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Neuroendocrine circuits governing energy balance and stress regulation: functional overlap and therapeutic implications

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Abstract

Significant co-morbidities between obesity-related metabolic disease and stress-related psychological disorders suggest important functional interactions between energy balance and brain stress integration. Largely overlapping neural circuits control these systems, and this anatomical arrangement optimizes opportunities for mutual influence. Here we first review the current literature identifying effects of metabolic neuroendocrine signals on stress regulation, and vice versa. Next, the contributions of reward driven food intake to these metabolic and stress interactions are discussed. Lastly, we consider the inter-relationships among metabolism, stress and reward in light of their important implications in the development of therapies for metabolism- or stress-related disease.

INTRODUCTION

Obesity and associated metabolic diseases have long been thought to exhibit significant co-morbidity with stress-associated psychological disorders like anxiety and depression [reviewed by (Anderson et al., 2001; Faith et al., 2002; Gariepy et al., 2010; Hryhorczuk et al., 2013; Stunkard et al., 2003)]. For example, two recent studies report that overweight or obesity during the baseline period increased the risk of developing depression during follow-up. On the other hand, baseline depression significantly increased the odds for developing obesity over time (Luppino et al., 2010; Pan et al., 2012). Such associations likely arise, at least in part, because neural circuits governing energy balance and stress reactivity are substantially intertwined, providing stress regulatory systems priority to redistribute fuels in response to acute threats (or perceived threats) to an individual's well-being. The result is a reciprocal interaction between stress and metabolism that has critical implications for

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understanding the etiology of both metabolic disease and stress-related psychological disorders, and for developing therapeutic interventions.

Homeostatic circuits

Energy balance—The amount of body fat an individual maintains reflects a tightly regulated homeostatic system matching energy intake with energy expenditure. The central nervous system (CNS) plays a key role to balance this energy equation. That is, the brain integrates signals from the environment and the periphery regarding energy needs and availability, and recruits appropriate effector systems to adjust behavioral and physiological responses that act to maintain the system in balance. Considerable progress has been made to elucidate the molecular and cellular processes, primarily in the hypothalamus and brainstem, comprising these circuits. This homeostatic regulation integrates acute satiation signals, arising in the gut and secreted phasically during meals, with more tonically-active adiposity signals to appropriately adjust nutrient intake and energy expenditure (Fig1) [reviewed by (Ryan et al., 2012; Schwartz et al., 2000; Woods and D'Alessio, 2008)].

Satiation signals provide information about acutely ingested food, and regulate meal size by acting locally at receptors on vagal afferent nerves, or by directly stimulating receptors in the brainstem. Several satiation signals have been identified, including glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK), peptide tyrosine-tyrosine (PYY), and amylin. These and other postprandial signals converge in key brainstem regions including the nucleus of the solitary tract (NTS) and area postrema (AP) [reviewed by (Adan et al., 2008; Moran, 2006; Woods and D'Alessio, 2008)]. The NTS represents a critical node of convergence that integrates meal-related signals from the periphery and also relays this information to the hypothalamus; neurons in the NTS project widely into the arcuate nucleus (ARC) and other hypothalamic nuclei implicated in the control of energy homeostasis (Grill, 2006; Grill and Hayes, 2012; Norgren, 1978). The end result of activating this system is termination of a meal.

Whereas satiation signals provide information about acutely ingested nutrients, the adiposity signals leptin and insulin provide information about stored fuel. Leptin is secreted from white adipose tissue, and insulin is secreted from pancreatic β-cells, in proportion to total adiposity—providing accurate information about the amount of body fat an individual maintains. These hormones cross the blood brain barrier, to signal directly at their receptors in the ARC, ventromedial hypothalamic nucleus (VMN), NTS and elsewhere. When an individual acutely gains weight, increased leptin and/or insulin signaling in the brain leads to reduced food intake and increased energy expenditure, thereby restoring body fat to defended levels [reviewed by (Grill and Hayes, 2012; Schwartz et al., 2000)].

Both leptin and insulin exert their effects on energy balance in part by activating the hypothalamic melanocortin system (Benoit et al., 2002; Seeley et al., 1997). This consists of first-order pro-opiomelanocortin (POMC) and agouti-related peptide (AgRP) expressing neurons in the ARC that project to melanocortin-4 receptor (MC4R) positive neurons in the paraventricular nucleus of the hypothalamus (PVN), the lateral hypothalamic area (LHA) and elsewhere [reviewed by (Cone, 2005)]. The pro-hormone POMC is cleaved to produce α-MSH, an agonist of MC4R, whereas AgRP acts as an inverse agonist at the receptor

(Haskell-Luevano and Monck, 2001; Haskell-Luevano et al., 1997; Nijenhuis et al., 2001). Brain leptin and insulin signaling activate POMC and inhibit AgRP neurons (Cowley et al., 2001; van den Top et al., 2004). The net effect is to increase MC4R signaling, and thereby to reduce food intake and increase energy expenditure.

Importantly, signaling by adiposity signals sets a background tone that modulates sensitivity to satiation signals. Meal-related signals relayed from the brainstem are integrated in leptin and/or insulin-receptor expressing neurons in the NTS and medial-basal hypothalamus (MBH). These in turn recruit appropriate downstream effectors (e.g., MC4R) in the PVN, LHA, parabrachial nucleus (PBN), NTS, dorsal motor nucleus of the vagus (DMV), and intermediolateral cell column of the spinal cord (IML) to appropriately modulate feeding behavior and energy expenditure [reviewed by (Williams and Elmquist, 2012)]. In the presence of greater CNS leptin and/or insulin signaling, for example, the anorectic responses to CCK (Morton et al., 2005; Riedy et al., 1995) and GLP-1 (Williams et al., 2006) are enhanced.

Stress—Stress is broadly defined as a real or perceived threat to homeostasis or well-being, and may be either physical or psychogenic in nature. Information regarding the presence of a stressor is conveyed by all major sensory systems to the brain, with threats to physiological homeostasis conveyed primarily via brainstem regions like the NTS while psychogenic stressors impinge primarily on forebrain limbic structures like the prefrontal cortex (PFC), hippocampus and amygdala [reviewed by (Ulrich-Lai and Herman, 2009)]. The PVN represents an important node of convergence that receives inputs from stress-activated brainstem and forebrain limbic structures. These signals are integrated in the PVN to recruit appropriate effector systems that adjust physiological responses—thereby minimizing the expected cost to the individual. Considerable progress has been made to elucidate the neural circuits and cellular processes, primarily in the limbic forebrain, hypothalamus and brainstem, which mediate these responses. These involve activation of both the sympathoadrenomedullary (SAM) system and the hypothalamic-pituitary-adrenocortical (HPA) axis (Fig 1).

