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Stress, eating and the reward system

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Abstract

An increasing number of people report concerns about the amount of stress in their life. At the same time obesity is an escalating health problem worldwide. Evidence is accumulating rapidly that stress related chronic stimulation of the hypothalamic–pituitary–adrenal (HPA) axis and resulting excess glucocorticoid exposure may play a potential role in the development of visceral obesity. Since adequate regulation of energy and food intake under stress is important for survival, it is not surprising that the HPA axis is not only the 'conductor' of an appropriate stress response, but is also tightly intertwined with the endocrine regulation of appetite. Here we attempt to link animal and human literatures to tease apart how different types of psychological stress affect eating. We propose a theoretical model of Reward Based Stress Eating. This model emphasizes the role of cortisol and reward circuitry on motivating calorically dense food intake, and elucidating potential neuroendocrine mediators in the relationship between stress and eating. The addiction literature suggests that the brain reward circuitry may be a key player in stress-induced food intake. Stress as well as palatable food can stimulate endogenous opioid release. In turn, opioid release appears to be part of an organisms' powerful defense mechanism protecting from the detrimental effects of stress by decreasing activity of the HPA axis and thus attenuating the stress response. Repeated stimulation of the reward pathways through either stress induced HPA stimulation, intake of highly palatable food or both, may lead to neurobiological adaptations that promote the compulsive nature of overeating. Cortisol may influence the reward value of food via neuroendocrine/peptide mediators such as leptin, insulin and neuropeptide Y (NPY). Whereas glucocorticoids are antagonized by insulin and leptin acutely, under chronic stress, that finely balanced system is dysregulated, possibly contributing to increased food intake and visceral fat accumulation. While these mechanisms are only starting to be elucidated in humans, it appears the obesity epidemic may be exacerbated by the preponderance of chronic stress, unsuccessful attempts at food restriction, and their independent and possibly synergistic effects on increasing the reward value of highly palatable food.

Keywords: Stress; Reward; Eating; Cortisol; Obesity

"People may very well choose to trade off years of their life, or the possibility of disease or injury, in exchange for the current pleasure, excitement, or stress relief they get from food" Jacob Sullum.

1. Introduction

Life is stressful! Daily life demands constant re-establishment and maintenance of a dynamic equilibrium in the face of a fast changing environment, also called 'allostasis' [1]. Allostasis inherently involves changes in energy flow — appetite and ingestion, energy storage and mobilization. This review addresses the intricate relationships between psychological stress, allostasis, and aspects of energy balance — eating, adiposity, and fat distribution.

Animal studies reveal that stress can lead in some cases to increases but mainly to decreases in food intake [2,3]. In fact, given the dose response relationship between stress and reduced food intake it has been suggested that decreased food intake and weight loss serve as the most reliable marker of stress severity, at least in rats [4]. However, when rats have a choice of highly palatable food, such as lard or sugar, stress increases intake of palatable food specifically [5,6].

In humans, the literature shows that stress affects eating in a bidirectional way; a subgroup, possibly around 30%, decreases food intake and loses weight during or after stress, while most individuals increase their food intake during stress [7,8]. Given, that people living in Westernized countries live in a palatable food environment, with an abundance of calorically dense food, it makes sense that most people complain of eating more during

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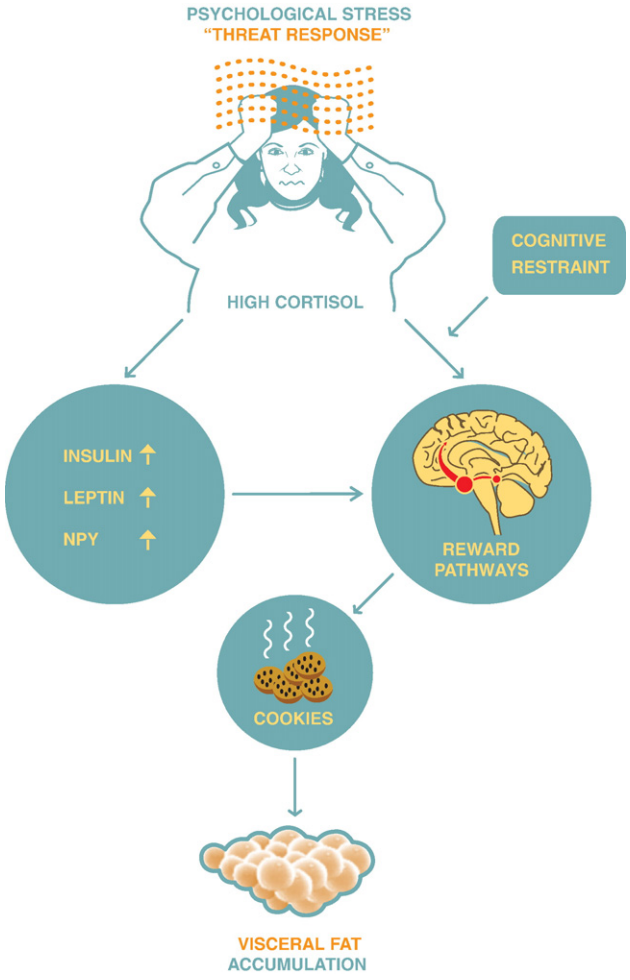

