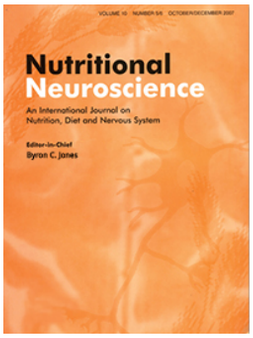

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REVIEW

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Ghrelin as a prominent endocrine factor in stress-induced obesity

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ABSTRACT

Objectives: Ghrelin acts on a variety of central- and peripheral organs causing an orexigenic effect, conclusively followed by increased caloric intake. Recent studies have indicated that ghrelin's function as an orexigenic agent does not entirely reflect the full functional properties of the peptide. Specifically, ghrelin regulates stress-hormone synthesis and secretion therewith affecting the stress-axis. The role of stress in the development of obesity has been extensively studied. However, the orexigenic and underlying stress-regulatory effect of ghrelin has not yet been further considered in the development of stress-induced obesity.

Methods: Therefore, this review aims to accentuate the potential of ghrelin as a factor in the pathological development of stress-induced obesity.

Results: In this review we discuss (1) the ghrelin-mediated intracellular cascades and elucidate the overall bioactivation of the peptide, and (2) the mechanisms of ghrelin signalling and regulation within the central nervous system and the gastro-intestinal system.

Discussion: These biological processes will be ultimately discussed in relation to the pathogenesis of stress-induced obesity.

KEYWORDS

Ghrelin; central nervous system; gastro-intestinal tract; stress; obesity

Introduction

Ghrelin was discovered in 1999 by Kangawa and Kojima [1] in their search for the then-unknown endogenous ligand for the growth hormone secretagogue receptor (GHS-R), a specific G protein-coupled receptor (for review [2,3]). The research conducted by Kangawa and Kojima demonstrated that ghrelin, a hormone derived from epithelial parietal P/D(1) cells in the gastro-intestinal mucosa, was the endogenous ligand for GHS-R (for review [4]). The main function of ghrelin is to regulate food consumption during fasting periods (for review [5]). This orexigenic effect before meals is predominantly achieved by ghrelin acting directly on hunger-regulating brain regions.

The obesity epidemic, which currently affects over one-third of the human population worldwide, is classified as a progressive global health issue [6,7]. A large part of obesity pathogenesis can be prevented, although this requires active behavioural or lifestyle interventions and in some cases medication to suppress hunger and appetite (for review [8]). Exposure to stress can affect dietary intake by influencing behavioural changes [9] and physiological processes such as elevating lipogenesis rate (for review [10]).

In this review, we aim to gain a better understanding of ghrelin as a potent factor in the pathogenesis of stress-induced obesity. Therefore, we will first review the main characteristics and background of ghrelin, and secondly, we will discuss the mechanisms of ghrelin signalling and regulation within the central nervous system and gastro-intestinal tract in greater detail. Finally, the functionality of ghrelin in the central nervous system and gastro-intestinal tract in relation to the pathogenesis of stress-induced obesity will be discussed.

Ghrelin

Ghrelin is a peptide hormone composed of 28 amino acids requiring an essential enzymatic (O-acyltransferase) modification to enable the bioactivity and capability of the compound to activate one of the two ghrelin receptors [1,11]. Two different ghrelin receptors have been isolated: GHS-R1a and GHS-R1b. GHS-R1a consists of a characteristic seven transmembrane helix

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(TM) structure with three intracellularly bound subunits (Gα, Gβ and Gγ) [12,13]. The GHS-R1b is metabolically inactive because it misses two of the seven TM domains (TM VI and VII) [14], preventing it from binding both extracellular ghrelin as well as the intracellular Gα-subunit [15].

The activation of GHS-R1a by ghrelin induces multiple cell signalling pathway cascades, which can in turn regulate large arrays of metabolic processes such as gluconeogenesis or fat deposition (Figure 1). Studies suggest that the GHS-R1a attains a constitutively active state, but that the binding of ghrelin significantly promotes the intracellular signalling pathways, such as the protein kinase C (PKC)-activation pathway or G protein-coupled inwardly rectifying potassium (GIRK)-channel regulation [16,17]. In more detail, extracellular binding of ghrelin to GHS-R1a promotes receptor activation through the intracellular binding of guanosine triphosphate (GTP) which subsequently causes the binding of the Gα-subunit to TM III-VI. The Gα-subunit consists of different sub-types (i.a. Gαq, Gαs, Gαi) of which each can target different intracellular signalling pathways either by stimulating GH-secretion, elevating gene expression or inducing plasma membrane depolarisation (Figure 1).