Activation of the sympathetic nervous system during acute stress provides a means for rapid physiological responses via direct neural innervation of peripheral organs [reviewed by (Ulrich-Lai and Herman, 2009)]. Stress activates a collection of pre-autonomic brain regions, including the NTS and PVN, which ultimately activate pre-sympathetic neurons in the IML and inactivate pre-parasympathetic neurons in the DMV and nucleus ambiguous. The IML neurons activate (1) postganglionic neurons in the pre- and paravertebral ganglia, which provide catecholaminergic innervation to nearly all peripheral tissues, and (2) the adrenal medulla, which releases catecholamines into systemic circulation. This SAM activity is responsible for the stereotypical ‘fight or flight’ response that includes increased heart rate and blood pressure, redirection of blood flow away from digestive and reproductive processes, and mobilization of stored energy. For example, increased sympathetic drive to white adipose tissue (WAT) increases the release of free fatty acids [reviewed by (Bartness and Song, 2007)]. Similarly, increased sympathetic drive to the liver in response to stress promotes glycogenolysis and increases glucose output [reviewed by (Yamaguchi, 1992)] whereas increased sympathetic drive to pancreas blunts insulin

secretion—contributing to the greater availability of circulating glucose [reviewed in (Halter et al., 1984)].

Activation of the HPA axis provides a slower, sustained, and amplified physiological response to acute stress [reviewed in (Ulrich-Lai and Herman, 2009)]. Specifically, information regarding a stressor is conveyed to hypophysiotropic neurons in the PVN. These neurons then release corticotropin releasing hormone (CRH), as well as other releasing factors, from their terminals in the median eminence. The CRH is carried through the portal circulation to the anterior pituitary where it stimulates the release of adrenocorticotropic hormone (ACTH) into systemic circulation. ACTH stimulates the synthesis and secretion of glucocorticoids (e.g., cortisol in humans and corticosterone in rodents) from the adrenal cortex. Glucocorticoids act on their receptors throughout the brain and body to exert numerous effects, including negative feedback on CRH and ACTH release, and mobilization of stored energy. Specifically, glucocorticoids mobilize fuel from the liver via increased gluconeogenesis [reviewed in (Baxter, 1976)], and from WAT by increased lipolysis (Campbell et al., 2011; Xu et al., 2009). The net effect is to increase the availability of fuel, facilitating a physiological response to the (real or perceived) threat. Taken together, rapid SAM action coupled with the somewhat slower and longer-lasting glucocorticoid actions work together to maintain physiological homeostasis and promote survival.

Frequent use of stress regulatory circuits under conditions of chronic stress exposure results in altered gene expression and synaptic plasticity, leading to persistent changes in stress system function (Ulrich-Lai and Herman, 2009). For instance, chronic stress leads to dendritic atrophy in stress-inhibitory brain regions (hippocampus, mPFC) (Magariños and McEwen, 1995; Radley et al., 2009), dendritic branching in stress-excitatory brain regions (amygdala) (Vyas et al., 2002), and increased neuronal inputs as well as increased CRH mRNA in the PVN (Flak et al., 2009; Herman et al., 1995; Makino et al., 1995). The net effect of these various changes to stress regulatory circuits is increased excitability, leading to elevated basal and stress-evoked HPA and SAM tone (Akana et al., 1992; Grippo et al., 2002; Ulrich-Lai et al., 2007). This stress facilitation insures that the system can respond to new stressors despite elevations in basal glucocorticoids and alterations in endocrine and immune function (Akana et al., 1992; Tauchi et al., 2008). In rodent models, exposure to chronic stress often elicits an increase in anxiety-like and depression-like behaviors. Therefore varying chronic stress paradigms have been developed to model these disorders. Consistent with this association, a history of stressful life events and/or circumstances is thought to be a significant risk factor for clinical diagnosis of depression and other mood disorders (Coyne and Downey, 1991; de Kloet et al., 2005; Mazure, 1998; Paykel, 1969).

Integration of energy homeostasis and stress regulatory responses

An emergent property of these overlapping circuits is that acute stress responses, initiated to maintain homeostasis across all major physiological systems and/or to respond to environmental threats, can commandeer metabolic circuits and endocrine responses to address acute threats to an individual’s well-being, as discussed above. Energy and glucose homeostasis is temporarily disrupted to provide fuel for these responses. Moreover, persistent exposure to circulating glucocorticoids during chronic stress promotes the

redistribution of body fat towards visceral depots (Dallman et al., 2003a; Lönn et al., 1994), which are thought to exhibit greater lipolytic response to adrenergic stimulation (Arner, 1995; Hoffstedt et al., 1997; Ostman et al., 1979). Thus fat redistribution associated with chronic stress may mirror stress facilitation in neural circuits, by insuring the system can rapidly mobilize fatty acids in response to new stressors.

Importantly, growing evidence now suggests that information regarding energy status conveyed by gut hormones, adiposity signals and other neurotransmitters involved in the regulation of energy balance likewise may impinge on stress regulatory systems, to directly activate or to modulate the intensity of these responses during acute and chronic stress. These findings are discussed below (and see Table 1).

Gut hormones and stress reactivity

CCK: Cholysystokinin (CCK) is a peptide hormone secreted by intestinal I-cells in response to ingestion of nutrients, particularly fat or protein. Systemic administration of CCK induces satiation, evidenced primarily by a reduction in meal size (Gibbs and Smith, 1977; Kraly et al., 1978). This can be attenuated by vagotomy or by the deactivation of vagal afferents with capsaicin (Kraly et al., 1978; Raybould, 1991). CCK activates vagal afferent fibers projecting to neurons in the NTS. Importantly, these further project directly to the PVN, and ultimately contribute to its activation of the HPA axis (Maniscalco and Rinaman, 2013). Systemic administration of CCK increases plasma ACTH and corticosterone, and these responses are attenuated by deactivation of vagal afferents in capsaicin-treated animals (Kamilaris et al., 1992). While these findings support the contention that exogenous CCK is capable of acting activating the HPA axis via vagal afferent stimulation, it is not yet clear if this reflects a physiological role for postprandial gut-derived CCK to regulate stress responses.

In addition to its secretion from the intestine, CCK is a widely-distributed neuropeptide. Neurally-derived CCK is implicated in a range of physiological processes including thermoregulation, nociception and cognition (Beinfeld, 2001). Increased central CCK has been observed following stressful social interactions in rats (Andre et al., 2005; Becker et al., 2008), suggesting both gut and brain-derived CCK may impinge on stress regulation. Brain CCK is implicated in the regulation of emotional and motivational states, and is generally associated with increased SAM activation. For example, exogenous administration of CCK can trigger panic attacks in patients with panic disorder and in a subset of the normal population, and this is associated with a dose-dependent activation of the SAM response (de Montigny, 1989; Zwanzger et al., 2012).

GLP-1: GLP-1 is a peptide hormone secreted from enteroendocrine L-cells into hepatic portal circulation in response to ingestion of nutrients (Kreymann et al., 1987). It acts at its receptor (GLP-1R) to augment insulin secretion from pancreatic β-cells, facilitating normal glucose tolerance (Baggio and Drucker, 2007; Holst, 2007), and it promotes satiety in both rodents and humans (Flint et al., 1998; Turton et al., 1996). Consistent with its anorectic effects, intracerebroventricular (icv) administration of GLP-1 activates CRH expressing neurons in the PVN. As might be expected, this not only reduces food intake, but also results

in activation of the HPA axis. Specifically, both icv and intra-PVN infusion of GLP-1 increases plasma ACTH and corticosterone (Kinzig et al., 2003; Larsen et al., 1997), and these hormonal responses can be abrogated by intra-PVN infusion of a GLP-1R antagonist (Kinzig et al., 2003). Chronic GLP-1 administration alone does not alter basal HPA tone. However, chronic activation of GLP1R-signaling contributes to chronic stress-induced facilitation of corticosterone responses to a novel stressor (Ghosal et al., 2013; Tauchi et al., 2008). Both peripheral and central administrations of GLP-1 also increase sympathetic tone. Specifically, peripheral administration of long-lasting GLP1-R agonists activates neurons in the AP that project to the NTS, PVN, PBN and rostral ventrolateral medulla (RVLM) (Yamamoto et al., 2002, 2003). In accordance with this, peripheral and central administrations of GLP-1 agonists increase heart rate and blood pressure in a dose-dependent manner (Griffioen et al., 2011; Yamamoto et al., 2002).

