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Review

Food-intake regulation during stress by the hypothalamo-pituitary-adrenal axis

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ABSTRACT

The prevalence of obesity is increasing worldwide with serious consequences such as diabetes mellitus type 2 and cardiovascular diseases. Emotional stress is considered to be one of the main reasons of obesity development in humans. However, there are some contradictory results, which should be addressed. First of all stress induces anorexia, but not overeating in laboratory animals. Glucocorticoids, the effector molecules of the hypothalamo-pituitary-adrenocortical (HPA) axis stimulate and stress inhibits food intake. It is also not clear if stress is diabetogenic or an antidiabetogenic factor. The review will discusses these issues and the involvement of the whole HPA axis and its separate molecules (glucocorticoids, adrenocorticotropin, corticotropin-releasing hormone) in food intake regulation under stress.

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1. Introduction

The prevalence of obesity is increasing worldwide with serious consequences such as diabetes mellitus type 2 (DM2) and cardiovascular diseases (Caballero, 2007). At the same time people in the developed countries are facing more stress, which might be one of the contributing factors for the development of obesity (Adam and Epel, 2007; Greeno and Wing, 1994; Nieuwenhuizen and Rutters, 2008; O'Connor and Conner, 2011). However, the stress-eating-obesity relationship is complicated (Moore and Cunningham, 2012). First of all, among experimental conditions stress induces anorexia, while in humans stress-induced obesity is more prevalent. In line with these observation glucocorticoids (GCs), the effector molecules of the hypothalamo-pituitary-adrenocortical axis (HPA or stress axis, Fig. 1) stimulate (Bartolomucci et al., 2009; Bjorntorp, 2001; King and Smith, 1985), while stress, as a whole, inhibits food intake (Bazhan et al., 2007; De Souza et al., 2000; Harris et al., 2001; Krahn et al., 1990; Rybkin et al., 1997). It is also not clear if stress is diabetogenic (Rosmond, 2003; Surwit et al., 1992) or an antidiabetogenic factor (Bates et al., 2008a,b; Kai et al., 2000).

Although GCs are the end hormones of the HPA axis, we assume that other components of the axis could also have a role in food intake regulation during stress (Fig. 1). Of course other systems could have been taken into consideration, like the stress-induced increase in sympatho-adrenomedullary activity or the serotoninergic system, but in our minireview we will focus on the molecules of the HPA axis. In the following we will summarize participation of stress, its end hormone (GCs), hypophyseal (adrenocorticotropin, ACTH) and hypothalamic components (corticotropin-releasing hormone, CRH) in food intake regulation, which is one of the crucial components of obesity.

2. Stress

CRH, originally characterized in the nucleus paraventricularis hypothalami (PVN) as the principal regulator of the HPA axis, has broad central and peripheral distribution and actions. CRH-1 and CRH-2 receptors relay signals from CRH and its paralogues urocortins (Ucn) (Kuperman and Chen, 2008). CRH-1 receptor is expressed on anterior pituitary corticotropes and induces the synthesis of ACTH from proopiomelanocortin (POMC) precursor in response to hypothalamic CRH (Vale et al., 1981). This release leads to the downstream secretion of GCs from the adrenal cortex via melanocortin 2 (MC-2) receptors. The endhormones of the axis, GCs have widespread effects through ubiquitous intracellular glucocorticoid receptor (GR), which could be found on most cells and tissues, and through another intracellular steroid receptor, the mineralocorticoid receptor (MR), which is more abundant in the hippocampus and regulates negative feedback on the HPA axis (Chrousos, 2000). Among others GCs stimulate the gluconeogenesis in the liver to increase circulating glucose levels.

There are several studies on the effect of stress on food-intake without dissecting a single molecule. Thus, in these cases we might assume the involvement of the molecules of the whole HPA axis, not only GCs, but also ACTH and CRH.

