An Emerging Role for Gut-Brain Signaling Involving Ghrelin in Chronic Stress

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Abstract

Our internal and external environments are not stable; these ever-changing contexts produce stress on bodily systems. In response, the body recruits numerous peripheral hormones to bring those systems back within a desired homeostatic range. When our environments change in extreme ways and for prolonged periods of time, a different set of hormonal stress responses are recruited. These chronic stress responses produce adaptive changes but can also drive maladaptation. This chapter begins by reviewing the peripheral hormones that are recruited as part of the acute stress response and describing their adaptive impact on brain and peripheral function. We then examine new research describing the role of ghrelin, a hormone produced by the gut, in chronic stress. We review the role of ghrelin in hunger and consider how energy deficiency, a state shared by both hunger and stress, might explain why ghrelin is elevated by both. We consider how the unique recruitment of ghrelin during chronic stress mediates responses in the brain that can help an organism respond to future stressors, but also how chronic elevation of ghrelin can produce additional adaptations that contribute to stress-sensitive psychiatric disorders. Lastly, we identify important future areas for research on the biology of ghrelin.

Keywords

Ghrelin · Stress · HPA axis · Sympathetic nervous system · Parasympathetic nervous system · Adaptation · Valenced behavior · Appetite · Metabolism · Brain-body

Abbreviation

ACTH	Adrenocorticotropic hormone
AUD	Alcohol use disorder
BChE	Butyrylcholinesterase

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BLA	Basolateral amygdala
CRF	Corticotropin-releasing factor
DRD1	Dopamine receptor D1
DRD2	Dopamine receptor D2
DRD5	Dopamine receptor D5
GC	Glucocorticoid
GHSR	Growth-hormone secretagogue receptor
GOAT	Ghrelin *O*-acyltransferase
GR	Glucocorticoid receptor
GRE	Glucocorticoid response element
HPA	Hypothalamic-pituitary-adrenal
5HT2C	Serotonin 2c receptor
LEAP2	Liver-expressed antimicrobial peptide 2
MC3R	Melanocortin-3 receptor
MDD	Major depressive disorder
MR	Mineralocorticoid receptor
NAc	Nucleus accumbens
PFC	Prefrontal cortex
PTSD	Posttraumatic stress disorder
PVN	Paraventricular nucleus
SNP	Single nucleotide polymorphism
SST5	Somatostatin receptor-5
VTA	Ventral tegmental area

7.1 Defining Stress: Adaptation and Maladaptation

Stress is characterized by a set of bodily responses to a demand or challenge. In everyday language, "stress" typically has a negative connotation, referring to a state of worry or the feeling of being overloaded. Indeed, in medicine, there is clear evidence that prolonged stress exposure elevates the risk of a broad array of diseases (Hughes et al. 2017), including cardiovascular illnesses (Basu et al. 2017; Dong et al. 2004), cancer (Kelly-Irving et al. 2013; Bellis et al. 2015), and psychiatric illnesses (Daníelsdóttir et al. 2024), and conditions such as diarrhea (Zhang et al. 2025), sweating, sleep disturbance (Kalmbach et al. 2018) and increased body temperature (Oka 2015). Thus, some of the responses to stress must contribute to disease. Yet, in science, we have come to appreciate that not all bodily responses to a stressor are "bad" or drive disease risk. Some stress responses may compensate for others, preserving function in the face of biological perturbation (Nestler and Russo 2024). For example, studies of 'resilient' individuals, who are able to retain functionality of biological systems despite stress exposure, reveal that they do not return to a pre-stress state after stressor exposure; instead, they actively engage new mechanisms to preserve function. Such mechanisms include stress-associated enhancement of connectivity between the prefrontal cortex (PFC) and nucleus accumbens (NAc), which is linked to greater resilience to stressors (Francis et al. 2015; Bagot et al. 2015). Understanding whether a stress response is adaptive or maladaptive is especially important in clinical contexts, where we want to bolster resilience but blunt pathways that drive maladaptation.

7.2 A Canonical Stress Signaling Pathway in the Periphery: the HPA Axis

One of the best-studied systems for coordinating stress responses is the hypothalamic-pituitary-adrenal (HPA) axis (Fig. 7.1, left). When stressors occur, stress-related neural circuits of the paraventricular nucleus (PVN) of the hypothalamus are activated. Many types of signals can activate the PVN, including internal changes in temperature, blood glucose, or blood pressure and external stimuli such as loud noises or predator cues. A subset of parvocellular neurons in the PVN release corticotropin-releasing factor (CRF) locally within the PVN to induce central stress effects directly. Some CRF-positive PVN neurons send their axons into the median eminence and onward to the portal capillary system of the pituitary. The capillaries allow CRF to be transported to the anterior pituitary, where it binds to receptors on a subset of endocrine cells (corticotrophs) that then exocytose vesicles containing adrenocorticotropic hormone (ACTH) into the blood. ACTH acts at its receptor in the adrenal glands to drive the secretion of glucocorticoids (GCs; cortisol in humans, corticosterone in rodents) into the bloodstream. Glucocorticoid receptors are found throughout most tissues in

