminal domain forms a β-hairpin structure
- TM II and TM III are considered the ligand activation domains
- Two conserved cysteine residues (Cys116 and Cys198) on extracellular loops 1 and 2 form a disulfide bond
- The cysteine residues are essential for binding and activation of GHSR1a by different ligands

The intracellular ends of TM VI and TM VII move away from the center of the receptor toward TM III, exposing the sites subsequently recognized by G-proteins and β-arrestin.

Ligand binding stabilizes the active conformation of GHSR1a.

Yin, et al 2014;
Mear, et al 2013
GHSLR1a dimerizes with other receptors

These heterodimers are part of the complexity of the ghrelin system

- dopamine 1 receptor (D1R)
- dopamine 2 receptor (D2R)
- melanocortin-3 receptor (MC3R)
- serotonin 2C receptor (5-HT$_{2C}$)
- cannabinoid type 1 receptor (CB1)

GqPCRs: GH Secretagogue Receptors
Interaction between GHSR and dopamine receptors

- Coexpression of GHSR and DA receptors at a number of sites
- These regions are associated with food intake and reward seeking behaviors
- Recall, dopamine receptors have two families
  - D1-like, which includes D1R and D5R, and D2-like, which includes D2R, D3R, and D4R
Ghrelin and Dopamine

In the presence of both dopamine (DA) and ghrelin, the ghrelin receptor (GHSR1a) is induced, amplifying cAMP accumulation via the D1R. This process is further amplified by GHSR1a dimerization with the D1R, enhancing D1R signaling.
Dimerization between D1R and GHSR1a.

When dimerized with D1R, GHSR1a switches G-protein coupling from $G_{q/11}$ to $G_{i/o}$. Coadministration of a D1R agonist with a GHSR1a agonist leads to a fourfold amplification of D1R-associated cAMP accumulation. It is believed that the $G_B^Y$ subunit associated with GHSR1a adopts a stimulatory role on adenylyl cyclase activity due to the proximity of the $\alpha_S$ subunit derived from D1R’s trimeric G-protein.

Martin Wellman, and Alfonso Abizaid eneuro
the absence of ghrelin...

D2 receptor inhibits adenylyl cyclase activity through a G\(\alpha_i\) pathway

DA

GHSR1a

anorexigenic effects

D2R

GHSR1a oligomerizes with D2R
Dimerization between D2R and GHSR1a.

Proposed signaling through D2R involves coupling to a G\textsubscript{i} pathway, which typically does not involve intracellular Ca\textsuperscript{2+} accumulation from the endoplasmic reticulum.

Dimerization with GHSR1a, in the absence of a ghrelin ligand leads to a PLC-dependent accumulation of Ca\textsuperscript{2+}. D2R’s G\textsubscript{βγ} subunit acts to stimulate PLC activity, and α\textsubscript{i} coupling by D2R is also required for Ca\textsuperscript{2+} accumulation.

In contrast, G\textsubscript{q} activity associated with GHSR1a is not required for D2R-induced Ca\textsuperscript{2+} accumulation.

It is believed that the D2R-GHSR1a dimer is responsible for the anorectic effects of D2R agonists such as cabergoline.
Hypothalamic integration of energy intake. The hypothalamus receives innervation from several areas, notably the nucleus tractus solitarius and area postrema in the brainstem, that relay many neural and hormonal signals from the gastrointestinal tract, such as mechanical signals indicating stretch of the stomach and other areas of the intestine, and hormonal signals indicating the presence of food in the gut, such as cholecystokinin. Additional signals regarding smell, sight, memory of food, and the social context under which it is ingested are also integrated and may also influence energy intake by modulating output from the hypothalamus. Hormones also alter hypothalamic gene expression resulting in modulation of energy intake.

Leptin and insulin decrease appetite by inhibiting the production of neuropeptide Y (NPY) and agouti-related protein (AgRP), while stimulating melanocortin-producing neurons in the arcuate-nucleus region of the hypothalamus. NPY and AgRP stimulate eating, and melanocortins inhibit eating.

Ghrelin stimulates appetite by activating the NPY/AgRP-expressing neurons. PYY3–36, released from the colon, inhibits these neurons and transiently decreases appetite. Integration of these signals results in the activation of gene expression of mediators implicated in the regulation of satiety, control of thermogenesis, and energy expenditure.

CART, cocaine- and amphetamine-regulated transcript; α-MSH, α-melanocyte-stimulating; PYY, polypeptide YY.

Source: Chapter 10. Endocrine Integration of Energy and Electrolyte Balance, Endocrine Physiology, 4e
Citation: Molina PE. Endocrine Physiology, 4e. 2013 Available at: https://accessmedicine.mhmedical.com/content.aspx?sectionid=42540510&bookid=507&jumpsectionId=42541696&Resultclick=2
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The chronic activation of the mechanisms that restore homeostasis results in alterations in function in virtually all organ systems. The short-term activation of these stress response mechanisms ensures that energy substrates are available to meet the increased metabolic demands of the individual. However, prolonged duration and increased magnitude of their activity leads to erosion of lean body mass and tissue injury. GH, growth hormone; GnRH, gonadotropin-releasing hormone; HPA, hypothalamic-pituitary-adrenal axis; IGF-1, insulin-like growth factor 1; SNS, sympathetic nervous system; TSH, thyroid-stimulating hormone.
GHRELIN

Growth hormone

Liver

- Adipose tissue: Lipolysis, Release of fatty acids
- Most tissues: Decreased glucose utilization

Insulin-like growth factor 1

- Cartilage and bone: Growth
- Muscle and other organs: Protein synthesis, Growth
Central ghrelin resistance at the level of the hedonic/reward system = inability to cope with anxiety = increased susceptibility to depression (ex. obesity)

Ability to mobilize ghrelin in response to stress and to induce normal hedonic/reward response = reduced anxiety

- Obesity
- Chronic Stress (CSDS)
- Ghrelin
- Hedonic/reward response
- Emotional eating
- Alcohol/Drugs craving

Anxiety/Depression

+ +

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