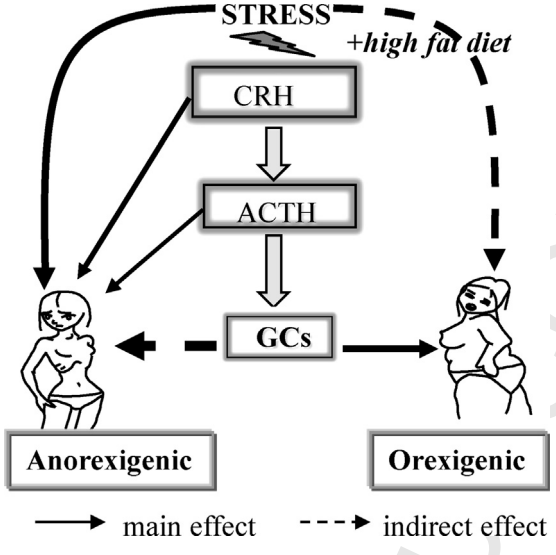

Fig. 1. Possible contribution of the molecules of the hypothalamo-pituitary-adrenocortical axis to food intake regulation. Stress per se is anorexigenic. However, in combination with comfort food it might induce obesity. In this respect glucocorticoids are very important. They exert orexigenic effect among rest, but the anorexigenic factors may overcome their effect during stress. However, in the presence of high calorie diet the addictive potential of glucocorticoid may come into highlight and strongly contribute to development of obesity. CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropin; GCs, glucocorticoids.

2.1. Stress-induced anorexia

Emotional stress is known to suppress appetite in humans (Fryer et al., 1997) and laboratory rodents (Bazhan et al., 2007; De Souza et al., 2000; Harris et al., 2001; Krahn et al., 1990; Rybkin et al., 1997) (Table 1 and Fig. 1). The stress-induced reduction in food intake has been demonstrated both as an acute response after a single stress and as a maintained decrease in 24 h food intake during and after repeated daily restraint stress (Krahn et al., 1990; Shimizu et al., 1989). Moreover, once stress has ended, restrained rats fail to return to normal weight (Bazhan et al., 2007; Levin et al., 2000; Rybkin et al., 1997).

Central mechanisms involved in the stress-induced inhibition of food intake have not been fully elucidated, but certain brain areas were already suggested to have a role. The major central nervous system structure involved in food-intake regulation is the hypothalamus (especially the ventromedial hypothalamus (VMH), lateral hypothalamus, PVN and nucleus arcuatus (ARC)) (Palkovits, 2003; Schwartz et al., 2000) being the center of stress response, too. Indeed, hypothalamic CRH and melanocortin systems are well recognized to connect stress with anorexia in rodents (Ohata and Shibasaki, 2011). CRH system is a mediator of the appetite-suppressing effects of stress also in fish (Bernier, 2006).

Other brain areas, like amygdala (Holsen et al., 2012; Solomon et al., 2010), dorsal vagal complex (Charrier et al., 2006) and dorsal raphe (Holsen et al., 2012), may contribute to stress-induced anorexia without affecting the HPA axis activity.

2.2. Stress-induced comfort food eating

Anorexia induced by acute and repeated restraint stress was followed by increased proportion of comfort food eating (with high fat/sugar contents) (Dallman, 2010; Dallman et al., 2005; Foster et al., 2009; la Fleur et al., 2005; Pecoraro et al., 2004). In contrast to normal diet, when sweet food was presented to the stressed animals repeated mild pinch resulted in hyperphagia and considerable gain in body weight (Rowland and Antelman, 1976) (Table 1). Chronic life stress seems to be associated with a greater preference for energy- and nutrient-dense foods (Torres and Nowson, 2007). During the course of prolonged/repeated food intake the sensory-specific satiety (SSS) can reduce the intake of the same food. Stressors may induce a disruption of this signal, thereby resulting in a relative increase in consumption of the same food (Ahn and Phillips, 2012). Comfort food per se might have similar effect. E.g. in an unstressed human population habituation could develop to SSS effect of the same, although palatable diet (Tey et al., 2012). Development of obesity to monotonous high fat diet in animals (DIO

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Table 1
Q4 Effects of stress on the food intake.