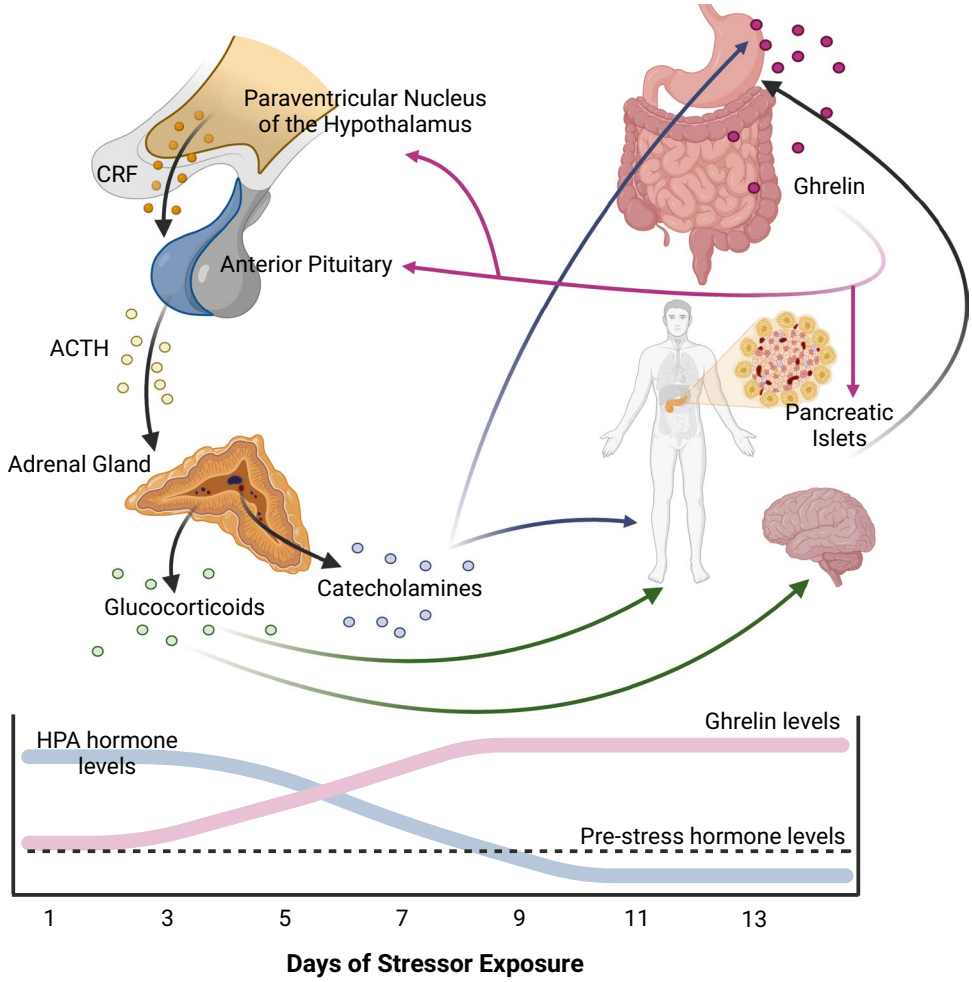

Fig. 7.1 The hormones of the HPA axis and ghrelin axis and their interactions are depicted. The green arrows indicate synergistic stimulatory actions between the two hormonal axes. The lower panel shows the differential recruitment of these axes over the course of a two-week stressor. While the HPA responses typically show habituation, eventually reaching slightly suppressed basal levels, ghrelin levels are not significantly enhanced early in stress exposure but reach roughly double the basal levels after approximately a week of stress exposure. (Created in BioRender. Goosens (2025) https://BioRender.com/w44p992)

the periphery and the brain, and thus, stress-induced elevation of GCs is poised to have broad effects.

There are two primary GC receptors: the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). The two receptors can be co-expressed (Herman et al. 1989), but MR has a higher affinity for GCs than does GR (Joëls and de Kloet 2017). Thus, at lower levels of GCs, i.e., under non-stress conditions, MR signaling is expected to dominate. In contrast, when GCs are elevated, MR signaling reaches an asymptotic level and GR signaling pathways are increasingly recruited with increasing high levels of GCs (Reul et al. 1987).

Both MR and GR are ligand-activated transcription factors (Alvarez de la Rosa et al. 2024). Accordingly, there are many studies showing how activation of MR and GR by GCs causes the receptors to translocate to the nucleus and bind to glucocorticoid response elements (GREs) in open chromatin (John et al. 2011). MR is a tran-

scriptional activator of many genes, including neuropeptides and growth factors (Pascual-Le Tallec and Lombès 2005; Meinel et al. 2014). In contrast, GR can bind to GREs to activate genes or to negative GREs to repress their transcription (Surjit et al. 2011); it is estimated that more than 1% of all transcripts in the human genome are regulated by GR (Wiley et al. 2016). GR can also bind to mRNA to induce degradation (Boo et al. 2024). However, membrane-bound MR can also mediate the rapid effects of GCs on neuronal excitability (Karst et al. 2010, 2005).

GRs also play an important role in terminating the acute HPA stress response, both in terms of ACTH secretion (Jacobson et al. 1988) as well as GC secretion (Herman et al. 2020). Within the PVN, GCs bind to GR to induce endocannabinoid synthesis in the CRF-containing neurons of the PVN, which leads to retrograde inhibition of the excitatory drive entering the PVN (Tasker and Herman 2011; Di et al. 2003). GC activation of the hippocampus (Herman et al. 2003) and PFC (Jones et al. 2011) also terminate HPA-mediated stress hormone responses (Radley and Sawchenko 2011). The multiple robust mechanisms by which GCs terminate their own secretion likely contribute to the observation that repeated stressor exposure produces fairly mild elevations of basal circulating GCs that persist for only a few weeks after stress terminates in rodents (Johnson et al. 2002; Sterlemann et al. 2008). In humans with posttraumatic stress disorder (PTSD), there are not clear links between altered GC levels and the disorder; a recent meta-analysis suggests that there is a trend towards observing mild hypocortisolism in PTSD (Sbisa et al. 2023). Interestingly, a recent meta-analysis also suggests that childhood stressors lead to blunted cortisol responses to stressors in adulthood (Brindle et al. 2022). Thus, the contributions of HPA activity to chronic stress responses are unclear.

As an acute stress response, HPA hormones drive multiple short-term adaptations that facilitate coping with stress. These include GC-dependent mobilization of energy stores (Swarbrick et al. 2021), increased cardiovascular tone (Yang and Zhang 2004), analgesia (Lewis et al. 1980), and inhibition of growth (Baxter 1978), immune function (Coutinho and Chapman 2011) and reproduction (Domes et al. 2024). Thus, collectively, the evidence supports a role for the HPA axis in short-term adaptations to acute stress. The decreased recruitment of the HPA axis when a stressor persists across days to weeks (Grissom and Bhatnagar 2009) (Fig. 7.1, lower panel), coupled with the observation that basal HPA activity is not dramatically altered following chronic stress, suggests that the HPA axis may not be the only system altered by chronic stress and that other mechanisms may contribute to changes following chronic stress. However, it is important to note that HPA activity can induce changes in behavior that emerge gradually, perhaps due to the genomic actions of GCs, and also sensitize the HPA axis itself so that a greater HPA response is mounted to subsequent novel stressors (Belda et al. 2015; Akana et al. 1992).