Fig. 1. Theoretical model of reward based stress eating.

stress, rather than less. Almost 50% of a US representative sample is concerned with the amount of stress in their life copes by engaging in unhealthy behaviors such as smoking as well as eating for relief [9]. Another survey study shows increased food intake during times of stress, especially in women [10]. The stress-induced drive for dense calories is alarming in the face of the growing obesity epidemic [11].

Here we attempt to link animal and human literatures describing how different types of psychological stress and resulting states of arousal affect eating, adiposity, and fat distribution. We focus on neuroendocrine mediators, such as cortisol and insulin. Lastly, we review the burgeoning new field linking the reward center, the neural circuitry of addiction, to ingestive behavior and weight. Finally, we propose a model of stress-induced food reward dependence, highlighting the psychoneuroendocrine basis to stress eating (Fig. 1). As described in more detail in Section 5, the model summarizes several key relationships from stress to visceral fat. Chronic stress can lead to greater cortisol exposure. In turn, this has direct and indirect effects on the reward system. Greater sensitization of the reward system can lead to excessive intake of highly palatable food. In turn, the combination of high cortisol, dense calories, and consequently high insulin, contributes to visceral fat distribution. Each of these links is reviewed below.

2. The stress response

The stress response, which maintains allostasis, is comprised of a cascade of adaptive responses originating in the central nervous system as well as in the periphery. It leads to dramatic but time-limited physiological, psychological and behavioral changes that affect appetite, metabolism and feeding behavior [12]. The acute stress response includes behavioral, autonomic and endocrinological changes promoting heightened vigilance, decreased libido, increased heart rate and blood pressure, and a redirection of blood flow to fuel the muscles, heart and the brain [13]. Stressors evolutionarily required an immediate fight or flight, so energy is diverted to the brain and muscle tissue to save life. Under such circumstances energy spent on housekeeping activities–such as food intake, digestion and reproduction–would be potentially life threatening [14]. Thus, part of the stereotypical stress response includes suppression of appetite and food intake. Given that, the association of weight gain with the stress response seems counterintuitive. Below we try to elucidate potential explanations for the stress-eating paradox, the fact that stress can lead to both under-and over-eating. Little is known about what determines direction of eating, although it is clear that the hypothalamic pituitary adrenal (HPA) axis is at least one of the central players in explaining changes, both undereating and overeating due to stress.

2.1. Anatomy of the HPA axis

Although the stress response depends on intensity, duration and 'type' of stressor, the key components involve activation of the hypothalamus pituitary adrenal (HPA) axis and the sympathetic–adrenomedullary (SAM) system. The central control stations of the stress response are located in the hypothalamus and the brain stem. Corticotropin-releasing hormone (CRH) neurons of the paraventricular nucleus initiate the stress response and comprise the principal hypothalamic regulator of the hypothalamus–pituitary–adrenal (HPA) axis. CRH stimulates the secretion of ACTH from the anterior pituitary. Circulating ACTH acts on the zona fasciculata of the adrenal cortex where it stimulates the release of cortisol or corticosterone. In turn, cortisol feeds back to the brain to shut off further cortisol secretion. This negative feedback loop protects the organism from prolonged, detrimental cortisol exposure and keeps its concentration within a wide but stable operating range [15]. The sympathetic–adrenomedullary system (SAM) originates in the locus ceruleus, and–together with the HPA axis–builds the effector limbs of the stress response [16].

2.2. Psychology of the stress response and eating

The cognitive model of stress explains how stress appraisal, the value and meaning we assign to the stress stimuli, determines how 'harmful' a stressor is [17]. Animal studies can differentiate two antithetical stress responses, characterized by either uncontrollable stressors, and high HPA axis activation, or controllable stressors, and high SAM activation [18]. This crudely translates to human stress responses. Research has

shown that if the stressor is viewed as a 'threat,' a demanding situation that one does not have the resources to cope well with, or has the associated components of 'distress' (feeling defeated, fearful), the neural stress response specifically activates the HPA axis [19]. In humans, when "threat stress" includes a threat to one's social self concept, such as having some aspect of public embarrassment or failure, it is an even more potent trigger of cortisol release [20]. In contrast, if the stressor is perceived as a 'challenge' — a demanding but controllable situation, or that the person has adequate resources to cope the stress response differentially activates the SAM over the HPA axis. Given that cortisol stimulates hunger and feeding, and that adrenaline is part of the fight/flight response which shuts down digestion, we hypothesize that threat stress will stimulate eating more than challenge stress, addressed further in Section 3.1.2.