High calorie food	Is not available	Is available
Food intake	Anorexia (Bazhan et al., 2007; De Souza et al., 2000; Fryer et al., 1997; Harris et al., 2001; Krahn et al., 1990; Rybkin et al., 1997)	Hyperphagia (Dallman, 2010; Dallman et al., 2005; Foster et al., 2009; la Fleur et al., 2005; Pecoraro et al., 2004)
Mechanisms	*Stress induces anorexia due to decreased signaling of:* AgRP (Chagra et al., 2011; Kas et al., 2005) NPY (Tempel and Leibowitz, 1994; White, 1993) *due to increased signaling of:* insulin? (Chavez et al., 1997; Warne, 2009) leptin? (Dagogo-Jack et al., 1997; Miell et al., 1996; Newcomer et al., 1998; Slieker et al., 1996; York, 1996) CRH and Ucn 3 (Bernier, 2006; Ohata and Shibasaki, 2011; Smagin et al., 1998) CART (Kask et al., 2000; Xu et al., 2010) Nesfatin-1 (Goebel et al., 2009; Stengel et al., 2011) NPW (Beck et al., 2010) Melanocortins (Liu et al., 2007; Yamano et al., 2004) central monoaminergic systems (Gibson, 2006) autonomous nervous system (Seematter et al., 2004)	*Stress induces hyperphagia due to reduction of:* sensor specific satiety (Ahn and Phillips, 2012; Ortolani et al., 2011) stressor aversiveness (Piazza and Le Moal, 1997) CRH signaling? (Foster et al., 2009; la Fleur et al., 2005; Pecoraro et al., 2004) *due to activation of central reward pathways* (Piazza and Le Moal, 1997), *due to alterations in gut microbiota* (Tehrani et al., 2012) *Glucocorticoids induce hyperphagia* (Dallman, 1993; Drapeau et al., 2003; Epel et al., 2000; Tataranni et al., 1996) *due to increased signaling of:* NPY (Gyengesi et al., 2010; Krysiak et al., 1999; McKibbin et al., 1992; White et al., 1994; Wilding et al., 1993), AgRP (Coll et al., 2005; Savontaus et al., 2002), Nociceptin (Green and Devine, 2009; Nativio et al., 2011; Olszewski and Levine, 2004);

AgRP, agouti related peptide; NPY, neuropeptide Y; CRH, corticotrophin-releasing hormone; Ucn+, urocortin 3; CART, cocain-amphetamine related peptide; NPW, neuropeptide W.

model) suggests a similar habituation to the SSS effect in rodents (Auvinen et al., 2011; Ryan et al., 2012). Moreover, rats submitted to footshock stress decreased the intake of commercial chow, but kept unaltered the intake of comfort food (Ortolani et al., 2011).

According to Dallman, energy stores are critically important for normal activity in the central stress–response network (Dallman, 2010). When a chronic stressor results in high GCs levels, the steroids act in brain in a feed-forward fashion to recruit a stress–response network that biases ongoing autonomic, neuroendocrine, and behavioral outflow as well as responses to novel stressors (Dallman et al., 2006). When rats are allowed to eat fat or sucrose under acute or repeated restraint stress, CRH expression in the hypothalamus and bed nucleus of stria terminalis (BNST), as well as ACTH and GC secretion are reduced (Foster et al., 2009; la Fleur et al., 2005; Ortolani et al., 2011; Pecoraro et al., 2004).