7.3 Additional Stress Signals in the Periphery: Acyl-ghrelin

The peptide hormone acyl-ghrelin, hereafter referred to as ghrelin, was discovered in the search for the ligand of the growth-hormone secretagogue receptor (GHSR) (Kojima et al. 1999). The posttranslational modification of ghrelin, an octanoylated serine, is necessary for it to bind and activate GHSR (Bednarek et al. 2000). GHSR was originally characterized as a receptor that regulated growth hormone secretion from the pituitary (Howard et al. 1996). It was surprising, then, that ghrelin was observed to be predominantly expressed in the stomach and has been subsequently confirmed to be almost exclusively in gastric endocrine cells (Kim et al. 2012; Date et al. 2000), with a smaller population of endocrine cells being in the small intestine (Wierup et al. 2007). A short time after its initial discovery, ghrelin was found to regulate energy balance: the administration of ghrelin promotes food consumption. Additionally, ghrelin is elevated by either short-term fasting (energy depletion) (Hollstein et al. 2022; Schéle et al. 2016) or chronic food restriction (Tezenas du Montcel

et al. 2023; D'Cunha et al. 2020; Méquinion et al. 2013). Lastly, ghrelin increases sharply prior to expected meal times (Cummings et al. 2001) and decreases in a sated state (Tschöp et al. 2000).

Many additional studies confirmed and expanded the role of ghrelin in aspects of appetitive processing. Ghrelin influences the rewarding value of the food itself. In rodent studies using conditioned place preference, administration of ghrelin increased the amount of time rodents spent in the compartment previously paired with access to a high-fat diet (Perello et al. 2010). Consistent with these studies, ghrelin administration also enhances the activity of dopaminergic neurons in the ventral tegmental area (VTA) (Navarro et al. 2022; Cornejo et al. 2018) and enhances dopamine release into the downstream NAc (Jerlhag et al. 2007). Humans receiving intravenous ghrelin rate food cues as more pleasant (Han et al. 2018) and intravenous ghrelin also increases the neural response to food cues in multiple areas thought to encode the incentive value of food (Goldstone et al. 2014). Ghrelin also increases the preference for high-fat, sweet foods in both rodents (Perello et al. 2010; Disse et al. 2010; King et al. 2011; Chuang et al. 2011a; Shimbara et al. 2004) and humans (Zoon et al. 2018) and increases the intake of rewarding food (Egecioglu et al. 2010).

Elevated ghrelin also enhances the motivation to work for rewards. For example, mice who are bar-pressing for high-fat food pellets show a higher breakpoint in a progressive ratio schedule of reinforcement when given peripheral ghrelin injections compared to controls (Perello et al. 2010). Rats receiving peripheral ghrelin injections (Skibicka et al. 2012) or intra-VTA infusion of ghrelin (Skibicka et al. 2011) increase bar presses for sucrose pellets even when satiated. Intra-VTA ghrelin in rodents also increases cue-induced reinstatement of bar presses for high-fat food pellets (St-Onge et al. 2016).

Interestingly, the ability of ghrelin to mediate reward appears to extend well beyond food. Ghrelin receptor antagonism reduces drug-induced conditioned place preference for a number of drugs of abuse (Charalambous et al. 2021; Sustkova-Fiserova et al. 2020; Dunn et al. 2019; Jerlhag and Engel 2011). In male mice, impaired ghrelin signaling decreases interest in female mice in estrus, as well as sexual engagement with female mice (Egecioglu et al. 2016). Intravenous ghrelin enhances the craving for alcohol in alcohol-dependent humans (Leggio et al. 2014). Lastly, intravenous ghrelin administration decreases neural activity in response to anticipation of monetary losses in healthy human subjects (Pietrzak et al. 2023a). However, some types of reward do not seem to be related to ghrelin levels in humans, including social rewards (Sailer et al. 2023) and caressing touch (Pfabigan et al. 2024).

Collectively, the data suggest that elevated levels of ghrelin accompany hunger, a state of energy deficit, and that lower levels of ghrelin are observed with satiety, a state of energy excess (Mani et al. 2019). Interestingly, chronic stress represents another state of energy deficit. Chronic stress tends to produce elevated core body temperature (Marazziti et al. 1992; Oka 2018; Nakamura 2015) and also decreases body weight gain in rodents (Kuti et al. 2022; Shin et al. 2024). It should perhaps, then, not be surprising that ghrelin is elevated after chronic stress exposure in multiple species, including rodents (Lutter et al. 2008; Meyer et al. 2014; Harmatz et al. 2016), fish (Jönsson 2013), horses (Hemmann et al. 2012), and humans (Yousufzai et al. 2018; Jaremka et al. 2014; Malik et al. 2020; Wittekind et al. 2023) (Fig. 7.1), suggesting that elevated ghrelin may be a conserved response to chronic stress. Much like MR and GR, GHSR is found throughout the brain and body (Ueberberg et al. 2009; Mani et al. 2014; Zigman et al. 2006; Guan et al. 1997), which enables the stress-induced change in ghrelin levels to have a widespread impact. Consistent with the idea that stress-induced elevation of ghrelin may produce important behavioral adaptations to cope with the energy deficit produced during a chronic stressor, ghrelin receptor knockout mice do not have the same stress-induced changes in body weight and caloric intake that are observed in wild-type mice, and they also have different neurotransmitter alterations in the brain after stressor exposure (Patterson et al. 2010). Similarly, ghrelin receptor

knockout mice do not exhibit the metabolic adaptions shown by wild-type mice during chronic stress, such as hyperleptinemia and hyperinsulinemia or changes in hypothalamic peptides associated with consummatory behaviors (Patterson et al. 2013).