Ghrelin and the central nervous system

Studies demonstrated that the blood-to-brain influx of ghrelin is remarkably low compared to other peptides [18]. It has been shown in a mouse model that the n-octanoylation of des-acyl ghrelin directly affects the ability of the peptide to cross the blood brain barrier (BBB). In detail, des-acyl ghrelin has a relatively high blood-to-brain influx, but a low brain-to-blood efflux, whilst n-octanoylated (acyl-)ghrelin shows an opposite BBB transportation influx and efflux ratio [18]. Although the presence of such a BBB-regulating mechanism was found in mice, it is unknown whether this mechanism is also present in humans. The regulation of ghrelin transport across the BBB is not mediated through GHS-R1a activation in the brain and instead occurs independently of the receptor [19]. Moreover, it is suggested that ghrelin mainly reaches brain tissue located near the circumventricular organs (CVOs) such as the median eminence (for review [20]). CVOs are known to contain a highly leaky vasculature, which allows the dispersal of ghrelin through highly fenestrated capillaries (for review [21]). The ability of ghrelin to reach target brain tissues has now been considered to be mainly appointed to the dispersal through capillaries near CVOs and the limited amount of blood-to-brain influx through the BBB. However, multiple studies suggest that ghrelin is also able to reach brain regions such as the hypothalamic arcuate nucleus by crossing the blood-cerebrospinal fluid (CSF) barrier at the choroid plexus [22,23] (for review [20,21]). In addition, it has been hypothesised that small amounts of ghrelin might be synthesised within the brain itself [24], completely circumventing the requirement of ghrelin to cross the BBB, however, this hypothesis has been questioned by multiple studies (for review [25]).

The ghrelin receptor GHS-R1a is expressed in hypothalamic neuropeptide Y- (NPY) and agouti-related peptide- (AgRP) expressing neurons (NPY/AgRP neurons), somatotropic cells and luteinising hormone (LH)-, thyroid-stimulating hormone (TSH)-, adrenocorticotropic hormone (ACTH)- and prolactin- (PRL) releasing cells in the anterior pituitary [26–29]. A lower expression of GHS-R1a is found in other brain regions such as the cingulate gyrus [30–32], amygdala, olfactory bulb and in hypothalamic ghrelin-receptive neurons adjoining the dorsal vagal complex (DVC) [33]. The expression of GHS-R1a is found across three distinct brain areas: pituitary gland (i.a. GH and ACTH release stimulation), hypothalamus (i.a. orexigenic and energy-saving, growth hormone-releasing hormone [GHRH] release stimulation) and in brain regions involved in food perception such as the midbrain and olfactory bulb (i.a. taste, reward sensation and olfaction) for review [34].

Hypothalamus

The orexigenic and energy preserving effect of ghrelin in the hypothalamus is achieved through the stimulation of NPY/AgRP-expressing neurons and the subsequent inhibition of pro-opiomelanocortin (POMC)- expressing neurons in the ventral region of the hypothalamic arcuate nucleus (Figure 1) [35,36]. NPY/AgRP and POMC neurons are located near the median eminence, allowing access to peripherally derived ghrelin through the fenestrated capillaries [37]. NPY is one of the most dominant orexigenic regulating peptides that act directly on the paraventricular, dorsomedial and ventromedial regions of the hypothalamic nuclei which stimulates (carbohydrate) food consumption [38,39]. Chronic NPY expression has also been reported to elevate insulin plasma levels and increase fat deposition, indicating the impact of NPY on insulin secretion [39,40]. AgRP has an orexigenic and energy-saving effect by functioning as a paracrine inhibitor of alpha-melanocyte-stimulating hormone (α-MSH), a cleavage product of ACTH which in turn is a cleavage product of POMC (for review [41]). GABA-releasing AgRP neurons additionally exert an inhibitory effect on