3. Stress, food intake and obesity — cause or consequence?

3.1. Stress and food intake

To tease apart the intricate relationship between stress, food intake and the development of obesity it is important to take into account the different stress models, the severity of stress, the type of stress and the species that is investigated. In animal as well as in human literature evidence is accumulating rapidly that excess glucocorticoids play a role in the development of obesity via increased food intake as well as via facilitating visceral fat deposition.

3.1.1. Animal models of stress and food intake

In animal studies glucocorticoids stimulate pleasurable behaviors such as drug taking [21] and palatable feeding [5,22,23] probably through facilitating stimulus salience[23]. Animal models of stress include stressors such as hunger, cold exposure, inescapable food shock, tail pinch, physical restraint or exposure to a socially dominant member of the same species [24]. These stressors have varied effects on food intake. We briefly focus on tail pinch stress [3] and social stressors such as the resident-intruder paradigm or social defeat [25]. Tail pinch appears to elicit feeding but also a variety of situation specific behaviors, suggesting that the increased food intake may merely be part of a general stress arousal response rather than a specific or unique response [26]. Further, rats exposed to daily pinch sessions ate more during the stressor but subsequently ate less during their 24 h rest period to compensate for their excess calories, so did not gain weight [2]. However, with prolonged tail pinch, and when offered a calorically dense diet, rats no longer show compensation for extra food eaten during the stressor and gain weight [27]. This situation may be roughly analogous to the modern human condition, with numerous chronic stressors and unlimited exposure to energy dense, highly palatable food. One study comparing chronic physical stress (footshock) vs. emotional stress in rats revealed that physical stress reduced consumption and preference for saccharin drink compared to water, whereas emotional stress increased saccharin preference and consumption compared to water [28]. Others [29] found increased preference for palatable food with physical stress (footshock), but only when rats were previously exposed to a history of dietary restriction.

Social stressors have varied effects on food intake and adiposity, depending on the type of stressor, the species investigated and the outcome measure. In the visible burrow system both dominant and subordinate animals eat less and lose weight, but the subordinate animal loses more than the dominant animal [30]. However, during recovery, subordinate animals regain most of their weight as fat and have elevated plasma insulin and leptin concentrations compared to the dominant rats [30]. The subordinate rats are experiencing a more severe threat stress, which has the ultimate effect of increasing relative adiposity. In contrast, a study using the resident-intruder stress paradigm in hamsters showed increased food intake, body mass and adiposity [31]. The two social stress models also differ with regard to circulating glucocorticoid concentrations. While socially defeated hamsters in the latter study [31] showed attenuated cortisol levels compared to those of control animals with repeated stress exposure, corticosterone concentrations of animals in the visible burrow system did not appear to attenuate over time [30]. These different psychological stressors appear to have different effects on cortisol but both lead to increases in relative adiposity while the differences in the two studies may be stressor specific, they also may be related to the species. The hamsters seem to resemble what can be seen in human beings — weight gain under nontraumatic stress.

To examine the effect of corticosteroids on food intake in a more mechanistic way, studies have investigated adrenalectomized (ADX) rats. ADX allows replacement of cortisosterone in a controlled manner. Removing the endogenous corticosterone source, largely or completely eliminated obesity in the leptin deficient ob/ob mice as well as other phenotypes of obesity, possibly due to increased central insulin sensitivity [32]. These findings strongly support the involvement of glucocorticoids in the development of some types of obesity.

Studies manipulating glucocorticoids and insulin suggest that corticosterone primarily affects food drive and food salience for all foods, including low fat lab chow, whereas insulin appears to shape the drive for fat specifically. When given a choice of macronutrients, ADX rats specifically reduce their fat intake, while maintaining their carbohydrate and protein intake [33]. With corticosterone replacement, and a choice of lard and chow, ADX rats increase their intake of chow in a dose dependent fashion. In the presence of simultaneously increasing insulin concentrations, preference shifts towards fat intake [34,35]. Thus, insulin appears to play a critical role mediating the effect of cortisol on fat intake. These animal studies suggest that the combination of high cortisol and high insulin together may have a strong effect on our diets and waistlines (also see Section 4.2.1). Next we review the human studies to examine support for translation of these findings.

3.1.2. Human research on stress and food intake

Although the complex relationship between stress and eating has long been recognized in humans [3], the underlying psychobiological mechanisms that shape the direction of change–whether one eats more or less during stress,–are

largely unknown. Past research has shown that being female, overweight, or scoring high on dietary restraint are all predictors of eating more during stress [26].