On the other hand, increased ingestion of palatable foods during and after stressors may simply reflect a pleasurable activity that reduces the discomfort of stress. Eating a meal alters mood and emotional predisposition, typically reducing arousal and irritability, and increasing calmness and positive affect (Gibson, 2006). Since food intake has reinforcing effects, we can assume that severe obesity and addiction disorders share, at least in parts, common neuronal circuits (Berridge, 2009; Kiefer and Grosshans, 2009; Volkow et al., 2008). Indeed, eating of high calorie food is known to counteract some effects of stress, probably via the same mechanism as in alcoholics (Kiefer and Grosshans, 2009). Chronic stress has been known to potentiate addictive behaviors in both human addicts and experimental animals (Stamp et al., 2008). By stimulating central reward pathways, high levels of corticosterone (the main GC in rodents) can reduce the aversiveness of the stressor (Piazza and Le Moal, 1997).

Another possible mechanism, how stress can affect obesity is the bidirectional interaction between HPA axis and the gastrointestinal tract (Dinan and Cryan, 2012; Sudo, 2012). Stressor exposure induces negative changes in several gastrointestinal parameters including microbiota (Konturek et al., 2011). Alteration in gut microbiota may be an initial event leading to altered feeding behavior than to weight gain and metabolic syndrome (Tehrani et al., 2012). High-calorie diet has been also associated with changes in the gut microbiota in mice and in humans, thus stressor-induced comfort food intake can induce obesity also through an influence on microbiome (Pedersen et al., 2013).

Taken together, the scheme proposed by Dallman is very simple: stress induces comfort food eating and comfort food eating reduces stress (Dallman et al., 2005). Although we should take into consideration the rewarding nature of meal, Dallman's theory on the stress-induced palatable eating is of great importance for understanding mechanisms of obesity development. However, it concerns only human, since animals cannot prefer "palatable food" in the wild nature. Despite the more prevalent stress-induced obesity in human, there is no animal model, where single or repeated stress exposure leads to development of obesity under normal diet. GCs may potentiate the development of obesity and other aspects of metabolic syndrome only in those animals, which fed a high calorie, fat or sugar diet during the stress (Rasmusson et al., 2010). Thus, stress per se, without high calorie input does not result in obesity. Although this idea is not really new, but should be emphasized since changes in eating behavior seem to be an essential tool in the fight against obesity.

2.3. Stress and glucose metabolism

It is well known that acute stress induces temporary elevation in blood glucose levels, although this acute increase maybe due mostly to sympathetic activation (Seematter et al., 2000). Nevertheless, a rise in peripheral blood glucose concentration inhibits the appetite (Blazquez Fernandez, 2003; Burdakov et al., 2005).

On the other hand, prolonged stress-induced excess of GCs may lead to hyperphagia (Drapeau et al., 2003), thereby to obesity and insulin resistance together with hyperglycaemia leading to development of DM2 (Rosmond, 2003; Surwit et al., 1992). In this case the hypophagic effect of high glucose levels cannot be detected as the insulin resistance prevents glucose action on the neurons involved in the food intake regulation.

On the contrary, adaptation to intermittent restraint stress (Bates et al., 2008a,b) and immobilization (Kai et al., 2000) delays development of hyperglycemia and hyperinsulinemia (Bazhan et al., 2007) in rodent genetic models of DM2. It is partially due to stress-induced anorexia that likely improves insulin sensitivity and maintains β-cell compensation (Bates et al., 2008a,b; Kelley et al., 1993). Another possible mechanism is the intermittent stress-induced adaptations that reduce the hyperglycemic effect of GCs (Bates et al., 2008a,b).

Importantly, these later findings contrast with common view that all stressors are deleterious for diabetes and illustrate that intermittent exposure to stressors and the ensuing adaptations

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may instead be important for normal physiological functioning by preparing the body to deal with threats to homeostasis.

3. Glucocorticoids

Although there are many functions related to GCs from permissive one till stimulations (Sapolsky et al., 2000), but till now we do not know what is the exact role of stress-induced elevation of GCs (Vinson, 2009). Perhaps the first described role, the regulation of the blood glucose levels is the most important one. GCs stimulate glucose output from the liver by inducing gluconeogenic enzymes and by mediating, through their metabolic action on muscle, the provision of the gluconeogenic substrate.