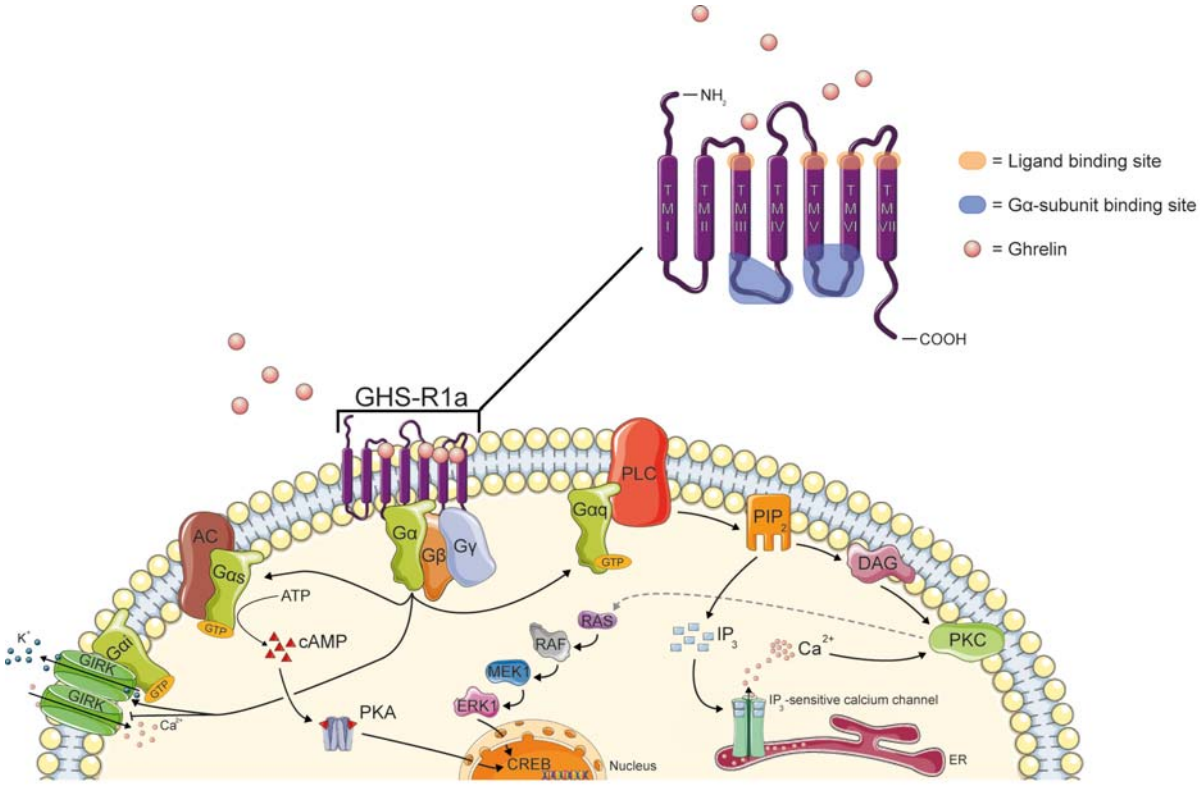

Figure 1. Schematic overview of the major cell signalling pathways regulated by GHS-R1a activation. Inactive ghrelin (des-acyl ghrelin) is activated through the n-octanoylation of Ser3 by the enzyme GOAT. Ghrelin can activate three major signalling pathways regulated through different Gα-sub-types: PLC – PIP_2 – IP_3/DAG – PKC pathway**,** AC – PKA – CREB pathway and GIRK pathway. In detail, the Gαq sub-type induces GH-release by promoting cytosolic Ca2+ concentrations through activation of the PLC – PIP_2 – IP_3/DAG – PKC pathway. Secondly, the Gαs sub-type elevates gene expression through the AC – PKA – CREB pathway. Lastly, the Gαi sub-type induces plasma membrane depolarisation through regulating GIRK channels. The MAPK/ERK pathway is mainly regulated by tyrosine-kinase receptor activation, but is also stimulated by PKC to a lesser extent (dashed grey line). Abbreviations: Ser3: serine3. GOAT: ghrelin-O-acyltransferase. PLC_PIP2_Ip3/DAG-PKC pathway: phospholipase C (PLC) – phosphatidylinositol 4,5-biphosphate (PIP2) – inositol triphosphate (IP3)/diacyl glycerol (DAG) – PKC pathway. AC-PKA-CREB pathway: adenylyl cyclase (AC) – protein kinase A (PKA) – cyclic adenosine monophosphate (cAMP)-responsive transcription factor (CREB) pathway. GIRK pathway: G-protein-coupled inwardly rectifying potassium pathway. MAPK/ERK pathway: mitogen-activated-protein-kinase (MAPK) / extracellular-signal-regulated kinase (ERK) pathway.