Elevated levels of cortisol can increase caloric intake, such as for people taking prednisone for various medical conditions or cancer treatment. In a well controlled study, administration of glucocorticoids markedly increased food intake [36]. Presumably, high stress reactivity, which increases cortisol, should lead to greater intake of calories, at least phasically. Thus, one's psychological stress reactivity may be a clue as to differences in psychobiological characteristics that explain stress eating or food cravings. In one study of healthy medical students, self identified stress eaters had significantly higher urinary cortisol and insulin during a stressful period (medical student exams) compared to a control period (summer vacation), and also gained more weight than non-stress eaters, during stress [7]. It is possible that the stress eaters have underlying high stress reactivity, which promotes their overeating, although this has not been tested directly.

Several studies have investigated stress reactivity in different eating pathologies. People with anorexia, bulimia, and binge eating disorder (BED) tend to show either greater basal cortisol or greater cortisol reactivity, as reviewed by Gluck [37,38]. In a small but well controlled laboratory stress study, BED compared to control women tended to have greater cortisol reactivity and desire to binge after a cold pressor lab stressor [37].

In humans it is difficult to characterize types of psychological stress responses since they tend to include blends of emotions and aspects of threat and challenge appraisals simultaneously. Therefore, we have induced threat and challenge stress responses in the lab and observed feeding *ad libitum*. In one study, inducing threat stress with the Trier Social Stress Test [39], those who responded with high cortisol were likely to consume more calories after the stressor, particularly of high fat food (Fig. 2A, B). There were no difference in caloric intake between high and low cortisol reactor groups on the control day [40]. In a second study, we compared a similar threat stressor to a positive challenge stressor (identical tasks but with positive feedback from the audience). Preliminary results suggest that indeed, the 'threat' condition stimulated greater food intake, particularly of calorically dense food, than the "challenge" condition [41]. Further, the difference in fat intake by condition was mediated by psychological threat appraisals.

A recent study aimed to test whether high cortisol reactivity assessed in the lab predicted greater stress related eating in the field [42]. With a method similar to Epel at al. [40] high and low cortisol reactors were identified in the lab. In this study, however, food intake was examined outside the lab, in a naturalistic setting. Daily stressors were related to greater intake of snack food, but only in the high cortisol reactors. Thus, high cortisol reactivity to stress appears to predict greater intake of calorically dense food naturalistically, as well as in the lab. As with rats [43,44], people experiencing high cortisol reactivity may choose dense calories to blunt their stress response [40] or reduce anxiety. The co-elevation of insulin and cortisol is probably important in comfort food preference, although it is difficult to test their independent effects in people. The relationship between cortisol and food intake in humans may also involve effects of glucocorticoids on Neuropeptide Y (NPY), CRH [45], leptin [32] as well as opioid [46] and endocannabinoid [47] signaling, as described in more detail below.

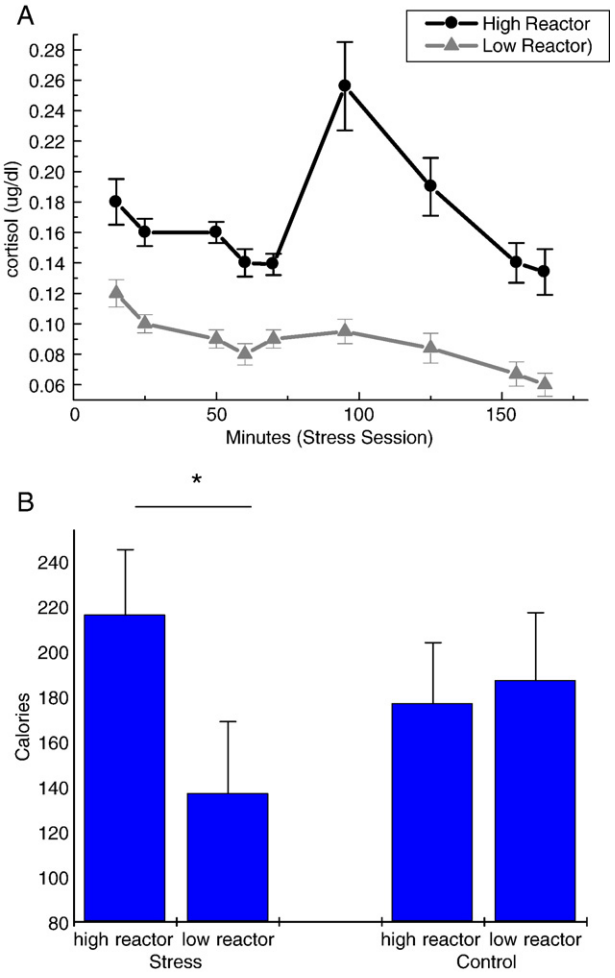

Fig. 2. A Cortisol reactivity profiles of high and low reactors during a stress test. Values are means±SE. Adapted with permission from [40]. B. Mean calories consumed by reactivity group (high cortisol reactors vs. low cortisol reactors) on stress day and control day. Values are means±SE. High cortisol reactors consumed more calories on the stress day compared to low cortisol reactors. *$P<0.03$. Adapted with permission from [40].