Since abdominal adipose tissue has more cells per mass units, higher blood flow and more GC receptors, GCs affect abdominal fat to a greater extent than subcutaneous adipose tissue (Drapeau et al., 2003). Therefore it is likely that some types of abdominal obesity may be due to increased GC access (Dallman et al., 1995). Cushing's syndrome is the best evidence. A mutation of the corticosterone-binding globulin with increased free GC levels has been also associated with a higher waist-to-hip ratio and a higher risk on obesity development (Barat et al., 2005; Joyner et al., 2003). The abdominal obesity is specially important as obese with a more peripheral body fat distribution does not show health risk markers (Nieuwenhuizen and Rutters, 2008).

Under normal physiological conditions, endogenous GCs may have a primary function in controlling nutrient ingestion and metabolism over the natural circadian cycle (Tempel and Leibowitz, 1994). Low basal levels of circulating corticosterone tonically activate MRs leading to fat ingestion and deposition. In contrast, GRs are phasically activated during the circadian or stressor-induced peak of GCs. Activation of this receptor is required for carbohydrate ingestion which provides additional substrate for glucose homeostasis thereby ensuring energy to stress. Through these actions GCs have impact on total calorie intake and on long-term regulation of body weight. There are many polymorphisms both of GR and MR with enhanced GC effects, which are associated with obesity (Nieuwenhuizen and Rutters, 2008).

3.1. Central orexigenic effects

Although GCs are primarily catabolic at the periphery (lipolysis, proteolysis, but glycogenesis), they have anabolic effects in the central nervous system (CNS) (Dallman et al., 1995), where they act to increase food intake (Drapeau et al., 2003; Tempel et al., 1992) (Fig. 1). Appetite in humans and animals follows changes in adrenal steroid levels. Anorexia and weight loss are hallmarks of adrenal insufficiency in Addison's disease, whereas increased appetite correlates with GC overproduction in Cushing's syndrome and with exogenous GC administration in normal volunteers (Tataranni et al., 1996). In women experimental stress-induced cortisol secretion increased appetite and craving for sugar (Epel et al., 2000). Adrenalectomy (ADX, surgical removal of the adrenals) or GC treatment, respectively, prevent or restore weight gain in both normal rodents and many models of genetic or experimentally induced obesity, often through an effect on food intake (Dallman, 1993; Jacobson, 1999; Santana et al., 1995; Tokuyama and Himms-Hagen, 1989).

Besides a possible direct effect GCs may promote food consumption through stimulation of orexigenic hypothalamic neuropeptides like neuropeptide Y (NPY) and agouti related peptide (AgRP) (Gyengesi et al., 2010) (Table 1). ADX reduces the number of excitatory synapses onto NPY/AgRP neurons (Gyengesi et al., 2010), and decreases NPY and AgRP gene expressions in the medial basal hypothalamus in rats (Savontaus et al., 2002). All of these changes were reversed by GC replacement (Gyengesi et al., 2010). In addition, GCs produce an increase of NPY mRNA and protein in the ARC (Wilding et al., 1993) and in PVN (Krysiak et al., 1999; McKibbin et al., 1992) in rats. Different stressors such as brief session of inescapable foot shocks and 1-h restraint increase NPY mRNA levels in the ARC of rats (Conrad and McEwen, 2000; Kas et al., 2005).

Nociceptin/orphanin, a peptide closely related to dynorphin A, moderately increases food intake under various conditions (Olszewski and Levine, 2004). Both stress (restraint) and GC administration increase the level of nociceptin in the hippocampus (Nativio et al., 2011). Stress induced by social defeat elevated the mRNA level of nociceptin receptor in the PVN (Green and Devine, 2009).