POMC neurons [42]. The decreased plasma levels of α-MSH following α-MSH and POMC inhibition lead to increased food consumption and decreased energy expenditure [39,43,44].

Pituitary gland

Ghrelin has also been found to elevate the secretion of the stress hormone cortisol from the adrenal gland through ACTH release in two separate pathways, which indicates a plausible involvement in stress-induced obesity. Firstly, ghrelin stimulates the cleavage of POMC to ACTH by CREB-mediated prohormone convertase-1 gene expression in somatotropic cells located in the anterior pituitary [26,45,46]. Secondly, ghrelin stimulates corticotropin cell proliferation and hypertrophy, which consequently enhances somatotropic ACTH synthesis and secretion in the anterior pituitary [47]. The regulation of ACTH by ghrelin suggests a role of ghrelin in the hypothalamic–pituitary–adrenal (HPA) axis, which can further accentuate ghrelin's role in stress-induced pathologies (see 'Ghrelin and stress-induced obesity'). Apart from GH and ACTH, other hormones that are synthesised and released in the pituitary have also been found to be regulated by ghrelin, such as LH [48], PRL [49] and TSH [27].

Other brain regions involved in reward and food perception

The effect of ghrelin is not limited to the hypothalamus and pituitary. Multiple studies demonstrate that ghrelin can influence reward and taste sensory regions in the

midbrain and olfactory bulb. Ghrelin affects reward sensation by elevating locomotor activity, dopamine gene expression and signalling, and it elicits impulsive behaviour in animal models by acting on neurons co-expressing dopamine receptor and GHS-R1a in the ventral tegmental region and substantia nigra of the midbrain [50–52]. The impact of ghrelin on taste sensation is in turn realised through the stimulation of olfactory sensory neurons. Ghrelin was found to promote olfactory function by adjusting sniffing patterns and the detection threshold of olfactory neurons in the olfactory bulb [53], which consequently stimulates the orexigenic effect of NPY/AgRP neurons in the hypothalamus (for review [54]).

Concluding, the effects of ghrelin on the CNS are highly sophisticated and roughly divided across three areas: the pituitary gland, hypothalamus and brain regions involved in reward and food perception. Of these three areas, the pituitary gland and hypothalamus, in particular, show an abundant expression of GHS-R1a; in hypothalamic NPY/AgRP neurons and in LH-, TSH-, ACTH- and PRL-releasing cells in the anterior pituitary (Figure 3). The ramification of GHS-R1a activation and subsequent GH(RH) release by ghrelin in the CNS is well understood presently, however further research has to be conducted on the underlying BBB transport mechanisms of the (in)activated ghrelin hormone in humans as this might give more insight in the workings of ghrelin regulation and signalling in the CNS.