3.2. Cortisol and visceral fat accumulation

Obesity is associated with HPA axis dysregulation that may originate from increased forward drive, decreased sensitivity to negative feedback regulation, or altered peripheral tissue sensitivity of fat and skeletal muscle tissue to glucocorticoids [48,49].

Excess cortisol concentrations have been associated with visceral fat accumulation. One explanation for this may be increased glucocorticoid metabolism due to increased glucocorticoid receptor density in intra-abdominal adipose tissue compared to other regions [50]. Glucocorticoids also affect visceral fat via their effect on lipid metabolism. Acutely, physiological cortisol concentrations stimulate whole body lipolysis [51]. In the presence of insulin, increased cortisol

concentrations inhibit lipid mobilization and favor lipid accumulation either directly by stimulation of lipoprotein lipase, or indirectly by inhibiting the lipolytic effects of growth hormone [52,53].

It is possible that subtle differences in HPA axis regulation may promote changes in fat distribution. In a highly controlled laboratory stress study, when comparing high and low waist to hip ratio (WHR) in women, there were no differences in baseline cortisol concentrations between the groups. However, in the response to the stressor, high WHR women showed exaggerated cortisol reactivity [54], in accordance with other studies [55,56]. Another group found lower awakening salivary cortisol and increased cortisol response to food intake in women with greater abdominal fat distribution vs. peripheral fat distribution [57].

Intracellular cortisol also plays an important role in adiposity and disease risk. Increased tissue sensitivity to glucocorticoids has gained significant attention with the discovery of 11-β hydroxysteroid dehydrogenase (11β HSD), an enzyme that regulates glucocorticoid access to the receptors in peripheral and brain tissue and converts inactive glucocorticoids such as cortisone to active glucocorticoids [58]. That process is critical since active glucocorticoids promote the differentiation and proliferation of the human adipocyte [59]. 11β HSD concentrations are reportedly increased in visceral as well as in subcutaneous adipose tissue in obese compared to lean subjects [60].

Taken together, in synergy with insulin, chronically heightened blood cortisol concentrations, usually centrally driven, favor visceral fat accumulation directly via inhibition of lipolysis and indirectly via inhibition of the otherwise lipolytic growth hormone and sex steroids [52]. Visceral fat accumulation further contributes to the perpetuation by providing increased intracellular glucocorticoids.

4. Stress eating — mediators and sequellae

4.1. Cognitive mediators — restrained eating

Restrained eating refers to the voluntary cognitively controlled effort to restrict food intake to control body weight [61]. Many studies have shown that cognitive restraint, particularly when measured by the Restraint Scale, is a consistent predictor of overeating under stress, with highly restrained eaters increasing and free eaters decreasing their food intake under stressful conditions [62,63]. Others have pointed out that neither psychological stress per se nor restrained eating alone are specific causes of stress induced overeating [61]. Rather, some latent factor, likely a biological difference that causes one to be especially responsive to the food environment, has been implicated. This 'third variable' then causes both the need for high restraint, as well as tendency to eat in response to a variety of cues, including both stress as well as non stressful cognitive load [61].

Recent studies on the effect of cognitive restraint on stress induced eating have used more specific measures of restraint and other eating attitudes [63–65]. They have shown different effects of restrained eating vs. emotional eating (overeating in response to negative emotions). For example, Wallis and Hetherington [65] showed that while restraint was associated with greater food intake after stressors, as commonly found, emotional eating was linked to increased intake only after an ego-threat stressor. In another study, emotional eating but not restraint was related to an increase in intake of sweet fatty foods after stress [64]. Thus, restraint may exacerbate eating in response to food cues and other stimuli, including stress, whereas emotional eating may serve to ameliorate negative self focused emotions.

Cognitive restraint appears to have physiological correlates that may help explain the moderating role of restraint on direction of change in food intake under stress. For example, several studies have found that high cognitive restraint is associated with increased cortisol concentrations in both pre-and postmenopausal women [66–68]. Given that high restrainers tend to consume the same number of calories as free eaters, restraint may represent unsuccessful attempts at food restriction, eating less than one would like under normal (low stress) conditions, as well as the tendency to overeat during stress. Given that high cognitive restraint is common, even in children, increased restraint may play an important role in promoting obesity, or at least serve as a surrogate marker for a reward system sensitized to palatable food. In our hypothetical model (Fig. 1), stress eating occurs independently of dietary restraint, but high levels of restraint can exacerbate the effect of stress on the reward system, resulting in stronger reward based stress eating.

4.1.1. Animal models of 'restrained' eating, and reward

Repeated stressors in rats generally seem to reduce food intake and body weight. That observation was modified by the introduction of highly palatable food.