GLP-1 is also produced in neurons in the brain, including in the NTS. Notably, GLP-1 immunoreactive fibers originating in the NTS project to important stress-regulatory regions, including CRH-containing neurons in the PVN (Sarkar et al., 2003). This brain GLP-1 system clearly plays a role in regulating stress reactivity [reviewed by (Ghosal et al., 2013)], but the relative physiological importance of gut-derived GLP-1 in stress regulation remains to be determined. GLP-1R is expressed on vagal afferent nerves, including those located in the nodose ganglia (Nakabayashi et al., 1996; Vahl et al., 2007), and may thereby impinge on stress circuitry via vagal afferent stimulation of the brainstem, but this remains untested.

Ghrelin: Ghrelin is a peptide hormone secreted by specialized cells in the stomach and duodenum, and is the only gut hormone known to act in the brain to increase food intake and body weight (Tschöp et al., 2000; Wren and Bloom, 2007). It circulates in an acylated and des-acylated form, with acylation thought to be necessary for full agonism at its receptor, the growth hormone secretagogue receptor (GHSR) (Kojima et al., 1999). Ghrelin acutely activates AgRP neurons and inhibits POMC neurons in the ARC, contributing to its effects on feeding behavior (Andrews et al., 2008; Cowley et al., 2003).

Intriguingly, circulating ghrelin and/or its mRNA is increased following stress in both rodents and humans (Asakawa et al., 2001; Lutter et al., 2008; Rouach et al., 2007), suggesting ghrelin may play a physiological role to regulate stress responses. Exogenous administration of ghrelin inhibits sympathetic tone in rodents (Lin et al., 2004) and rabbits (Matsumura et al., 2002), and in control, but not in vagotomized, human subjects (Huda et al., 2010). Local administration of ghrelin directly into the NTS decreases blood pressure and renal sympathetic nerve activity by suppressing sympathetic drive (Lin et al., 2004), while its i.c.v. administration activates the cardiac vagal nerve (Shimizu et al., 2011).

Ghrelin signaling also impinges on HPA axis function. Specifically, exogenous ghrelin administration increases activation of CRH-producing neurons in the PVN and enhances both CRH gene expression and circulating corticosterone (Cabral et al., 2012). Ghrelin has likewise been reported to increase anxiety and depressive-like behavior (Asakawa et al., 2001; Carlini et al., 2002, 2004; Kanehisa et al., 2006). On the other hand, however, ghrelin-deficient mice also express more anxiety-like behavior in the open field, and their stress-induced neuronal activation in the PVN is increased relative to wild-type controls. This can

be rescued with exogenous ghrelin (Spencer et al., 2012). These discrepancies have been difficult to reconcile, but are thought to result from different experimental conditions as well as the type and duration of stressor used [reviewed by (Chuang and Zigman; Stengel et al., 2011)]. Importantly, and consistent with the effect of exogenous ghrelin to increase circulating glucocorticoids, the corticosterone response to acute stress was substantially *decreased* in ghrelin knockout mice—but this was attributed to direct action of ghrelin to stimulate ACTH release from the anterior pituitary (Spencer et al., 2012). Therefore while it seems clear that ghrelin acts to increase HPA axis output (i.e., circulating glucocorticoids), further investigation is required to better delineate the underlying mechanisms and neural substrates [see (Schellekens et al., 2012) for a more thorough review]. In addition growing evidence suggests ghrelin action in brain reward circuitry can modulate motivational aspects of food intake, impinging on the critical interaction between food reward and physiological responses to acute and chronic stress. This is further discussed below.

Adiposity signals and stress reactivity

Leptin: As discussed above, leptin acts at its receptor (Lepr) in the hypothalamus and brainstem to reduce food intake and increase energy expenditure. Consistent with this, acute leptin infusion activates the SAM system. Leptin increases sympathetic nerve activity to multiple organs, including brown adipose tissue, the adrenal gland, and the kidney and its chronic infusion increases heart rate, arterial blood pressure and circulating catecholamines (Ren, 2004; da Silva et al., 2006). Thus, increased circulating leptin is thought to play a key role in obesity-associated hypertension [reviewed by (Hall et al., 2010; Rahmouni, 2010)]. Conversely, leptin-deficient (*ob/ob*) mice fail to exhibit hypertension, despite massive obesity and Zucker rats, lacking the Lepr, exhibit decreased basal and stress-induced plasma catecholamines suggestive of decreased basal and stress-induced sympathetic tone (Mark et al., 1999; Pacak et al., 1995).

Lepr positive, leptin-responsive AgRP and POMC neurons in the ARC project to and activate CRH-containing neurons in the PVN, and at least some of leptin's anorectic effects are mediated by increased expression of CRH (Lu et al., 2003). In agreement with this, it has been reported that leptin activates the HPA axis in unstressed rats (van Dijk et al., 1997). However, in contrast to its effects on the SAM system, leptin blunts HPA axis responses to stress. Peripheral administration of leptin reduces both ACTH and glucocorticoid responses to an acute psychogenic stressor in mice (Heiman et al., 1997) and in rhesus monkeys. In addition leptin enhances glucocorticoid negative feedback and blunts CRH-induced increases in both cortisol and ACTH in monkeys (Wilson et al., 2005). Zucker rats and *ob/ob* mice exhibit exaggerated corticosterone responses to stress (Pacak et al., 1995). Furthermore, evidence supports a role for leptin to blunt chronic-stress induced depression-like behavior and neural plasticity. Exogenous leptin administration to rats undergoing chronic unpredictable stress abrogates stress-induced increases in immobility during the forced swim test and attenuates stress-induced suppression of hippocampal neurogenesis (Garza et al., 2012).

Insulin: In addition to its critical role in the regulation of glucose homeostasis, insulin acts at its receptors in the brain to reduce food intake and increase energy expenditure.

Consistent with increased energy expenditure, both peripheral and icv administration of insulin increase basal sympathetic nerve activity (Muntzel et al., 1994; Rowe et al., 1981). Brain insulin action also facilitates the sympathetic counter-regulatory response to hypoglycemia (Diggs-Andrews et al., 2010; Fisher et al., 2005), but its ability to facilitate SAM activation in response to other stressors remains uncertain. For example, while intranasal insulin modulates the HPA response to the Trier Social Stress Test (TSST) in human subjects (discussed below) it did not alter the cardiovascular/autonomic response to this potent psychological stressor (Bohringer et al., 2008).