On the other hand, GCs may inhibit the release of the anorexigenic signals like CRH (Foster et al., 2009; la Fleur et al., 2005; Pecoraro et al., 2004). The picture is even more complicated as it was proposed that GCs increased orexigenic hypothalamic NPY concentrations and NPY gene expression via both direct mechanisms and indirectly through inhibition of the CRH system (Cavagnini et al., 2000). However, genetic CRH deficiency neither augmented basal food intake nor attenuated decreases in feeding after ADX, furthermore, restoration of food intake in ADX mice by GCs did not depend on inhibition of CRH (Jacobson, 1999). These results suggest that, at least in mice, factors other than or in addition to CRH are more important for controlling basal and GC associated effects on food intake.

3.2. Central anorexigenic effect

Our assumption is that primary effect of GCs is orexigenic and anorexigenic effects are secondary. However, the orexigen effect of GCs is expressed only in nonstress conditions, as during stress inhibition of food intake obscures it, despite the dramatically high plasma GC concentrations (Bazhan et al., 2007; De Souza et al., 2000; Harris et al., 2001; Krahn et al., 1990; Rybkin et al., 1997). It is not entirely clear, what shifts the behavioral outcome of orexigenic GC administration to anorexigenic stress-induced GC elevation.

One possible target could be the NPY/AgRP neurons. Although GC administration stimulates both orexigenic neuropeptides (see earlier), but during stressful events their expressions are differentially regulated (Kas et al., 2005). More precisely, acute and repeated restraint reduces the number of AgRP-expressing cells (Chagra et al., 2011), and brief session of inescapable foot shocks *down*-regulates AgRP mRNA levels in ARC in the rat hypothalamus (Kas et al., 2005). AgRP is known to be the natural antagonist for the type 4 melanocortin (MC-4) receptors mediating anorexigenic signals of melanocortins (Leibowitz and Wortley, 2004). Stress-induced reduction in AgRP expression may contribute to food intake inhibition through activation of melanocortin signaling. Indeed, melanocortinergic pathway can be rapidly recruited by acute emotional stress (Liu et al., 2007).

Previous studies considered the elevation of insulin as the most important anorexigenic factor during stress. It is known that exogenous GCs stimulate insulin production in ADX rats (Warne, 2009) and ADX increases sensitivity to the effect of central insulin administration to reduce food intake (Chavez et al., 1997). However, we should mention, that restraint stress does not increase, but decreases insulin levels (Kiba, 2004; Macho et al., 1999; Nonogaki, 2000). Moreover, stressors-induced adrenal epinephrine and sympathetic norepinephrine release is known to inhibit insulin secretion (Kiba, 2004; Nonogaki, 2000). Therefore other mechanisms should be considered.

An elevation in plasma leptin levels is also anorexigenic (Ortolani et al., 2011; Won et al., 2009; Zareian et al., 2011). GCs can interact with leptin in the long-term regulation of energy intake and body adiposity. For example, hyperphagia in animals with leptin

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or leptin receptor deficiency is attenuated by ADX (York, 1996), supraphysiological doses of exogenous GCs increase leptin mRNA levels in ob/ob mice, leptin secretion in cultured rat adipocytes (Slieker et al., 1996), and circulating leptin concentrations in normal and obese humans (Dagogo-Jack et al., 1997; Miell et al., 1996; Newcomer et al., 1998). But these authors did not measure food intake, and it remains unknown whether GC-induced hyperleptinemia is followed by anorexia in humans. Moreover, acute elevation of plasma GCs, in a physiological range, induced with central pharmacological or physiological stimuli (stress, naloxone, vasopressin and/or CRH) does not appear to influence plasma leptin concentrations in humans (Nye et al., 2000; Tataranni et al., 1997) and adipose leptin gene expression in rats (Rybkin et al., 1997). Thus, further studies are required to determine whether GCs can inhibit food intake during stress by stimulating plasma leptin levels (Leal-Cerro et al., 2001).