In addition to the impact of ghrelin on reward processing, an increasingly large body of work supports the idea that ghrelin influences the processing of aversive stimuli (also called punishment or costs). The basolateral amygdala (BLA) is one brain region that is particularly tied to the processing of aversive memories (Perumal and Sah 2021), and it also happens to be a region where GHSR is highly expressed (Meyer et al. 2014; Alvarez-Crespo et al. 2012). Infusing ghrelin into the BLA inhibits the acquisition of conditioned taste aversion memories (Song et al. 2013). It also inhibits the formation of aversive Pavlovian fear conditioning memories (Harmatz et al. 2016). Consistent with these rodent studies, studies in healthy humans show that intravenous ghrelin decreased sensitivity to punishment (loss of monetary reward) in decision-making tasks (Pietrzak et al. 2024, 2023b) and also reduced neural activity during anticipation of monetary losses (Pietrzak et al. 2023b). This suggests that, in unstressed subjects, ghrelin inhibits aversive processing in multiple ways. However, rodents exposed to chronic stress display both higher levels of ghrelin and stronger fear memories than controls (Meyer et al. 2014; Harmatz et al. 2016). This suggests that ghrelin is no longer inhibiting aversive memories effectively after chronic stress exposure. In another aversive domain, chronically high ghrelin is positively associated with symptoms of physiological anxiety in otherwise healthy humans (Wittekind et al. 2022).

Further studies demonstrated that high levels of ghrelin were associated with a profound loss of GHSR binding sites in the BLA (Harmatz et al. 2016). This functional 'ghrelin resistance' is likely a compensatory mechanism by which receptors are downregulated in response to excessive ligand-dependent signaling. However, it should be noted that not all brain regions respond to elevated ghrelin by downregulating GHSR; in fact, in the VTA, GHSR levels are increased (Smith et al. 2024a). Thus, the elevated ghrelin observed after chronic stress reduces the ability of ghrelin to serve as an endogenous inhibitory signal for aversive processing.

7.4 The Adaptive Values of Persistently Elevated Ghrelin After Chronic Stress

Unlike the HPA axis, ghrelin remains approximately doubled long after stressors cease. Studies have shown elevated ghrelin in rodents for weeks (Lutter et al. 2008; Meyer et al. 2014; Harmatz et al. 2016; Smith et al. 2023; Kumar et al. 2013) to months (Yousufzai et al. 2018) after stressor cessation and there is increased brain penetrance of ghrelin after chronic stress (Smith et al. 2024b). In humans, elevated ghrelin has been demonstrated years after stressor exposure (Malik et al. 2020; Rossi et al. 2021). The increased ghrelin levels could be mediated by increased synthesis, increased release, increased posttranslational octanoylation, decreased breakdown, or a combination of these modulatory factors (see Fig. 7.2 for a summary of possible mechanisms). Excitation of the gastric afferent vagal nerve (Date et al. 2002) and repeated activation of β1-adrenergic receptors (Gupta et al. 2019), likely in the gastric ghrelin cells (Zhao et al. 2010a; Engelstoft et al. 2013), both increase circulating ghrelin, suggesting that increased vagal tone or enhanced catecholaminergic activity might be responsible for chronic stress-induced elevation of ghrelin. However, adrenalectomy, which eliminates the circulating catecholamines released by the adrenal glands, does not prevent stress-induced elevation of ghrelin (Meyer et al. 2014), suggesting that stress may elevate ghrelin via other pathways (for example, through sympathetic inputs to the gut). Ghrelin secretion is negatively regulated by increased blood glucose (Shiiya et al. 2002; Nakagawa et al. 2002). This raises the possibility that repeated hypoglycemia induced by chronic stress could also contribute to enhanced ghrelin secretion. One report demonstrated that gastric ghrelin cells express many types of G protein-

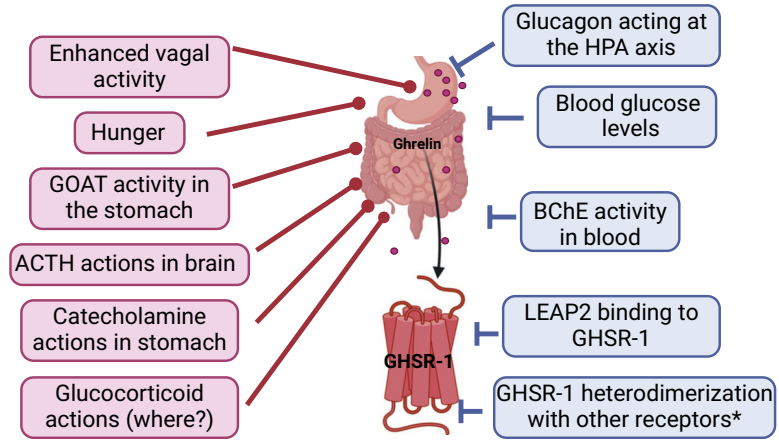

Fig. 7.2 Mechanisms by which stress could potentially elevate ghrelin or its signaling. Pink boxes indicate mechanisms that increase ghrelin. Blue boxes represent mechanisms that suppress ghrelin or its signaling. To enhance ghrelinergic activity, chronic stress would need to increase the mechanism(s) shown in pink or decrease the mechanism(s) shown in blue, or do both. *It is possible that heterodimerization with some receptors could elevate signaling through GHSR. (Created in BioRender. Goosens (2025) https://BioRender.com/w23c571)

coupled receptors (Engelstoft et al. 2013), suggesting that the control of ghrelin secretion is likely even more complex than described above. Regardless of the potential mechanisms, it is not understood how or why these mechanisms remain engaged after stress terminates (see Fig. 7.3 green boxes for a summary of adaptive changes). One potential adaptive value of the persistence of elevated ghrelin is that it renders the organism better prepared for the next encounter with stressors. This theory remains to be tested.