Both increased HPA axis activity and hyperinsulinemia are frequently observed in patients with diabetes. However, the effect of insulin per se on basal and stress-induced HPA tone is less clear. Brain insulin signaling is thought to play a role to stimulate the HPA axis during hypoglycemia counter-regulation (Davis et al., 1995; Fruehwald-Schultes et al., 1999), yet this may not occur basally or during other types of stress. For example, in apparent contrast to these findings, both lean and obese individuals receiving chronic intranasal insulin, which first reaches the cerebral spinal fluid without being absorbed into the blood stream, exhibit significantly blunted morning HPA axis activity (Bohringer et al., 2008). In addition, a single intranasal insulin administration prior to a TSST significantly blunted the stress-evoked rise in cortisol (Bohringer et al., 2008).

MC4R: MC4R is a well-described downstream effector of leptin and insulin action on energy balance, and there is a growing appreciation that it also plays an important role in brain stress integration. ARC POMC neurons projecting to both the PVN and medial amygdala (MeA) are rapidly activated by both acute restraint and forced swim stress. Moreover, pharmacological activation of MC4R in the PVN increases CRH mRNA as well as circulating ACTH and corticosterone (Dhillo et al., 2002; Lu et al., 2003). Pharmacologic activation of MC4R in the MeA also acutely increases circulating corticosterone, whereas its inhibition abrogates the rise in corticosterone elicited by acute restraint-stress (Liu et al., 2013). Consistent with this, stress-induced activation of the HPA axis is attenuated in a rat model of *Mc4r* loss-of-function (Ryan et al., 2014). In addition, evidence supports a role for MC4R to facilitate an increase in anxiety-like and depression-like behavior pursuant to chronic stress. Relative to control mice, MC4R-deficient mice spent significantly more time exploring the open arm of the elevated plus maze, less time immobile in the forced swim test, and more time interacting with a social target following chronic social defeat stress (Chuang et al., 2010).

With regard to the SAM system, it is thought that MC4R is a key downstream effector of leptin and/or insulin action on sympathetic drive, 1) since the effect of exogenous leptin and insulin to increase renal sympathetic nerve activity (Rahmouni et al., 2003) and of exogenous leptin to increase blood pressure (Tallam et al., 2006) was abolished in MC4R-deficient mice and 2) since deleting Lepr specifically in POMC neurons abolishes the rise in blood pressure associated with chronic leptin infusions (do Carmo et al., 2011). In agreement with this, humans with a loss of function mutation in MC4R have normal blood pressure despite extreme obesity (Greenfield et al., 2009). The effects of MC4R-signaling on the SAM system likely involves direct action in the brainstem and spinal cord, since ex-vivo application of MC4R agonists inhibit parasympathetic pre-ganglionic neurons in the DMV

and activate sympathetic pre-ganglionic neurons in the IML of mice (Sohn et al., 2013). Although these findings support a role for MC4R to regulate basal (unstressed) sympathetic drive, it is not yet known whether MC4R plays a role in SAM activation following acute or chronic stress.

It is interesting to note that, with regard to HPA axis regulation, the effects of leptin and MC4R are dissociated. That is, while it is well-known that leptin stimulates MC4R, contributing to its downstream effects on energy balance, leptin and MC4R-signaling seem to have opposing effects on HPA axis regulation. Leptin blunts, whereas MC4R-signaling facilitates, the HPA response to stress. This may reflect that MC4R-ergic tone integrates both short- and long-term regulators of energy balance. MC4R is a downstream effector not only of leptin and insulin action, but also contributes to the effects of various other anorectic and orexigenic signals [reviewed by (Ellacott, 2004)]. Likewise, CNS leptin action has both MC4R-dependent and – independent effects.

Brain reward circuits

Reward and energy balance—Despite a robust homeostatic system governing energy balance, evidence suggests the initiation of a meal, particularly in humans, is motivated primarily by non-homeostatic cues rather than a depletion of fuels per se. These include time of day, social signals, and importantly, the hedonic attractiveness or palatability of certain foods. The drive to pursue such pleasurable experiences is largely mediated by the brain reward system.

Food palatability cues, primarily taste and smell, and macronutrient composition (Sclafani and Ackroff, 2012), ultimately activate brain reward pathways. Taste information passes through two brainstem relays, the first located in the NTS and the second in the PBN (Saper et al., 2002). The taste pathway then bifurcates in the PBN, with information passing from the PBN to thalamus and onto gustatory cortex to encode taste discrimination. In contrast, taste information passes from the PBN to the ventral tegmental area (VTA), via either direct or multi-synaptic pathways involving limbic structures (e.g., amygdala/bed nucleus of the stria terminalis (BNST), hypothalamus, medial PFC) to encode food reward. As a result, highly palatable foods activate dopaminergic neurons in the VTA that project to the nucleus accumbens (NAc), PFC and amygdala. This dopaminergic system is linked with the motivating or ‘wanting’ component of food reward, promoting behaviors (e.g., food searching, lever pressing for a reward) that are directed towards reward receipt (Berridge, 2009). In addition, opioidergic and cannabinoid activity in the NAc is liked with the hedonic or ‘liking’ component of food reward, promoting increased pleasure from the consumption of these foods (Berridge, 2009; Kelley and Berridge, 2002).

Importantly, there is considerable crosstalk between the homeostatic and reward circuits, mediated by in part by direct actions of insulin and leptin at their receptors within the corticolimbic system, as well as by secondary hypothalamic effector systems (Davis et al., 2011; Figlewicz, 2004; Figlewicz et al., 2001; Hommel et al., 2006). For example, VTA dopamine neurons expressing Lepr reduce their firing rate in response to leptin administration. This is associated with decreased food intake (Hommel et al., 2006). Conversely, reduced leptin signaling in the midbrain/VTA heightens behavioral responses to

palatable food (Davis et al., 2011; Hommel et al., 2006). When an animal is food deprived, circulating leptin and insulin are decreased. Consequently, hedonically pleasing sensations of food become exaggerated. This results in more food being eaten, even in the face of inhibitory signals from the periphery (Ryan et al., 2012).

Stress and the consumption of palatable food

Stress exerts divergent effects on total caloric intake: Stress exerts bi-directional effects on total caloric intake. When individuals are asked to self-report food intake, for example, approximately 25-40% report that they eat less than usual, whereas 35-60% report that they eat more than usual during stress (Epel et al., 2004; Oliver and Wardle, 1999; Weinstein et al., 1997). The reasons for this divergence remain unclear. Current evidence suggests this apparent bimodal pattern may result from 1) differences in the nature or intensity of the stressor(s) involved, with high-intensity stressors more likely to elicit anorexia whereas milder ‘everyday’ social stressors are associated with increased food intake, 2) differences in individuals’ prior experience with food, and/or 3) individual differences in the neuroendocrine and reward responses to stress and/or food. Limited data from both animal and human studies support each of these possibilities, though further investigation is needed.