We assume that orexigenic effects of GCs are not expressed in response to acute and chronic stresses in laboratory rodents, because they are counteracted by other stress-induced anorexigenic mechanisms, which are not dependent on the increased GC levels, e.g. melanocortin system, CRH and Ucn 3 signaling (Bernier, 2006; Ohata and Shibasaki, 2011; Smagin et al., 1998), cocaine- and amphetamine-regulated transcript (CART) (Kask et al., 2000; Xu et al., 2010), nesfatin-1 (Goebel et al., 2009; Stengel et al., 2011), neuropeptide W (NPW) (Beck et al., 2010), melanocortins (Liu et al., 2007; Yamano et al., 2004) and others, but the exact mechanism is not clear (Table 1).

4. Adrenocorticotropin

The importance as well as the bimodal effect of ACTH in obesity is demonstrated by the fact that autoantibodies against ACTH could be found in 74% of patients both with anorexia nervosa and bulemia nervosa (Fetissov et al., 2002). Moreover, a rare mutation in exon 2 of POMC, that causes ACTH insufficiency, has been associated with early-onset obesity (Krude et al., 1998). There is no information available concerning the involvement of pituitary and peripheral ACTH on the central mechanisms of food-intake regulation, but related effects could be detected at the periphery.

4.1. Metabolic effects

In normal animals injection of ACTH increased both plasma glucose and insulin levels. In contrast, in adrenalectomised rabbits ACTH administration further increased the ADX-induced insulinemia along with hypoglycemia. Therefore it is reasonable to conclude that ACTH through GCs increases glucose levels, while, through stimulation of the pancreatic secretion of insulin, decreases it (Lesault et al., 1991).

ACTH may increase local blood flow in the brown adipose tissue influencing fat metabolism (Kuroshima et al., 1968). Indeed, MC-2 receptors are expressed in white and brown adipocytes both at the mRNA and protein levels (Iwen et al., 2008) and ACTH stimulates free fatty acid release from epigastric adipose tissue of rabbits (Lewis and Matthews, 1968). Thus, ACTH has a direct lipolytic activity – present also in ADX rats – however, this effect is substantially lower than that of GCs (Spirovski et al., 1975). Insulin-induced glucose uptake in white adipocytes is reduced by ACTH treatment, thereby here not only the indirect (through GCs), but also the direct effect of ACTH is antagonistic to insulin. Thus, ACTH directly promotes insulin-resistance and enhances energy combustion. Taken together, the ACTH–adipocyte interaction may contribute to dysregulated energy balance, insulin resistance and cardio-metabolic complications in obesity and metabolic syndrome, however this assumption is not fully confirmed, yet.

4.2. Behavior

In the hypothalamus, proopiomelanocortin (POMC)-derived peptides, α-MSH and ACTH, play a central role in the regulation of food intake via MC-4 receptor (Gantz et al., 1993). A potential role for ACTH in energy homeostasis is supported by observations that ACTH has a similar potency to α-MSH at the MC-4 receptor in vitro (Gantz et al., 1993), ACTH is secreted by the neurons of PVN (Pritchard et al., 2003), and ACTH can inhibit feeding when administered centrally to rats (Al-Barazanji et al., 2001). Single and repeated injections of ACTH antibodies into PVN resulted in persistently increased food intake during the light period. These data demonstrate extra-hormonal effects of ACTH and provide evidence that endogenous ACTH without further processing acts in the PVN to reduce food intake (Schulz et al., 2010).

Some data indicate that acute stressors stimulate melanocortin signaling, e.g. electrical shock increases MC-4 receptor and POMC mRNA, restraint and forced swimming evoke neuronal activation of POMC neurons in rat and mouse hypothalamus (Liu et al., 2007; Yamano et al., 2004). These data suggest the possible involvement of the hypothalamic melanocortins, including ACTH, in the development of stress-induced anorexia.