Boggiano and colleagues showed that rats exposed to either repetitive bouts of stress or food restriction alone did not differ from control rats in their total intake, when ignoring food type. With restriction alone, rats increased their intake of chow as a response to the negative energy balance. Adding stress to the restricted condition led to greater cookie intake over chow, suggesting feeding for reward value and stress arousal reduction rather than feeding for metabolic need alone [62].

The importance of food reward when stress co-occurs with food restriction has been demonstrated elegantly by the same group. Treatment with Naloxone, an unspecific opioid antagonist, powerfully suppressed intake of highly palatable food (Fig. 3). Compared to control groups that were exposed to either stress or restriction or neither condition, the group with combined stress and restriction showed the largest reduction in food intake after the opioid-receptor antagonist treatment [28]. An important aspect of that model for human research is the fact that rats are unlikely to engage in the higher cognitive processes that are needed to follow a strict regimen of restraining food intake voluntarily, like human beings do. This emphasizes the importance of biological components in stress induced eating, such as alterations in the brain reward system. In support of those findings it has been shown that intermittent access to and consumption of highly palatable food increases mu-opioid receptor binding and precipitates symptoms of opioid withdrawal [63].

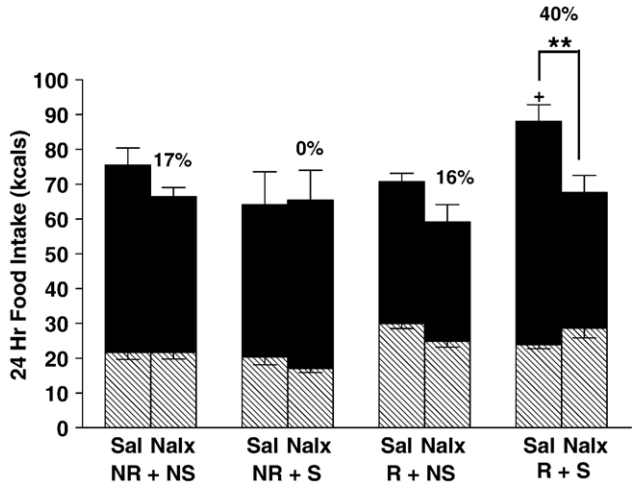

Fig. 3. Effect of 1 mg/kg ip opioid antagonist naloxone and saline on intake of chow and cookies (highly palatable [HP] food) when given as a choice after the 8th and 9th restriction–refeeding cycles in rats serving as controls (NR+NS), with stress only (NR+S), with a history of caloric restriction only (R+NS), or with a history of caloric restriction and stress (R+S) at 24 h postinjection; no significant effect of naloxone within or between groups was observed for chow intake. Error bars represent standard error of the group's mean. $^{**}P<.01$ significant naloxone-induced suppression of HP food intake (% is percentage reduction of saline-treated HP food intake). Sal=saline; Nalx=naloxone. Adapted with permission from [29].

4.2. Inter-relations between HPA axis activity and hormones in regulating food intake

Adequate regulation of food intake under stress is important for survival. Therefore it is not surprising that the HPA axis is not only the 'conductor' of an appropriate stress response, but is also tightly intertwined with endocrine parameters that regulate appetitive behaviors. In addition to regulation by the circadian rhythm, characterized by increased cortisol concentrations in the morning, low concentrations in the evening and fast feedback under stress activation [69], glucocorticoid release is also food-entrainable [70,71]. Studies suggest feedback loops between glucocorticoids, leptin, insulin and NPY under acute HPA activation [45]. The interactions between these hormones facilitate storage, distribution and release of energy according to needs and contribute to initiation and termination of a meal.

Insulin and leptin are crucial adiposity signals that are released in proportion to white adipose tissue. If weight gain occurs, an increased signal sensitization of the brain to satiety signals leads to reduced intake so that excess weight will be lost [72]. As mentioned earlier, there is growing evidence for increased cortisol secretion in primary obesity [55,73]. Under normal, unstressed circumstances insulin and glucocorticoids have antagonistic effects on metabolism in the periphery [74], creating a finely balanced system in order to provide sufficient fuel for the organism proportionate to demands. In a chronic stress environment the system becomes out of balance. The actions of the stress-related counter regulatory catabolic hormones (cortisol and catecholamines) remain unopposed and lead to metabolic disturbances [75]. Increased glucocorticoid concentrations have been associated with insulin resistance [69] as well as leptin resistance [52]. Thus, elevated stress induced cortisol could lead to impaired sensitization of satiety signals and inadequate adjustment for excess weight gain of the organism.

The adiposity signals insulin and leptin not only play a role in energy regulation but also have a direct or indirect influence on the brain reward circuitry [76] (Fig. 1). Figlewicz et al. [77] demonstrated the ability of intraventricular administered insulin and leptin to decrease sucrose self-administration and conditioned place preference in rats [78]. The latter was shown to be dependent on intact dopaminergic signaling in the brain. Additional support for the crosstalk between energy regulatory signals and reward comes from the observation of insulin and leptin receptors on the ventral tegmental area [79], a key structure of the brain reward circuitry [80]. While insulin and leptin decrease the rewarding effect of food, NPY may increase reward [81]. Other authors found no effect of NPY on brain reward [82] or demonstrated that NPY is important in response to energy deficiency rather than the rewarding effects of food [83,84]. Lastly, NPY has been shown to play an important role in the stress response [85] and thereby may play an indirect role in the effects of stress on food intake.