First, although rodent models of chronic stress have traditionally been associated with decreased total caloric intake, these paradigms typically include both psychogenic stressors (e.g., restraint) and stressors that are primarily physical in nature (e.g., cold; forced swim) (Ulrich-Lai et al., 2007; Willner et al., 1996). In contrast, Bartolomucci and colleagues have developed a model of chronic psychosocial stress, in which defeated subordinate mice consuming a high fat diet are hyperphagic and become obese (Bartolomucci et al., 2009). Likewise, chronic psychosocial stress in subordinate female rhesus monkeys is orexigenic when a high fat and high sugar diet is offered (Michopoulos et al., 2012). In agreement with this, when considering the human literature, it is apparent that studies reporting stress-induced anorexia tend to involve higher-intensity stressors like military combat or imminent surgery (Bellisle et al., 1990; Popper et al., 1989) whereas studies reporting stress-induced hyperphagia tend to involve daily-life stressors like school, work and interpersonal relationships (Epel et al., 2001; McCann et al., 1990; Pollard et al., 1995; Rutters et al., 2009; Wardle et al., 2000).

Second, stress-induced hyperphagia in humans may occur predominantly among individuals that self-describe as normally ‘restrained’ or ‘emotional’ eaters (Oliver and Wardle, 1999; Rutters et al., 2009; Wardle et al., 2000). Specifically, chronic stress decreases neuronal activation induced by viewing high calorie foods in brain regions related to planning and emotional control (Tryon et al., 2013a), which may predispose to emotional eating. In agreement with this, stress interferes with behavioral modifications like ‘dieting’ [reviewed in (Calu et al., 2013)], and is associated with disinhibited food intake (Groesz et al., 2012). Likewise, a rat model that combines acute foot shock stress with a history of repeated bouts of food restriction meant to mimic yo-yo dieting, increases total caloric intake when palatable food is made available (Hagan et al., 2002).

Finally, individual differences in the responsiveness of homeostatic and reward circuits governing energy balance and stress regulation (discussed above) may predict the effects of

chronic stress on food intake. For example, the stress-induced rise in circulating leptin during a TSST was negatively associated with food intake immediately following the stressor (Tomiyama et al., 2012). In addition, when well-characterized substrains of diet-resistant and diet-induced obese (DIO) rats were exposed to 5 weeks of chronic stress together with exposure to a palatable diet, DIO rats had significantly diminished HPA, autonomic and metabolic responses to stress (Levin et al., 2000).

Stress increases consumption of palatable food: Importantly, stress promotes the choice of calorically-dense, highly palatable foods relative to more nutritious less-tasty alternatives, potentially contributing to its adverse metabolic effects (Fig 2) (Groesz et al., 2012; Kim et al., 2013; Laugero et al., 2011; McCann et al., 1990; Oliver and Wardle, 1999; Tryon et al., 2013a). This can occur even among people who decrease their total overall caloric intake (Oliver and Wardle, 1999) Similarly, when chronically-stressed rodents are provided a choice, they will maintain or increase consumption of sugar or lard despite decreasing chow intake (Pecoraro et al., 2004; Ulrich-Lai et al., 2007). Although a history of dietary restraint might facilitate this behavior, the rodents in these paradigms presumably did not previously 'restrain' their eating behavior. Thus increased motivation to consume palatable foods during stress may also be important. Consistent with this possibility, stress increases the willingness of both humans and rodents to work for palatable food (Lemmens et al., 2011; Willner et al., 1998), and increases neuronal activation in brain reward and motivation structures following exposure to palatable foods (Rudenga et al., 2013; Tryon et al., 2013a). Collectively, these findings support that stress increases the 'wanting' or motivation to obtain highly-palatable foods, a phenomenon that may be related to food craving (Willner et al., 1998).

Notably, this increased motivation to consume palatable foods may occur independent from a decrease in palatable food 'liking' during stress. For instance, stress induces anhedonia in rodents in which the intake of weakly preferred substance (saccharin or dilute sucrose drink), but not highly preferred substance (concentrated sucrose drink), is reduced during chronic stress (Sampson et al., 1992; Ulrich-Lai et al., 2007; Willner et al., 1996). Similarly, experimentally-induced depressed mood in people can reduce the perceived pleasantness of food (Willner and Healy, 1994).

In agreement with the observation that chronic stress promotes the consumption of palatable food, glucocorticoid receptor-signaling in brain increases caloric intake, particularly of palatable foods, thereby promoting body weight gain (Green et al., 1992; Tataranni et al., 1996; Tempel et al., 1992; Zakrzewska et al., 1999). Moreover, glucocorticoids contribute to changes in the synaptic input organization of AgRP and POMC neurons in the ARC, favoring increased excitation of AgRP and increased inhibition of POMC neurons (Gyengesi et al., 2010). Finally, circulating glucocorticoid concentration is positively associated with increased food intake in people (Francis et al., 2013; George et al., 2010) and saccharin intake in rats (Bhatnagar et al., 2000), supporting that glucocorticoids increase reward-driven food intake.

The gut hormone ghrelin is also implicated in stress-induced changes in palatable feeding. In addition to promoting food intake by its action in homeostatic circuits, ghrelin enhances the

rewarding properties of food via its signaling in the VTA (Disse et al., 2011; Egecioglu et al., 2010; Perello et al., 2010). Using a chronic social defeat stress (CSDS) paradigm, Zigman and colleagues report that the CSDS-induced increase in the conditioned place preference for a high-fat diet, observed in wild-type mice, is absent in CSDS-exposed GHSR-deficient mice (Chuang et al., 2011). Furthermore, expression of GHSR in tyrosine hydroxylase-containing neurons, including dopaminergic neurons of the VTA, is permissive for the induction of hedonic feeding elicited by CSDS (Chuang et al., 2011; Perelló and Zigman, 2012).

Food reward and stress reactivity—Colloquial wisdom suggests that individuals increase their relative intake of palatable foods during chronic stress as a mechanism for self-soothing. In other words, ingestion of so-called “comfort-foods” is thought to blunt unpleasant physiological responses to stress (Fig 2) (Dallman et al., 2003b; Gibson, 2006). In agreement with this possibility, palatable food intake improves mood and decreases perceived stress and plasma glucocorticoid levels in people (Gibson, 2006; Macht and Mueller, 2007; Tomiyama et al., 2011; Tryon et al., 2013b), particularly those with high stress proneness (Markus et al., 2000). Similarly, rodents that are provided the option of consuming palatable foods like sucrose and lard have reduced CRH mRNA expression in the PVN, accompanied by blunted HPA, sympathetic and behavioral responses to acute stress (la Fleur et al., 2005; Pecoraro et al., 2004; Shide and Blass, 1989; Strack et al., 1997; Ulrich-Lai et al., 2007, 2010). At least some of the stress-relieving effects of consuming such palatable food results from its pleasurable and rewarding properties (Barr et al., 1999; Macht and Mueller, 2007; Ulrich-Lai et al., 2010), though caloric and macronutrient composition likely also play a role (Laugero et al., 2001). For example, when rats with free access to normal chow and water are given additional brief, twice-daily access to a limited amount of sucrose drink, both plasma corticosterone and tachycardic responses to restraint are attenuated, and anxiety-like behavior is reduced. Brief, twice-daily access to the non-caloric sweetener saccharin replicates this stress relief, indicating the pleasurable and rewarding properties are sufficient to elicit these effects. Moreover, delivering sucrose by intragastric gavage, which provides its post-ingestive consequences while minimizing taste and palatability, does not provide stress relief, suggesting the hedonic and rewarding properties are necessary as well as sufficient in this model (Ulrich-Lai et al., 2010). Importantly, lesions of the basolateral amygdala prevent the stress blunting provided by limited sucrose access, implicating this structure as a critical link between the reward and stress systems in this model (Ulrich-Lai et al., 2010). Additional studies will be necessary to understand the relative importance food reward and other post-ingestive consequences of palatable food consumption in other “comfort-feeding” models, including stress-associated high-fat diet feeding.