Ghrelin and the gastro-intestinal tract

The peripheral organs involved in digestion and uptake of nutrients supported by the microbiota found in the intestinal tract form a bidirectional communication system with the CNS to regulate energy homeostasis using a combination of neural, immune, humoral and endocrine signals (for review [55–57]). The gut-colonising microbiome plays an important role in the bidirectional communication of the gut-brain axis through the production and release of various hormones [58,59] and through receptor expression [60,61]. The gut microbiome consists of a highly intricate composition of different types of bacteria, archaea, viruses and eukaryotic microbes which assists or influences physiological functions in the body (for review [62]). This composition of microorganisms, mainly consisting of bacteria, is able to directly impact the regulation of different gastro-intestinal tract-derived hormones, such as ghrelin (for review [63–66]). The role of ghrelin on the gut-brain axis with regard to obesity is suggested to act via two different ways. Firstly, ghrelin acts as an endocrine regulator of peptide YY (PYY), cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1) release in the gastro-intestinal tract [67]. In more detail, ghrelin functions as an antagonist of PYY, CCK and GLP-1 signalling by inducing orexigenic sensations and by simultaneously inhibiting the secretion of these gut-derived peptide hormones. PYY, CCK and GLP-1 affect a large number of processes in both the central nervous system (e.g. stimulation and inhibition of POMC/α-MSH neurons) as well as in peripheral organs (e.g. gastro-intestinal motility and gastric emptying), which are actuated with food intake and consequently result in satiety [68,69] (for review [70]). Thus, the aforementioned inhibition of PYY, CCK and GLP-1 by ghrelin indirectly results in an inhibition of these central and peripheral homeostatic processes regarding satiety regulation (Table 1). Secondly, circulating ghrelin plasma levels are significantly affected by the gut microbiome composition [63]. Multiple studies identify different bacterial genera that might influence the production of ghrelin in the epithelial parietal cells of the gastro-intestinal mucosa. This implies that the gut microbiome is also able to influence downstream regulation by altering the overall presence of circulating ghrelin. Inhibition of ghrelin through the gut microbiota is induced by an abundance of *Prevotellaceae* [71], *Helicobacter pylori* [65], *Lactobacilli*, *Enterobacteriaceae* and *Bifidobacteria*, whilst an abundance of acetate-producing microbes suggestively correlates with an elevated ghrelin plasma concentration [72]. However, *Bifidobacterium* [63,73], *Lactobacillus* [63], *Faecalibacterium* [74], *Prevotellaceae* [71] and *Bacteroides* [75] are negatively associated with ghrelin. Nevertheless, some species of bacteria have been associated with bot negatively and positively with ghrelin, which indicates this field is evolving and needs further research. For instance, glucose homeostasis, (neuro)- inflammation and homeostatic as well as hedonic regulation of food intake should also be considered to be implicated in the complex mechanisms involved in the interplay between microbiota and ghrelin [72]. A possible mechanism by which the microbiome may affect ghrelin levels and signalling could be via the microbiome-mediated regulation of fatty acids necessary for ghrelin acylation by GOAT, short-chain fatty acids and/or ghrelin-reactive immunoglobulins [72,76,77]. However, the exact effect of the gut microbiome on ghrelin has to be further investigated as the gut microbiome could pose as a noteworthy regulatory factor for ghrelin synthesis and secretion.

All in all, the gastro-intestinal tract is a highly convoluted and intricate regulator of many different

Table 1. Summary of indirect orexigenic effects of ghrelin through PYY-, CCK- and GLP-1 inhibition.

	Inhibition target	Result
Ghrelin	PYY	↓ POMC/α-MSH neuron activation [67,72]
		↓ Satiated sensation [67,72]
		↑ NPY neuron activation [72]
		↑ Food intake [67,68,72]
	CCK	↓ Pancreatic enzyme secretion [68,69]
		↓ Gall bladder contraction [68,69]
		↑ Gastric emptying [68,69]
		↑ Food intake [68,69]
	GLP-1	↓ Insulin synthesis and secretion [63,72,119]
		↓ β-cell proliferation [63,119]
		↑ Gastro-intestinal motility [63]
		↑ Gastric emptying [63,68,72,119]
		↑ Food intake [63,68,72,119]

homeostatic bodily processes through paracrine, endocrine and neuronal signalling between peripheral organs and the brain.

Ghrelin and stress-induced obesity

Stress can be described as a physical state of being wherein homeostasis is threatened, as it induces different physiological and behavioural changes in an individual (i.e. sharpened attention, increased respiration and glucose utilisation) through neuroendocrine interactions within the HPA-axis (for review [78,79]). Brief responses to stress are generally considered harmless, however, the exposure to chronic or repeated stressors is now known to cause different mental and physical stress-induced disorders such as depression or obesity [80–84]. Stress-induced obesity is the encapsulating term of disproportionate fat accumulation in adipose tissue caused by homeostatic, metabolic and behavioural changes provoked by prolonged stress exposure [85–87]. Interestingly, ghrelin appears to be involved in two distinct ways in the development of stress-induced obesity on the HPA-axis through ACTH stimulation, and through the overall elevation of plasma ghrelin levels in chronic or repeated exposure to stress.