Another important role of elevated ghrelin is to maintain blood glucose levels during times of energy expenditure. Ghrelin may do this by promoting the release of glucagon in the short term (Chuang et al. 2011b), or enhancing growth hormone-mediated stimulation of glucose production in the liver and kidneys and driving insulin resistance (Kim and Park 2017; Zhao et al. 2010b; Zhang et al. 2015). In healthy subjects, glucagon exerts negative feedback to reduce ghrelin levels (Arafat et al. 2006). Administration of exogenous ghrelin is known to elevate blood glucose in both rodents (Chuang et al. 2011b) and humans (Broglio et al. 2001, 2004). It also promotes glucose intolerance (Tong et al. 2010; Page et al. 2018; Dezaki et al. 2004). In these studies, glucose intolerance was observed with acute elevation of ghrelin; it is tempting to speculate that chronically elevated ghrelin might produce even greater intolerance and contribute to elevated basal levels of blood glucose. Mice with either low blood levels of ghrelin or low levels of GHSR exhibit mild hypoglycemia after short-term caloric restriction (Longo et al. 2008; Sun et al. 2008) but display dangerously low blood glucose levels during prolonged caloric restriction (Zhao et al. 2010b; Li et al. 2012). It is possible that the energy deficit driven during chronic stress exposure enhances ghrelin levels to maintain blood glucose levels during stressor exposure, but it is not known why this mechanism would remain engaged after stress. It may be that these mechanisms evolved in response to environmental stressors, such as resource scarcity, that displayed less volatility than many contemporary stressors, and thus, having long-term elevations of ghrelin had more beneficial effects than detrimental effects when exposure to stressors was more consistent across time.

By promoting exploration or food-seeking behaviors, elevated ghrelin can also help indirectly to maintain blood glucose levels. Ghrelin signaling in the olfactory bulbs is important for promoting exploratory behavior, even in the absence of fasting, and also helps locate food (Stark et al. 2024). Ghrelin increases sensitivity to food odors in humans (Ginieis et al. 2022;

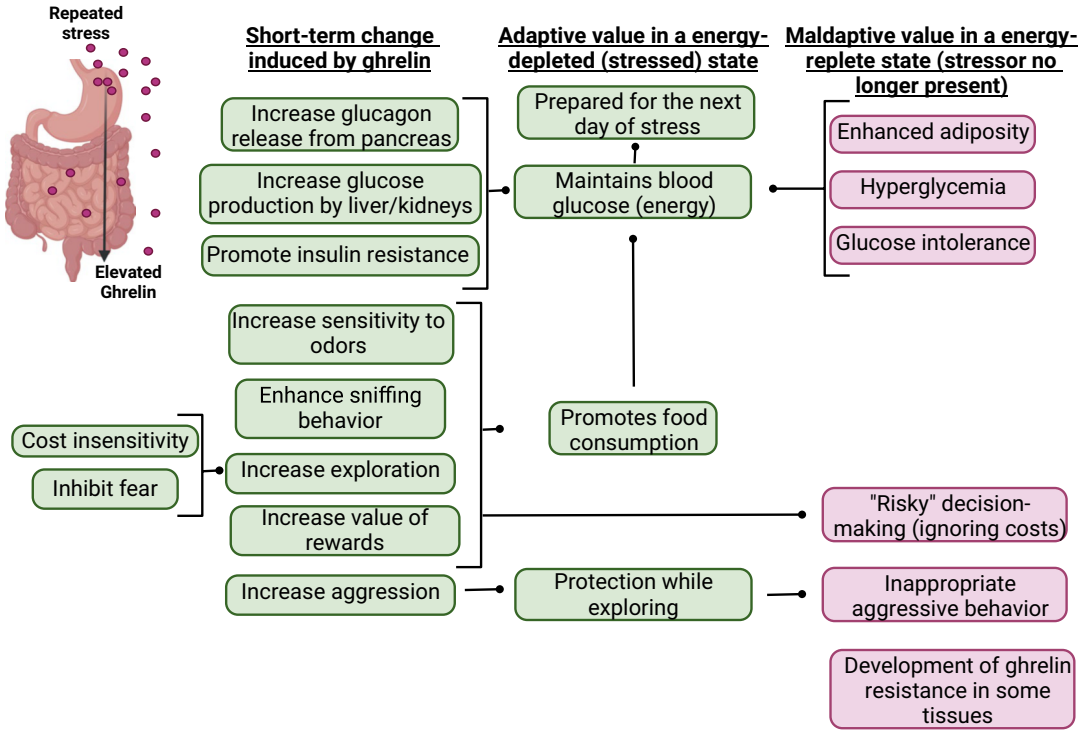

Fig. 7.3 Beneficial and maladaptive changes that can be mediated by increased ghrelin. The green boxes depict the changes that benefit an organism while remaining in a stressed state. The pink boxes depict the consequences of these changes when the stressor is no longer experienced. (Created in BioRender. Goosens (2025) https://BioRender.com/j66v932)

Tong et al. 2011) and rodents (Tong et al. 2011) and enhances the speed of responding to them (Han et al. 2018). These changes in behavior facilitate the ability to locate and identify foods, which indirectly facilitates the maintenance of blood glucose levels.

Lastly, for some types of stressors, like the presence of conspecifics encroaching on an organism's territory, elevated ghrelin may have an additional adaptive value of promoting aggressive behaviors. Male mice with persistently elevated ghrelin display enhanced aggression towards cagemates (Chen et al. 2015). Conversely, systemic administration of a GHSR antagonist reduced aggressive behaviors displayed by male mice towards conspecific intruder mice (Vestlund et al. 2019). People with antisocial personality disorder have elevated ghrelin (Tasci et al. 2022) and young men with polymorphisms in the ghrelin gene displayed significantly different scores on a questionnaire measuring overtly aggressive behaviors (Vestlund et al. 2019). To date, such studies have focused only on aggression in males; an important area of future research is to determine whether elevated ghrelin increases aggression in females. Regardless, a ghrelin-dependent increase in aggressive behaviors may help secure environmental resources when there is competition for such resources.

The ghrelin-dependent connection between stress and mechanisms controlling energy levels and growth positions ghrelin as a hub between metabolism and the stress-dependent exacerbation of neuropsychiatric conditions. The mechanisms connecting glucose metabolism and bioenergetics to psychiatric outcomes are *described in Chap. 3, Brain-body Communication in Glucose Metabolism*, and *Chap. 5, Neuronal Synaptic Communication and Mitochondrial Energetics in Human Health and Disease*, of this book.