Therapeutic implications

Pharmacology—In light of the substantial overlap between neuroendocrine circuits regulating energy balance and stress responses, it is perhaps not surprising that therapeutic interventions targeting either metabolic disease or stress-associated mood disorders have been beset by reciprocal unintended side-effects. Consistent with previous reports (Berken et al., 1984; Raeder et al., 2006), for example, a recent study demonstrates that users of both

selective serotonin reuptake inhibitors and tricyclic anti-depressant medications gain significantly more weight compared to non-users matched for depression-related characteristics. This was accompanied by a doubling of the risk of diagnosed type-2 diabetes (Kivimäki et al., 2010).

Conversely, pharmacological interventions in development for the treatment of obesity have been undermined by unintended psychological/behavioral consequences. Several of the CNS-acting drugs that have been used for weight-loss have powerful behavioral effects beyond their influence on energy balance (see Table 2). For example, endocannabinoid receptor (CB1)-signaling in both homeostatic and reward circuitry increases homeostatic and hedonic aspects of food intake [reviewed by (Silvestri and Di Marzo, 2013)]. In agreement with this, CB1 antagonists are effective to elicit weight loss and had been prescribed for the treatment of obesity. Unfortunately however, the CB1 antagonist Rimonabant was withdrawn from the European market in 2009, and was not approved for in the U.S., because its use was associated with a significant increase in symptoms of depression, anxiety and suicidal ideation (Christensen et al., 2007; Van Gaal et al., 2005). Phase III trials of the CB1 inverse agonist Taranabant were stopped due to similar side-effects (Aronne et al., 2010). As another example, the dopamine (D1/D5)- receptor antagonist, Ecopipam, produced a 3.1% to 4.3% greater weight loss than placebo in phase III studies, consistent with the role of dopaminergic signaling to increase appetitive motivation and palatable food preference (El-Ghundi et al., 2003; Yu et al., 2000). However, these trials were discontinued, due to unexpected adverse psychiatric effects again including increased incidence of depression, anxiety and suicidal ideation (Astrup et al., 2007).

Such behavioral effects of centrally-acting anti-obesity agents may occur because the targeted receptors and circuits not only modulate metabolic endpoints, but stress and reward pathways as well. Moreover, plasticity in these circuits occurring over periods of chronic stress, discussed above, may contribute to heterogeneity in the psychobehavioral responses to CNS-acting weight-loss drugs. That is, an individual's ongoing, and history of, stress exposure may modulate his/her behavioral response to these treatments. For example, CB1-signaling in stress-regulatory circuits inhibits physiological responses to acute stress, and may facilitate brain adaptations to chronic stress [reviewed by (Bermudez-Silva et al., 2012; Cota, 2008; Gorzalka and Dang, 2012)]. Importantly, repeat stress exposure affects various aspects of the endocannabinoid system including: concentration of the major endocannabinoids, activities of their degrading enzymes, agonist binding properties of receptors, and receptor-mediated control of neurotransmitter release (Bortolato et al., 2007; Dubreucq et al., 2012; Hill et al., 2005; Patel and Hillard, 2008; Reich et al., 2009). All of these changes may interact with CB1-targeted drug treatments to influence psychobehavioral responses. Similarly, stress-induced increases in NAc DA release depend on the type, duration, novelty and controllability of the stress exposure (Cabib and Puglisi-Allegra, 2012). Therefore, an individuals' recent and ongoing experience with psychological stressors may alter his/her response to dopamine receptor antagonists like Ecopipam, perhaps contributing to the varying presentation of psychobehavioral side effects.

Relevant to this, we note that dieting itself can be a significant stressor and that repeated episodes of dieting and weight loss may represent a form of chronic stress. As early as 1957,

for example, AJ Stunkard began documenting the incidence of anxiety, depression and 'emotional upset', among a subset of individuals, during weight loss achieved by enforced caloric restriction (Stunkard, 1957). Likewise, a mild caloric restriction paradigm, inducing 10-15% weight loss over 3 weeks, potently increased HPA responsivity to a novel stressor in mice, and increased depression-like behavior in the tail-suspension test. This was associated with brain region-specific alterations of corticotropin-releasing factor expression and promoter methylation (Pankevich et al., 2010). Such findings raise the possibility that an individual's history of dieting may alter brain homeostatic, stress and reward circuitry in a way that impacts key molecular targets of weight-loss drugs, resulting in variable behavioral responses to these drugs.

Finally, it is important to note that at least some of the CNS-acting drugs that have been prescribed for weight-loss are thought to have a relatively low risk profile for adverse neuropsychiatric events, and some may even improve mood. These include some of the various drugs known to increase monoamine neurotransmission directly, like bupropion, lorcaserin, and sibutramine (Nathan et al., 2011).

The link between CNS-acting weight-loss drugs and unintended mood effects has led some to suggest that ongoing efforts should target peripherally-acting mechanisms. For example, action at peripheral CB1 receptors is thought to contribute significantly to the metabolic benefits of CB1 antagonists (Kunos and Tam, 2011; Need et al., 2006; Nogueiras et al., 2008). Indeed, new CB1 compounds with limited CNS penetration are still effective to reduce body weight and improve insulin resistance, perhaps by reducing plasma leptin levels and reversing leptin resistance (Tam et al., 2012). Thus there is hope that such compounds may avoid the psychobehavioral responses previously observed with this class of drugs. Other peripheral strategies in varying phases of development include targeting intestinal digestion and uptake of lipids (e.g., Orlistat, Cetilistat) (Kopelman et al., 2010; Torgerson et al., 2004), bile acid signaling (Thomas et al., 2008) and BAT thermogenesis (Frühbeck et al., 2009). Although strategies focusing on peripheral targets may indeed promote fewer psychobehavioral side-effects, we caution that even strictly peripheral interventions may indirectly impinge on CNS stress and reward circuitry, due, for example, to consequent changes in CNS-acting adiposity and satiation signals.

Surgery—Bariatric surgical procedures like Roux-en-y gastric bypass and vertical sleeve gastrectomy are currently the most durable and effective treatment for obesity and associated metabolic disorders. Increasing evidence demonstrates that the efficacy of these procedures is not derived primarily from their potentially restrictive and/or malabsorptive anatomical effects. Rather, it is now appreciated that these benefits result from alterations in neurohumoral signals arising in the gut that may act in the brain and elsewhere to alter energy balance. These include, for example, substantial changes in circulating gut hormones like ghrelin, GLP-1, and CCK [reviewed by (Stefater et al., 2012)]. In light of the overlap between neuroendocrine circuits governing energy balance and stress reactivity (discussed above), changes in these peripheral "metabolic" signals may also alter stress-regulation and influence the etiology of stress-related mood disorders following bariatric procedures. Relevant to this, current evidence largely indicates an improvement in post-operative indices of depression (Karlsson et al., 2003; Papageorgiou et al., 2002; Stunkard and Wadden,

1992). However, enthusiasm for this apparent benefit is tempered by a recent meta-analysis suggesting risk of completed suicide may be increased after bariatric surgery (Peterhänsel et al., 2013). Additional study is clearly needed. Given the psychosocial and cultural implications of obesity and weight-loss in human subjects, metabolic and behavioral studies in appropriate animal models can provide a needed complement to clinical investigations, by focusing directly on underlying molecular and physiological mechanisms.