HPA-axis

The HPA-axis regulates circadian rhythm, and forms the backbone of the long-term stress response with the secretion of corticotropin-releasing hormone (CRH), ACTH and cortisol (for review [88]). The daily cycle of the human circadian rhythm starts with an increasing cortisol production during the night, followed by a peak of cortisol secretion in the early morning, and ending with a steadily declining cortisol production throughout the day [89,90]. Cortisol elevates fat and protein dissimilation, promotes glucose synthesis and further regulates a broad array of smaller metabolic and homeostatic functions [91]. The major regulatory factor of the HPA-axis is cortisol itself, which inhibits both CRH and ACTH secretion through negative feedback restraining the stress response after longer periods of time (for review [88,92]). In case of repeated or prolonged stressors, chronic stress ultimately can lead to hypoactivity of the HPA-axis and is associated with stress-induced eating [93]. It has previously been established that high plasma levels of ghrelin stimulate ACTH release from the anterior pituitary [26,45,46,94], thus stimulating the HPA-axis and circumventing the negative feedback regulation of cortisol. In addition to this, rodent studies have displayed significant increases in plasma ghrelin after repeated or prolonged stressors in rat [95], which further supports the role of ghrelin in chronic stress.

In more detail, ghrelin directly acts upon the HPA-axis by stimulating ACTH synthesis and secretion in the anterior pituitary, possibly by directly binding and regulating pituitary secretagogues such as ACTH [96,97]. It has also been suggested that ghrelin is able

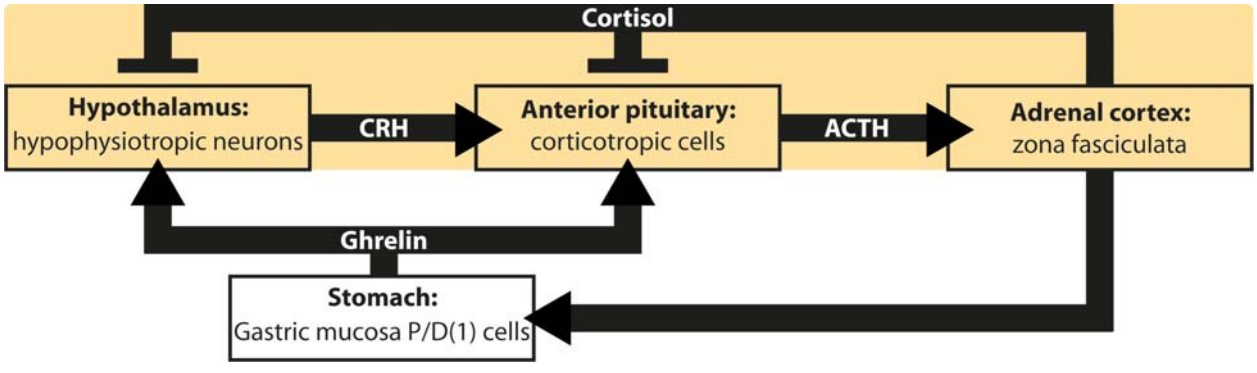

Figure 2. Proposed effect of ghrelin on HPA-axis feedback. Schematic view of the positive- and negative feedback regulation in the HPA-axis (yellow) during stress. Ghrelin suggestively enforces stronger CRH* and ACTH signalling, and restrains the negative feedback regulation of cortisol on hypothalamic* and anterior pituitary secretagogues. **in vitro*, not yet replicated *in vivo*.