4.2.1. Glucocorticoids and insulin

The relationship between cortisol and insulin is important to energy balance, and can become dysregulated with chronic stress. Glucocorticoids exert diabetogenic effects by interfering with insulin action on several levels [69,74]. Cortisol has been shown to directly inhibit insulin secretion from pancreatic b-cells [86] and impair insulin initiated translocation of the intracellular glucose transporter (GLUT 4) [87], eventually leading to insulin resistance.

Excess glucocorticoids induce insulin resistance in the liver and skeletal muscle via interference with insulin receptor binding as well intracellular events on a postreceptor level [88]. In animal studies the diabetogenic effect of glucocorticoids has been demonstrated either by means of synthetic glucocorticoids, such as dexamethasone [87,89] or in ADX rats, where the removal of the source of endogenous corticosterone clearly improved insulin sensitivity [32]. Are these findings reflected in human research?

A study in overweight human subjects revealed a similar effect of dexamethasone as has been found in animals [90]. Oral administration of dexamethasone increased plasma insulin levels by 83%, and plasma leptin levels by 80%. Interestingly, hyperinsulinemia in that study didn't affect plasma glucose concentrations. A similar effect was found by other researchers [91], suggesting that cortisol, through multiple mechanisms, can produce resistance to the action of insulin on glucose metabolism.

4.2.2. Glucocorticoids and leptin

Glucocorticoids and insulin also interact in the up-regulation of serum leptin concentrations [92,93]. Absolute increase in leptin concentrations from nadir to peak is related to meal induced insulin excursions [94]. For insulin to potentiate its effect on leptin secretion, sufficient endogenous cortisol secretion is necessary [95]. Due to its anorexigenic effect, cortisol-induced increases in leptin would be expected to decrease food intake. However, this

was not found in a study of exogenous glucocorticoid administration in overweight and normal weight subjects [36,90]. In rats, marked leptin sensitivity was gradually diminished with glucocorticoid replacement. Larger doses of glucocorticoids led to overeating and consequently to obesity, in spite of elevated leptin concentrations [96]. These results demonstrate a state of 'leptin resistant' obesity that is caused by glucocorticoid related leptin stimulation [52].

4.2.3. Glucocorticoids and NPY

In addition to insulin and leptin there is evidence for glucocorticoids to stimulate the food intake branch — the NPY system, thereby promoting obesity. Central dexamethasone infusion decreased hypothalamic CRH and increased NPY content [97]. Chronic NPY infusion resulted in marked hyperphagia and hyperinsulinemia in the rat [98]. Therefore, a classic feedback loop has been proposed between CRH and NPY on a hypothalamic level [45]. In that feedback loop, glucocorticoids stimulate NPY release via an inhibition of CRF.

NPY is an anxiolytic peptide, leading to decreased anxiety. It is known to play an important role in the response to stress and in psychiatric disorders[85,99,100], thus, potentially an important mediator of what is anecdotally described as 'emotional eating'. Low NPY concentrations have been observed in subjects with posttraumatic stress disorder and depression [85,101] — psychiatric conditions classically associated with a loss of appetite. Increased NPY is associated with stress resilience in subjects exposed to traumatic experience [100]. NPY increases in response to stress may be one biochemical signal underlying stress eating. A major obstacle for NPY research in humans is that central release and metabolism are difficult to access. Therefore, most studies use the easier accessible peripheral compartment, which may reflect sympathetic nervous system activity more than central NPY signaling [85].

4.3. Stress eating and reward

The new generation of food intake research has shown that there is a tremendous amount to be learned from the field of drug addiction, particularly about the role of stress and palatable food, on the reward center. Negative reinforcement in general is a major force driving addictions for drugs of abuse. Stress, a type of negative reinforcement, and cortisol, promote addiction to drugs of abuse. Experiments in animals emphasize that threat stress, particularly uncontrollable stress increases acquisition of drugs of abuse, such as cocaine, compared to a controllable stressor or a non-stress control condition [102]. Pretreatment with corticosterone exaggerates the effect and is thought to mimic a condition of chronic stress [103]. Conversely, ADX completely abolishes the effect of stress on drug acquisition. This emphasizes the key role of glucocorticoids in mediating the effect of stress on drug acquisition [104].