Summary and conclusions

Metabolic disease and stress-related disorders are thought to be significantly co-morbid. Likewise, energy balance and stress regulation are mediated by largely overlapping neural circuits, indicating important functional interactions between these systems. Consistent with this prediction, neuroendocrine signals that regulate energy balance are now appreciated to influence stress regulation. Conversely, stress responses have clear influence on food intake, energy expenditure and adiposity. These inter-relationships have important therapeutic implications, underscoring the importance of assessing the stress regulatory effects of potential metabolic therapies, as well as the metabolic consequences of potential therapies for stress-related disorders.

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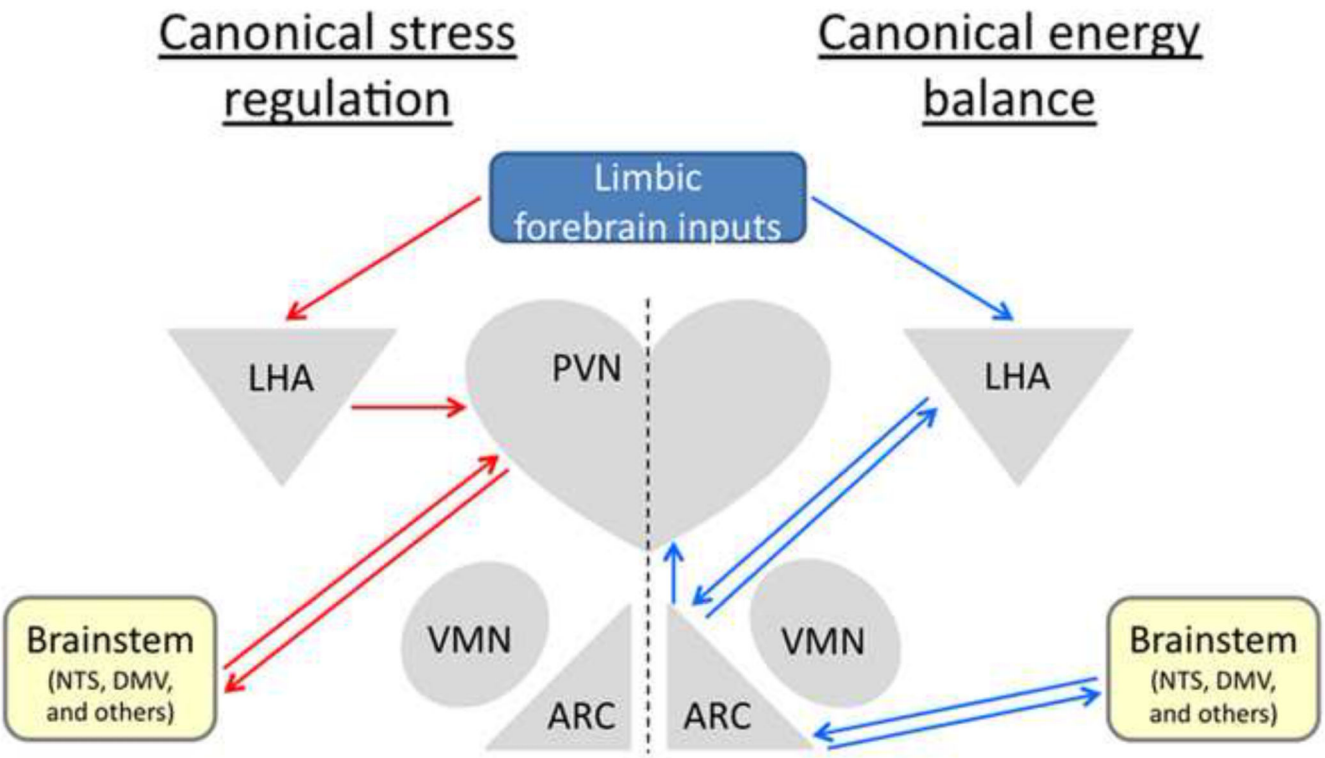

Figure 1. Canonical pathways that regulate stress responses (left; red arrows) and energy balance (right; blue arrows)

For the stress system, information from brainstem and limbic forebrain areas converges in the PVN, which directly activates the HPA axis and regulates autonomic nervous system responses via projections to brainstem. For energy balance, information from brainstem and limbic forebrain areas converges on the ARC, which regulates energy intake and expenditure via connections to the PVN, LHA and brainstem.