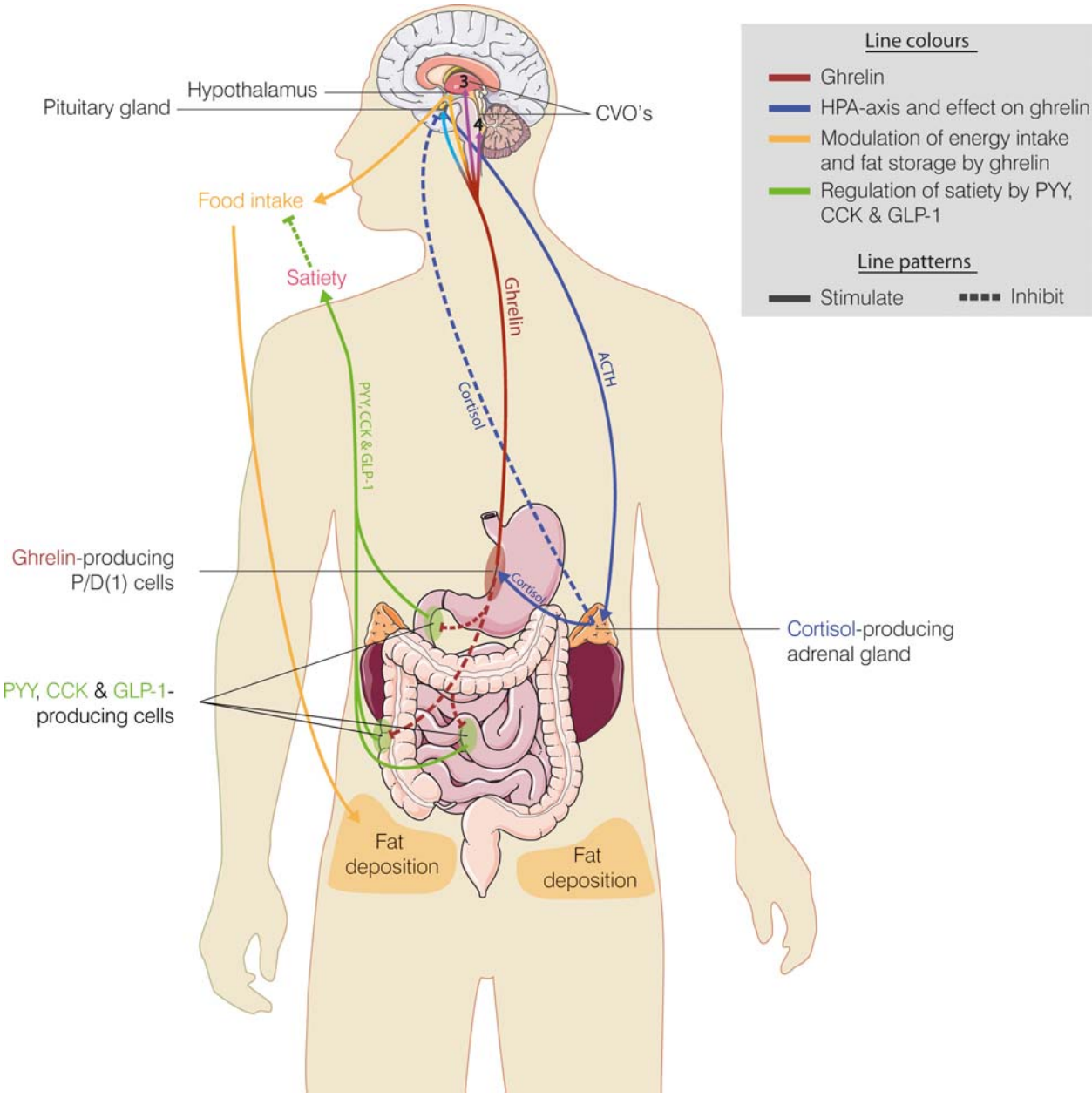

Figure 3. Schematic overview of the target tissues of ghrelin in the brain, HPA-axis and gut. Dashed lines: inhibit. Solid lines: stimulate. The production of ghrelin is regulated by P/D(1) cells in the stomach (red oval). Ghrelin targets multiple different brain regions (blue, yellow and purple lines) and most plausibly penetrates the brain through circumventricular organs (CVOs) around the third and fourth ventricle (purple lines). Just before a meal, ghrelin stimulates food intake through the hypothalamus which stimulates fat deposition in the periphery (yellow line). During the experience of stress, cortisol production is stimulated through the HPA-axis, and furthermore this increased level of cortisol stimulates the production of ghrelin (blue lines). Lastly, ghrelin inhibits the production of PYY, CCK and GLP-1 (Table 1) by enteroendocrine cells in the gut (green ovals), which subsequently results in suppression of satiety (green lines). Ultimately, prolonged stress and ghrelin activity results in elevated food intake and fat deposition in fat tissue (yellow lines).

to indirectly elevate ACTH through paracrine stimulation of hypothalamic CRH synthesis and secretion (Figure 2) [47,98]. However, this suggestion was based on findings obtained from *in vitro* experiments and has not yet been replicated *in vivo* [26].

The effect of chronically high plasma cortisol levels may impact a broad array of bodily processes and behavioural changes related to the pathologic development of obesity. Firstly, high cortisol levels aggravate emotions and enforce emotional eating [99]; either by increasing caloric intake overall [100] or by choosing fatty or sweet products over healthy food product alternatives [101]. Secondly, cortisol seems to elevate ghrelin plasma levels [102], which will increase the overall orexigenic effects of ghrelin such as raising caloric intake and fat deposition. During chronic stress

exposure, prolonged high plasma cortisol levels can stimulate the orexigenic effects of ghrelin and thereby caloric intake [102]. Lastly, the long-term shift towards comfort foods and increase in overall orexigenic effects of ghrelin can result in the reorganisation of energy storages in the body [103]. As a result of this reorganisation, energy storages shift from a peripheral to a central distribution, mainly as abdominal fat. A high level of abdominal fat is associated with an increased risk for cardiovascular diseases and type-II-diabetes mellitus (for review [104–106]). Additionally, increased cortisol levels directly correlate with a decrease in insulin sensitivity and the pathogenesis of hyperinsulinemia; a prolific symptom in type-II-diabetes mellitus [107–109].