7.5 Potential Maladaptive Tradeoffs of Persistently Elevated Ghrelin After Stress

As noted above, ghrelin can have many beneficial effects during stressor exposure. Thus, when a stressor is encountered repeatedly (for example, the organism lives in a food-scarce environment), then the behavioral and physiological changes produced by elevated ghrelin may be largely beneficial. However, when stressors are not reliably encountered, such as when an organism moves from a food-scarce (stressful) environment into a food-rich environment (no longer a source of stress), then the persistent physiological changes induced by high ghrelin may instead promote behaviors and physiological changes that are no longer needed (see Fig. 7.3, pink boxes for a summary of potential maladaptation). It is also possible that chronically elevated ghrelin may, itself, drive new adaptations to limit the impact of chronically elevated ghrelin.

There are several examples that one can consider where elevated ghrelin may no longer have beneficial effects in an energy-rich environment. First, ghrelin-induced elevation of blood glucose levels and insulin insensitivity are no longer adaptive when energetic demands return to normal levels following a stressor exposure. In this case, persistently heightened glucose levels and insulin insensitivity can contribute to adiposity and metabolic syndrome, two conditions that can ultimately contribute to diabetes. Indeed, there are strong links between stress exposure and the risk and severity of diabetes (Hackett and Steptoe 2017). Likewise, when ghrelin levels drive aggressive behaviors, it can help secure resources in a resource-scarce environment, but it also exposes the animal to greater potential for injury. In a resource-rich environment, aggression may expose an organism to injury without the positive benefit of increased resources. Also, for humans, who typically do not need to physically fight to gain resources, aggressive behaviors may only put one at risk for breaking the law. Stress exposure is known to increase the development of psychiatric disorders where aggression is a core feature (Veenema 2009). Lastly, while ghrelin can reduce sensitivity to costs, perhaps contributing to a willingness to explore and forage in new environments, ultimately leading to new food sources, a willingness to take on risk may not be beneficial when resources are not scarce. In humans, stress can increase risk-taking behavior (Reynolds et al. 2013; Pabst et al. 2013).

The adverse impact of ghrelin may be most apparent in enhanced risk for stress-sensitive human psychiatric conditions. In posttraumatic stress disorder (PTSD), which is the human disorder perhaps most closely linked to stress, prior lifetime stress exposure primes an individual for risk of PTSD following subsequent trauma (Catani et al. 2008; Gillespie et al. 2009). Consistent with the idea that elevated ghrelin drives an increased risk of PTSD, adolescents with PTSD have higher ghrelin levels than matched controls without PTSD (Yousufzai et al. 2018). One polymorphism in the ghrelin gene has been associated with PTSD symptom severity (Li et al. 2019).

Alcohol use disorder (AUD) is another stress-sensitive condition (Hughes et al. 2019) with compelling links to ghrelin. Ghrelin is generally positively correlated with alcohol craving in alcohol-dependent individuals (Koopmann et al. 2012, 2019), and intravenous delivery of ghrelin increased alcohol self-administration (Farokhnia et al. 2018) and craving (Leggio et al. 2014) in individuals with AUD. There are also multiple studies showing that polymorphisms in the ghrelin gene are associated with AUD (Landgren et al. 2008, 2010; Suchankova et al. 2016). Several studies suggest that antagonism of GHSR in mice would have beneficial effects on AUD. GHSR antagonism reduces binge-like alcohol drinking in mice (Richardson et al. 2024) and decreases alcohol intake in a two-bottle free choice test in dependent mice (Jerlhag et al. 2009; Kaur and Ryabinin 2010). GHSR antagonism also attenuates relapse consumption of alcohol after abstinence in rodents (Jerlhag et al. 2009; Suchankova et al. 2013), thought to reflect a reduction in alcohol craving. Disappointingly, the first study of a drug with GHSR antagonist activity (Kong et al. 2016) in humans with AUD observed no change in cue-elicited alcohol crav-

ing but did reduce the caloric content of food selected in a virtual food choice task (Faulkner et al. 2024). The role of ghrelin in *AUD is considered in greater depth in Chap. 8, Appetite-regulatory peptides ghrelin and GLP-1 in Alcohol Use Disorder*, of this book.

Major depressive disorder (MDD) is another psychiatric condition that is worsened by stressor exposure (Tafet and Nemeroff 2016), especially for childhood trauma (Heim and Nemeroff 2001), but the links to ghrelin are more equivocal for this disorder. Given that childhood trauma is shown to elevate ghrelin (Malik et al. 2020; Rossi et al. 2021), it is not surprising that some studies find elevated ghrelin in adults with MDD (Emül et al. 2007; Ozsoy et al. 2014; Kurt et al. 2007; Algul and Ozcelik 2018). On the other hand, some studies find no differences in ghrelin levels between people with MDD and healthy controls (Giménez-Palop et al. 2012; Matsuo et al. 2012; Schanze et al. 2008). One population that has yet to be examined is people with co-occurring MDD and PTSD. In rodents, the stressors used to induce depression-like behaviors elevate ghrelin reliably (Lutter et al. 2008; Kumar et al. 2013; Gupta et al. 2019), but it has been argued that elevated ghrelin actually buffers against depressive symptoms: stress-exposed GHSR knockout mice show greater stress-induced depressive behaviors than stress-exposed wild-type control mice (Chuang et al. 2011a; Lutter et al. 2008) and elevating ghrelin during stress reduces depression-like behaviors (Huang et al. 2017; Chang et al. 2024; Lu et al. 2019). Consistent with a positive role for ghrelin in depressive symptoms, short-term injections of ghrelin reduced depressive symptoms in men with MDD (Kluge et al. 2011). It is difficult to reconcile these disparate findings. One possibility is that GHSR knockout is functionally equivalent to 'ghrelin resistance' induced by high levels of ghrelin in some brain circuits and that loss of ghrelin signaling is what drives depressive behaviors. Another possibility is that the exploratory behaviors promoted by ghrelin may mask some of the depressive behaviors in mice. Yet another possibility is that GHSR knockout in mice is likely to impact signaling through other ligands in a manner that has nothing to do with ghrelin per se and is instead related to the complex modulatory effects of GHSR on other ligand systems (Shiimura et al. 2025; Ringuet et al. 2022). Further research will be needed to clarify whether elevated ghrelin is beneficial or detrimental to people with MDD and why.