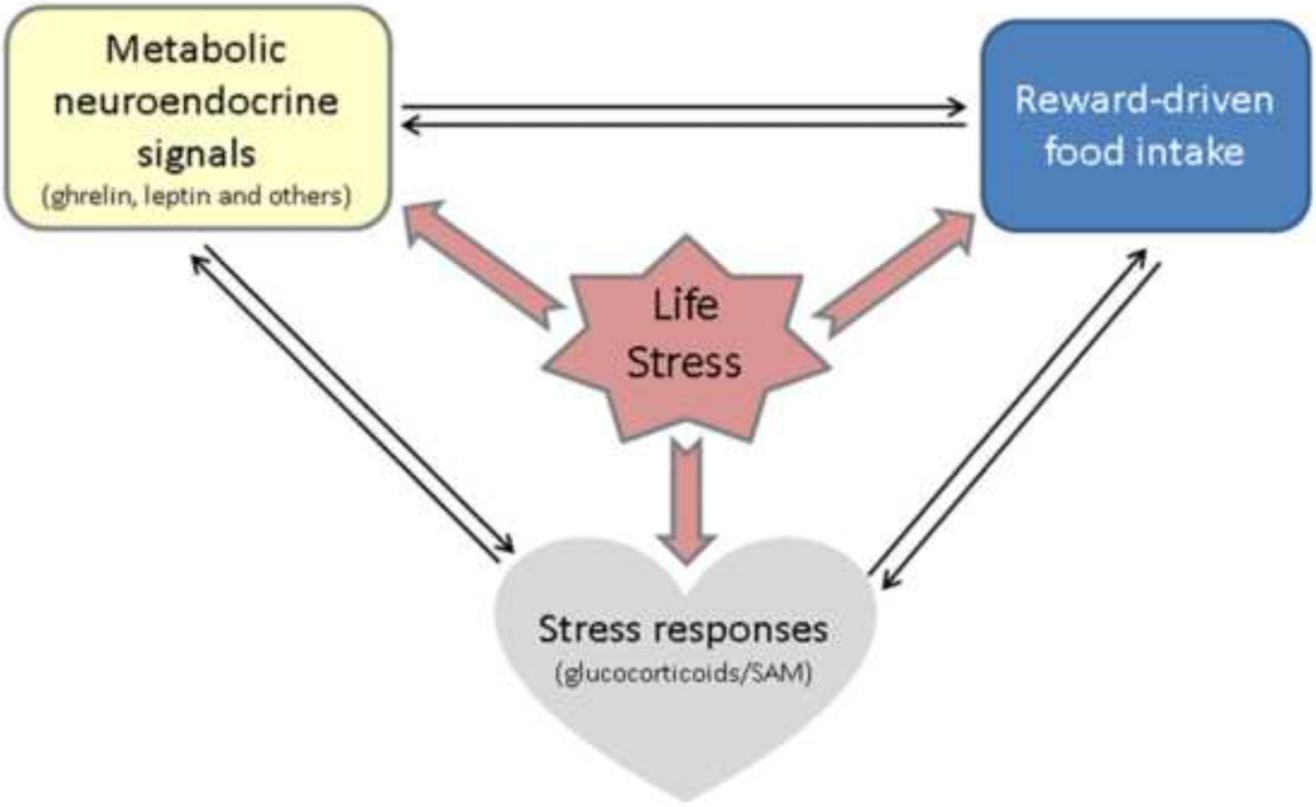

Figure 2. Schematic illustrating the complex functional interactions between homeostatic metabolic signaling, physiological responses to stress, and reward-driven food intake

These interactions likely occur, at least in part, as consequence of these systems' largely overlapping anatomical circuitry. Metabolic signals including leptin and ghrelin, influence reward-driven food intake-which in turn alters energy balance. These metabolic signals also modulate HPA and autonomic responses to stress. Moreover, stress-mediators can override metabolic homeostasis to re-distribute fuels in the face of a challenge. Finally, stress mediators like glucocorticoids promote reward-driven food intake, which reciprocally reduces stress responses. All of these systems are profoundly influenced by stress exposure. In stress-prone individuals, this results in increased motivation for food reward and increased intake of highly palatable foods, that in turn limit uncomfortable psychological and physiological responses to stress. However, over the long term, chronic stress exposure can contribute to the development of metabolic disease.

Table 1

Stress-regulatory effects of metabolic neuroendocrine signals

Considerable research has established that metabolism-related neuroendocrine signals influence basal and stress-evoked activity of the SAM and HPA systems. Upward arrows denote activation, whereas downward arrows denote inhibition.

Neuroendocrine Signal	Energy Balance	SAM System	HPA axis
CCK	↓ Gibbs and Smith,1977 Kraly et al., 1978	↑ de Montigny, 1989 Zwanzger et al., 2012	↑ Maniscalco and Rinaman, 2013 Kamilaris et al., 1992
Glp-1	↓ Flint et al., 1998 Turton et al., 1996	↑ Griffioen et al., 2011 Yamamoto et al., 2002	↑ Kinzig et al., 2003 Larsen et al., 1997 Ghosal et al., 2013 Tauchi et al., 2008
Ghrelin	↑ Tschöp et al., 2000 Wren and Bloom, 2007	↓ Lin et al., 2004 Matsumura et al.,2002 Huda et al., 2010 Shimizu et al., 2011	↑ Cabral et al., 2012 Spencer et al., 2012
Leptin	↓ Reviewed in: Grill and Hayes 2012 Schwartz et al 2000	↑ Ren, 2004 da Silva et al., 2006 Mark et al., 1999 Pacak et al., 1995	↑ BASAL: van Dijk et al., 1997 ↓ POST-STRESS: Pacak et al., 1995 Heiman et al., 1997 Wilson et al., 2005
Insulin	↓ Reviewed in: Grill and Hayes 2012 Schwartz et al 2000	↑ Muntzel et al., 1994 Rowe et al., 1981 Rahmouni 2003	↓ Bohringer et al., 2008
MC4R-signaling	↓ Cowley et al., 2001 van den Top et al., 2004 Benoit et al., 2002 Seeley et al., 1997	↑ Rahmouni et al., 2003 Tallam et al., 2006 do Carmo et al., 2011 Greenfield et al., 2009 Sohn et al., 2013	↑ Dhillo et al., 2002 Lu et al., 2003 Liu et al., 2013 Ryan et al., 2014

Table 2

Neuropsychiatric effects of CNS-acting drugs prescribed for weight-loss

Pharmacological weight-loss treatments are associated with altered HPA and SAM activity and in some cases may increase risk of other neuropsychiatric effects in some individuals.

Drug	Molecular mechanism of action	Effects on stress regulatory systems	Evidence for neuropsychiatric effects
Bupropion	NE and DA reuptake inhibitor	Decreased HPA axis activity (Viana et al., 2008)	In clinical use as an anti-depressant
Ecopipam	D1/D5 antagonist	Increased SAM activity (Zheng et al., 2013)	Depression, anxiety and suicidal ideation (Astrup et al., 2007)
Fenfluramine	Increases 5HT release	Increased HPA axis activity (Heisler et al., 2007) Increased SAM activity (Bray, 2000)	Increased 'CNS complaints' [this included insomnia, nervousness, depression, fatigue and increased dreaming] (Weintraub et al., 1984)
Liraglutide	GLP1R agonist	GLP1R-signaling increased HPA axis activity (Kinzig et al., 2003; Larsen et al., 1997) and increased SAM activity (Yamamoto et al., 2002)	Slightly more frequent incidence of 'psychiatric disorders' [this included insomnia, depressed mood, and nervousness] (Astrup et al., 2009, 2012)
Lorcaserin	$5HT_{2c}$ agonist	$5HT_{2c}$ activation increased HPA axis activity (Heisler et al., 2007)	None noted (Fidler et al., 2011; Smith et al., 2010)
Naltrexone	Opioid-receptor antagonist	Increased HPA axis activity (Eisenberg, 1984; O'Malley et al., 2002)	Insomnia; Limited evidence for mild depression/ dysphoria and nervousness/ anxiety (Atkinson et al., 1985; Hollister et al., 1981; Mendelson et al., 1978); No mood effects observed in combination with bupropion (Greenway et al., 2009, 2010)
Phentermine	Increases NE release	Increased SAM activity (Bays, 2010)	Increased 'CNS complaints' [this category included insomnia, nervousness, depression, fatigue and increased dreaming] (Weintraub et al., 1984); Anxiety, irritability, and disturbance in attention when given in combination with Topiramate (Gadde et al., 2011)
Rimonabant/ Taranabant	CB1 antagonist/ inverse agonist	CB1 antagonists increased HPA axis activity (Cota, 2008; Evanson et al., 2010; Hill and McEwen, 2010), and increased SAM activity (Bellocchio et al., 2013; Quarta et al., 2010)	Depression, anxiety and suicidal ideation (Christensen et al., 2007; Van Gaal et al., 2005)
Sibutramine	NE and 5HT reuptake inhibitor	Increased SAM activity (Bray, 2000)	Insomnia (Bray et al., 1996)
Tesofensine	NE, DA and 5HT reuptake inhibitor	Increased SAM activity (Bentzen et al., 2013)	Insomnia; Anger and hostility at high doses (Astrup et al., 2008)
Topiramate	Not well understood	Reduced HPA axis activity (York et al., 2000)	Cognitive impairment, nervousness, depression, mood problems (Bray et al., 2003; Wilding et al., 2004); Anxiety, irritability, and disturbance in attention when given in combination Phentermine (Gadde et al., 2011)