Elevated ghrelin levels in chronic or repeated exposure to stress

The overall cortisol induced elevation of ghrelin synthesis and secretion has pronounced effects on hunger and food reward sensations which greatly empowers the orexigenic effect [101]. For this reason alone, inverse GHS-R1a agonists have been suggested as potential drug targets to suppress hunger in obesity for years [101]. However, the role of ghrelin in the pathological development of the disease is not yet fully understood and might be even more complex considering stress in developing obesity. The effects of ghrelin on the central nervous system and on the gut-brain axis are broad, and can be affected by exposure to stress. Firstly, the stimulatory properties of ghrelin on NPY and AgRP expression directly result in increased NPY targeting of the hypothalamic nuclei to enhance (carbohydrate) food consumption and increased AgRP-mediated inhibiting of POMC expression [35,36,110]. The chronic expression of NPY can elevate insulin plasma levels and possibly also increase fat deposition, further supporting the potential role of ghrelin-mediated obesity development [39,40]. In addition, in rodent models it has been shown that high fat diet (HFD)-induced obesity suppresses the neuroendocrine ghrelin system via decreased acylated and total plasma ghrelin levels and decreased hypothalamic GHS-R expression [111]. Accordingly, peripheral and central ghrelin injection did not induce activity in the arcuate nucleus, AgRp or NPY secretion or food intake [111]. These findings indicate that HFD-feeding induces ghrelin resistance by overall GHS-R desensitisation in the hypothalamus [111]. This overall desensitisation decreases NPY/AgRP responsiveness to limit food intake [111]. Moreover, an intervention with caloric restriction is able to restore ghrelin sensitivity in mice [112]. Secondly, ghrelin not only affects homeostatic feeding behaviour, but several studies have indicated ghrelin can affect reward behaviour as GHSRs are present in the ventral tegmental area (VTA) [113–115]. The VTA plays a well-established role in incentive motivation. In rodent models central and intra VTA administration of ghrelin can induce reward-based eating via dopaminergic neurons of the parabrachial pigmented VTA sub-nucleus [113–115]. Thus, these findings indicate that ghrelin is also involved in the responsive circuits regulating food reward behaviour [114,116–118]. Thirdly, the inhibition of PYY, CCK and GLP-1 by high plasma ghrelin levels will show a direct effect on many processes (see Table 1), such as gastric emptying. An overall increase of ghrelin will inhibit PYY, CCK and GLP-1, therefore further suppressing satiety and inducing hunger sensation.

All in all, the efficacy of ghrelin as an orexigenic agent is highly potent, as ghrelin accomplishes this effect through variety of signalling cascades in both central and peripheral organs. Thereby, disruption in the homeostasis of circulating ghrelin can result in strong effects on food preference and caloric intake. Indisputably, chronic stress relates to an increase in circulating plasma ghrelin and cortisol levels which could effectively contribute to the pathogenesis of obesity. Firstly, prolonged stress-induced plasma ghrelin elevation will consequently lead to an increased caloric intake, suppressed satiety, increased gastric emptying and decreased insulin synthesis and secretion. Secondly, prolonged stress-induced plasma cortisol elevation will additionally increase abdominal fat deposition and disrupt lipolysis. Lastly, ghrelin could be considered as a regulatory factor in the pathogenesis of stress-induced obesity (Figure 3).

Conclusion

In conclusion, ghrelin plays a major role in hunger and satiety regulation but additionally acts as a potent endocrine factor in stress homeostasis. Therefore, a greater understanding and appreciation of ghrelin as a possible marker in the pathogenesis of stress-induced obesity could lead to an improved preventability or treatability of the disease. The classic description of ghrelin as 'the hunger hormone' undermines the complexity and importance of ghrelin signalling in the gut-brain axis and in stress homeostasis regulation.

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