One important reason for discrepancies between preclinical and clinical findings is that the drugs used to modify signaling through GHSR can have very diverse effects, depending on differences in how the compounds bind to GHSR (Shiimura et al. 2025). Both agonists and antagonists can bias G-protein coupling to GHSR (Shiimura et al. 2025). Some of the studies above showing that GHSR antagonism decreased alcohol consumption in preclinical rodent models (Jerlhag et al. 2009; Kaur and Ryabinin 2010) used pure GHSR antagonists, while the human study (Faulkner et al. 2024) used a drug with both inverse agonist (Bhattacharya et al. 2014) and competitive antagonist (Kong et al. 2016) properties. It is likely that the different compounds had distinct effects on GHSR signaling, which may have contributed to the different effects on the consumption of alcohol. Thus, a best practice is to compare the effects of the same drug in preclinical and clinical studies and not assume that drugs with similar activities (e.g., receptor antagonists) will exert their effects through the same mechanism.

7.6 Ghrelin: Interactions with the HPA Axis

Complicating the role of ghrelin in stress are multiple studies showing that ghrelin and the HPA axis can bidirectionally impact each other (Fig. 7.1, upper, green arrows). However, it should be noted that virtually all of these studies examine their interaction in healthy, unstressed subjects or subjects exposed to an acute stressor. It has been suggested that HPA-dependent elevation of ghrelin is GC-dependent: activation of the HPA axis with a single exogenous injection of ACTH elevates ghrelin, but this effect is blocked when metyrapone, a drug that blocks glucocorti-

coid synthesis, is administered (Azzam et al. 2017). On the other hand, adrenalectomy does not prevent chronic stress-induced elevation of ghrelin, suggesting that at least for chronic stress, glucocorticoids and circulating catecholamines released from the adrenal glands may not be the primary drivers of increased ghrelin.

In the other direction, ghrelin can modify the HPA axis. Infusion of ghrelin into the brain of chicks can increase ACTH and glucocorticoids (Gastón et al. 2017). Acute food deprivation, which elevates ghrelin, activates the HPA axis (Fernandez et al. 2022). Exogenous systemic ghrelin can activate CRF-positive neurons of the PVN and drive increases in plasma GCs (Fernandez et al. 2023). *Ghsr* mRNA is also observed in ACTH-expressing cells of the anterior pituitary (Reichenbach et al. 2012). In humans with AUD, intravenous administration of ghrelin elevated serum cortisol levels (Haass-Koffler et al. 2019). Thus, studies generally suggest that enhanced ghrelin activity drives increased HPA activity. In agreement with this, studies using methods to reduce ghrelin signaling generally find that a reduction in ghrelin signaling constrains HPA axis activation. For example, ghrelin receptor knockout mice show smaller increases of ACTH and GCs in response to acute stressor exposure compared to wild-type mice (Spencer et al. 2012).

Collectively, these studies suggest that ghrelin and the HPA axis both amplify each other. However, virtually nothing is known about these interactions in the context of chronic stress. In one relevant study, repeated injection of CRF into the PVN drove the elevation of ghrelin (Rayatpour et al. 2023). It is possible that repeated activation of CRF neurons by chronic stress may contribute to elevated ghrelin, especially considering that adrenalectomy enhances (rather than eliminates or reduces) activation of PVN neurons and the expression of CRF heteronuclear RNA in the PVN after acute stress exposure (Imaki et al. 1995; Pace et al. 2009). Yet, much remains to be understood about how the HPA and ghrelin systems interact in the face of chronic stress exposure, considering that the HPA stress response typically habituates for chronic stressors, particularly when the same stressor is experienced repeatedly (Grissom and Bhatnagar 2009; Belda et al. 2020). It is also important to note that the noradrenergic system is an important mediator of stress responses (*see Chap. 2, Noradrenaline Regulation of Brain-body Communication, for an overview of the role of this system in stress responses*), but even less is known about potential bidirectional interactions between this system and ghrelin; thus, we do not address this topic here.

7.7 New Frontiers for the Role of Ghrelin in Stress: Modulation of Ghrelin Signaling

One aspect of stress-associated ghrelin biology that is completely unknown is the mechanism by which ghrelin is persistently elevated. One enzyme that regulates the conversion of acyl-ghrelin to des-acyl-ghrelin is butyrylcholinesterase (BChE) (Chen et al. 2015; Schopfer et al. 2015). Single-nucleotide polymorphisms in the *BCHE* gene can considerably alter BChE enzymatic activity (La Du et al. 1990; Jensen et al. 1995; Dantas et al. 2011). While BChE is a ubiquitous enzyme whose levels are unlikely to be appreciably altered by chronic stress, it is possible that individuals with lower BChE activity may be more likely to have elevated ghrelin in response to chronic stress. Conversely, one might expect that individuals with higher BChE activity might be less likely to show elevated ghrelin after chronic stress exposure. These possibilities remain tantalizingly unexplored.

In the stomach, the cells that synthesize ghrelin also post-translationally activate it via the enzyme ghrelin *O*-acyltransferase (GOAT) in a process termed octanoylation (Yang et al. 2008; Gutierrez et al. 2008). In the gut, GOAT octanoylates proghrelin, the precursor molecule to ghrelin, so that proghrelin becomes acyl-ghrelin when cleaved (Yang et al. 2008; Gutierrez et al. 2008). In circulation, acyl-ghrelin is rapidly hydrolyzed into des-acyl-ghrelin (Schopfer et al. 2015), a form that does not act at GHSR (Kojima

et al. 1999; Fernandez et al. 2016). In the brain, locally produced GOAT is capable of converting des-acyl-ghrelin back to acyl-ghrelin (Murtuza and Isokawa 2018). Consistent with the essential role of GOAT in producing acyl-ghrelin and the importance of the stomach in producing the acyl-ghrelin found in circulation, levels of acyl-ghrelin are correlated with GOAT expression in the stomach (Gahete et al. 2010). One possible explanation for the stress-associated increase in ghrelin is increased expression of GOAT in the gut, a possibility that also remains unexplored.