5. Corticotropin-releasing hormone

It is generally accepted that decreased feeding in response to stress reflects an adaptive, defensive anorexia. Several investigators have attributed stressor-induced anorexia to activation of the CRH-system. It is well established that CRH influences feeding behavior and mediates behavioral and physiological responses to stress not only in laboratory rodents (Krahn and Gosnell, 1989), but also in steeres (Yayou et al., 2011) and fishes (Kang et al., 2011). Intracerebroventricular administration of CRH in rats inhibits feeding behavior (Cullen et al., 2001). Chronic administration of CRH into the hypothalamus also decreases food intake and body weight gain in rats (Tempel and Leibowitz, 1994). Pharmacological activation of the hypothalamic CRH-2 receptors results also in suppression of feeding (Fekete and Zorrilla, 2007). At this point Ucn1 and Ucn 3, the main ligands of these receptors, may also have a role (Kuperman et al., 2010).

5.1. Brain targets

The level of CRH is elevated in response to stress not only in the PVN, but also in many brain areas involved in the regulation of feeding behavior. E.g. the VMH is classically referred to as the satiety center because its electrical stimulation leads to inhibition of food intake. CRH-2 receptor mRNA has been demonstrated to be highly expressed here (Lovenberg et al., 1995). Basolateral amygdala mediates CRH-induced anorexia through CRH-1 receptors (Jochman et al., 2005), while lateral septum and BNST through the CRH-2 receptor (Ohata and Shibasaki, 2011; Smagin et al., 1998). However, pharmacological and neuromorphological studies have demonstrated that Ucn-3 rather than CRH is the most potent and specific endogenous ligand for CRH-2 receptor (Chen et al., 2010). In rats Ucn-3, injected into the VMH, significantly reduced the food intake without affecting the HPA axis activity (Chen et al., 2010; Kuperman and Chen, 2008).

Nevertheless, knocking out the CRH-1 or CRH-2 receptor does not influence body weight or basal food intake (Preil et al., 2001). Thus, neither CRH receptor is likely to play a critical role in the basal regulation of body weight and the total amount of food intake. Rather, they may be involved in biphasic control of Ucn-mediated feeding behavior (Bradbury et al., 2000; Coste et al., 2000), as well as in cross-talk among central leptin, melanocortin and CRH

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pathways (Marsh et al., 1999; Uehara et al., 1998). This assumption is supported by the fact that leptin up-regulates VMH CRH-2 receptor mRNA levels (Huang et al., 2006) mediating anorexigenic effects of CRH and/or Ucns.

5.2. Indirect effects

CRH may exert orexigenic effect through elevation of plasma GC concentrations. In line with this idea CRH infusion to healthy, non-obese adults resulted in elevated cortisol levels parallel with an increase in food-intake (George et al., 2010).

On the other hand, CRH may interact with orexigenic peptides. CRH inhibits NPY synthesis and release (White, 1993) and decreases NPY-induced food intake (Tempel and Leibowitz, 1994). Several studies indicate that nociceptin/orphanin acts in the BNST as a functional antagonist of CRH to inhibit its anorexigenic effect (Ciccocioppo et al., 2004).

6. Conclusions

In both animals and humans, stress affects food intake in a bidirectional way depending on stress intensity and environmental factors (Table 1). Any stress activates both anorexigenic and orexigenic pathways (Fig. 1 and Graphical abstract). Balance between the pathways shifts to anorexigenic if high calorie food is not available (it is not clear how), and shifts to orexigenic if high calorie food is available, obviously due to reduced aversiveness of stress and rewarding potential of the food. Thus, stress may potentiate the development of obesity and other aspects of metabolic syndrome only in animals and people, which fed a high calorie, fat and sugar diet. This is important since behavioral modification – do not eat in excess – is likely to have a major epidemiological impact on the obesity epidemic. In this context stress is diabetogenic only in combination with a special diet and intermittent stressors are rather antidiabetogenics, thus beneficial. In human, stress-induced excessive GC production leads to search for palatable food because of its rewarding, stress-reducing potentials.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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