There is accumulating evidence that highly palatable food has properties that promote dependence. As with drugs of abuse, palatable food can activate the brain reward system, comprising opioid, dopamine and endocannabinoid (for review see [105]) signaling in the limbic system, thereby producing powerful behavioral reinforcement for both acquisition of drugs as well as palatable food [106,107]. While drugs of abuse activate the reward pathway in a rather direct pharmacological way, palatable food acts via both, fast sensory inputs as well as slower post-ingestive processes such as increased blood glucose and adiposity and possibly gut signals [108]. The adiposity (and satiety) signals leptin and insulin are thought to decrease food intake partly by modifying the reward value of food [82,109,110]. Animal models have provided evidence that obesity is often characterized by decreased amounts of adipose signals or resistance at the receptor level [111]. In a state of insufficient adipose signals the brakes on food intake that typically work through decreasing hedonic value of food are impaired. This impaired "brake"–such as leptin resistance–may in part explain non-homeostatic eating—the epidemic of eating without metabolic need [76].

Repeated stimulation of the reward pathways through highly palatable food may lead to neurobiological adaptations that eventually increase the compulsive nature of overeating characterized by frequent drive to initiate eating [108]. Rada et al. [112] showed that an intermittent access paradigm evoked escalating sucrose intake and reliable dopamine release in rats. Several researchers also have provided evidence that palatable food can cause endogenous opioid dependence [112,113]. Opioid dependence was tested by using naloxone, an opioid antagonist, and defined as naloxone-induced withdrawal after sucrose exposure [113].

Activation of the HPA axis elicits–among other neurotransmitter systems–the release of endogenous opioids [114]. There is strong evidence suggesting that opioid release is part of an organisms' powerful defense mechanism against the detrimental effects of stress [115]. Opioids decrease activity of the HPA axis on different levels in order to terminate and attenuate the stress response, providing a negative feedback control mechanism [116]. Opioid release increases palatable food intake and palatable food sustains opioid release. Thus, food intake resembles a powerful tool to shut down stress-induced HPA axis activation. If stress becomes chronic and eating is learned to be effective coping behavior, highly palatable food may appear to be 'addictive' via the neurobiological adaptions mentioned earlier [108].

5. Summary and conclusion

Rats living in a stressful milieu may lose weight and regain weight in recovery, leaving them fattier than before [30]. How different are rats and humans in stress-related energy intake? People commonly describe a similar response to a severe stressor — short term appetite and weight loss and then weight regain, to a heavier weight than before. When a crisis state has resolved, there is likely a compensatory increase drive for food intake to attain weight recovery and a likely overshoot — leading to increased adiposity. Repeated bouts of minor daily stressors may keep the stress arousal system in chronically activated state. Indeed, cortisol tends to be higher on working days than weekend days [117,118]. This low but chronic level of stress may modulate appetite and food intake in ways that are only loosely related to true caloric need. Here we pose that

chronic stressors or repeated bouts of stress in humans can result in overdrive for highly palatable food or "stress-induced food reward dependence."

The relationship between stress and adiposity is complex, and here we have focused on an admittedly narrow or simplified model, emphasizing the role of cortisol. As shown in Fig. 1, threat related stress can lead to greater cortisol exposure. Cortisol clearly activates the reward system (Section 4). Intermittent access to food engages the reward system, and can enhance the effects of stress alone. We speculate that in humans, high levels of voluntary dietary restraint may have similar effects as food restriction in the rat model, potentiating the effects of stress on the reward system. Alternatively, the restraint is merely a response to a reward system highly sensitized to palatable food.

The effects of cortisol on the reward system may be partly mediated through increases in insulin, NPY, and leptin. Insulin has acute effects inhibiting the reward system [76] and we speculate that chronic exposure to circulating insulin may stimulate the reward system, as in the case of insulin resistance. The effect of those mediators on the brain reward center may contribute to a state of hedonic withdrawal, leading to the subsequent drive to relieve this negative state. People have learned that intake of highly palatable food can do just that. The natural reward of highly palatable food can directly or indirectly reduce activity of the HPA axis [5]. This has been described as 'self medication' with food [5,119]. Changes in neuroendocrine balance (high cortisol and insulin) from eating when under stress might further sensitize the reward center of the brain, leading to a positive feedback loop drive to maintain opioid stimulation from palatable food (not shown in Fig. 1). Thus, stress eating is a feed forward process. In the end, it is unclear whether continued stress is even necessary to maintain the drive for palatable food, since hedonic withdrawal may be enough to sustain continued drive without stress. Lastly, given that cortisol and eating stimulate insulin, the combination of stress and highly palatable food intake sets up potent conditions for visceral fat storage. While this model is speculative, the data at this point show that human's stress related energy intake is not very different than that of the rat. Further, a recent review suggests that stress induced cortisol exposure may impair right prefrontal cortex activity, thus impeding the more reflective cognitive control over eating that is distinct to humans [120]. While recent research has elucidated likely pathways for stress-eating, there is much progress to be made in trying to understand and prevent stress eating and non-homeostatic eating in general.

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