Liver-expressed antimicrobial peptide 2 (LEAP2) is a highly conserved peptide across mammals (Krause et al. 2003) and was originally named because of its structural similarity to other antimicrobial peptides in the liver, as well as its own antimicrobial properties (Henriques et al. 2010). However, it was suggested that LEAP2 likely had other functions (Henriques et al. 2010), and in 2018, it was discovered that LEAP2 is an endogenous inverse agonist and antagonist of GHSR (Ge et al. 2017; M'Kadmi et al. 2019), a role seemingly unrelated to its antimicrobial role. While most circulating LEAP2 comes from the liver, LEAP2 mRNA has been observed in other tissues including gut epithelium (Howard et al. 2010) and brain (Tufvesson-Alm et al. 2024; Islam et al. 2020). The expression of LEAP2 and ghrelin tend to inversely covary with each other (Mani et al. 2019; Islam et al. 2024), suggesting a shared, but opposing, mechanism of regulation. Consistent with inhibitory actions at GHSR, LEAP2 administration has been shown to attenuate many ghrelin-induced physiological changes, including food intake, blood glucose elevation, release of growth hormone, cFos expression in metabolic hypothalamus, and release of dopamine in the NAc (Tufvesson-Alm et al. 2024; Islam et al. 2020, 2024; Lugilde et al. 2022; Mustafá et al. 2021). Conversely, the reduction of endogenous LEAP2 actions enhances the impact of ghrelin and ghrelin-associated functions (Ge et al. 2017; Fei et al. 2024; Bhargava et al. 2023). Insofar as elevated ghrelin accompanies chronic stress, it seems likely that a decrease in LEAP2 accompanies chronic stress, but this has yet to be examined. Likewise, individual variability in LEAP2 expression may confer either vulnerability or resilience to the adaptations and maladaptation that accompany elevated ghrelin after chronic stress. Specifically, higher LEAP2 levels may protect against the stress-induced changes driven by elevated ghrelin, while lower LEAP2 levels may deepen the impact of elevated ghrelin post-stress.

Single nucleotide polymorphisms (SNPs) are another way that individual humans could have varied responses to chronic stress. SNPs in the genes encoding ghrelin and its receptor have been studied in the context of obesity (Gueorguiev et al. 2009; Mora et al. 2015; Vivenza et al. 2004), but not the context of stress responsivity; however, it is important to note that most studies do not show that ghrelin levels are impacted by studied variants in the ghrelin gene. Similarly, genetic variability in the LEAP2 gene (Andreoli et al. 2024a), some of which do predict LEAP2 levels (Andreoli et al. 2024b), would be interesting to study in the context of ghrelin-sensitive changes that accompany chronic stress.

Lastly, it would be remiss not to note that GHSR has a bidirectional modulatory effect on other types of signals. When GHSR forms heterodimers with other receptor types, it can impact the signaling of both the high level of constitutive activity observed in GHSR (Holst et al. 2003, 2004) as well as ligand-dependent signaling through GHSR. It has been suggested that the dimerization with other receptors may generally attenuate ghrelin-mediated signaling (Schellekens et al. 2013). For example, the serotonin 2c receptor (5HT2C) heterodimerizes with GHSR[217] and blockade of 5HT2C receptors potentiates the impact of ghrelin on food intake (Schellekens et al. 2015), suggesting that 5HT2C receptor activity limits signaling through GHSR. GHSR can heterodimerize with multiple types of prostanoid receptors, which reduces the constitutive activity of the GHSR (Chow et al. 2008). When GHSR forms heterodimers with the melanocortin-3 receptor (MC3R), it reduces both constitutive and ghrelin-induced signaling through GHSR (Rediger et al. 2011). In one case, instead of attenuating signaling through the GHSR, dimerization changes the type of signaling medi-

ated by GHSR: dimerization with the somatostatin receptor-5 (SST5) shifts the ghrelin receptor-G-protein coupling from Gαq11 to Gαi/o in order to drive ghrelin-mediated inhibitory tone in pancreatic β-cells (Park et al. 2012).

GHSR heterodimers can also impact signaling through the receptors that are paired with GHSR, and these interactions are not always ghrelin-dependent. That is, it is clear that GHSR can act as a receptor-modifying protein for other receptors (Ringuet et al. 2022; Hedegaard and Holst 2020). For example, GHSR forms heterodimers with multiple dopamine receptors, including Dopamine D1, D2, and D5 (DRD1, DRD2 and DRD5) (Kern et al. 2015, 2012; Jiang et al. 2006). In hypothalamic neurons, GHSR-DRD2 heterodimerization switches dopamine signaling from inhibitory to excitatory (Kern et al. 2012). GHSR heterodimerizes with the melanocortin-3 receptor (MC3R), where it enhances melanocortin-induced intracellular cAMP accumulation compared to MC3R homodimers (Rediger et al. 2011). GHSR heterodimerization with the oxytocin receptor (OTR) attenuates OTR signaling (Wallace Fitzsimons et al. 2019). In this regard, stress-induced changes in ghrelin levels, which can modify GHSR expression (Harmatz et al. 2016; Smith et al. 2024a), can regulate the availability of GHSR for heterodimerization and thus indirectly impact other types of signaling. Differential heterodimer expression across brain regions may also explain why some brain regions show downregulation of GHSR after chronic stress (Harmatz et al. 2016), while other brain regions show upregulation of GHSR (Smith et al. 2024a). Future research will undoubtedly shed light on these possibilities.

7.8 Conclusions

Chronic stress produces long-lasting enhanced risk for multiple types of disease, suggesting that there are biological changes induced by stress that have maladaptive value. Here, we considered the role of ghrelin in such changes because large increases in ghrelin are observed in multiple species long after chronic stressors cease and ghrelin receptors are found throughout the periphery and brain. We considered the adaptive value of elevated ghrelin when organisms remain exposed to the stressor but also discussed how physiological changes driven by elevated ghrelin may contribute to disease when the stressor is no longer present. Because the vast majority of ghrelin that acts on the brain comes from the stomach, ghrelin represents a new frontier for connecting the brain and the body during times of energy deficit and energy excess, and the ghrelin system may represent a new frontier for tackling stress-sensitive disease.

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