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REVIEW ARTICLE

Stress exposure, food intake and emotional state

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Abstract

This manuscript summarizes the proceedings of the symposium entitled, "Stress, Palatable Food and Reward", that was chaired by Drs. Linda Rinaman and Yvonne Ulrich-Lai at the 2014 Neurobiology of Stress Workshop held in Cincinnati, OH. This symposium comprised research presentations by four neuroscientists whose work focuses on the biological bases for complex interactions among stress, food intake and emotion. First, Dr Ulrich-Lai describes her rodent research exploring mechanisms by which the rewarding properties of sweet palatable foods confer stress relief. Second, Dr Stephanie Fulton discusses her work in which excessive, long-term intake of dietary lipids, as well as their subsequent withdrawal, promotes stress-related outcomes in mice. Third, Dr Mark Wilson describes his group's research examining the effects of social hierarchy-related stress on food intake and diet choice in group-housed female rhesus macaques, and compared the data from monkeys to results obtained in analogous work using rodents. Finally, Dr Gorica Petrovich discusses her research program that is aimed at defining cortical–amygdalar–hypothalamic circuitry responsible for curbing food intake during emotional threat (i.e. fear anticipation) in rats. Their collective results reveal the complexity of physiological and behavioral interactions that link stress, food intake and emotional state, and suggest new avenues of research to probe the impact of genetic, metabolic, social, experiential and environmental factors on these interactions.

Introduction

Acute or chronic exposure to stress (defined as an ongoing or anticipated threat to homeostasis or well-being) evokes a constellation of physiological and behavioral responses that markedly alter metabolic and behavioral state in humans and experimental animals (Dallman et al., 2003). Stress-induced activation of the neuroendocrine hypothalamic–pituitary–adrenal (HPA) axis increases glucocorticoid synthesis and glucose availability to fuel the metabolic demands of other physiological and behavioral stress responses. Glucocorticoids also regulate the accumulation and storage of body fat, and can increase appetite, food intake and body weight gain. Acute and chronic exposure to stress can alter both the quantity and quality of calories consumed, and stress-induced alterations in food intake and energy balance can interact with emotional state (Epel et al., 2001). However, although functional associations among stress, food intake/energy balance and emotion are readily apparent, mechanisms linking these outcomes are poorly understood. Compelling experimental evidence supports the view that stress can either increase or decrease caloric intake, and numerous reports indicate that chronic stress exposure can promote either hyperphagia and obesity, or anorexia and loss of body weight within certain dietary environments.

Stressors impact energy balance and affective state in a manner that depends on a multitude of biological and environmental factors, including temporal, genetic, social, contextual, species-specific, sex-dependent, nutritional, developmental, metabolic and experience-dependent elements. This profound complexity offers unique opportunities for researchers to selectively manipulate biological and environmental conditions in order to probe the functional underpinnings of causal relationships of interest. In this *Symposium*, four researchers present their experimental work investigating a variety of linkages among stress, food choice and intake, body weight gain and emotional behavior. The collective work of these investigators spans a broad array of biologically distinct models and approaches, and their findings highlight key similarities and differences in the complex relationship between stress and food intake that depend on both biological and environmental contexts.

In the second section of this *Symposium* report (Stress relief by palatable food reward), Dr Yvonne Ulrich-Lai presents

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findings by her research group exploring the ability of ''comfort foods'' to reduce physiological and behavioral stress responses in rats. In her experimental paradigm, rats that receive twice-daily limited access to 30% sucrose solution display no significant changes in body weight or adiposity, but display markedly attenuated behavioral and physiological stress responsiveness. The stress-reducing effect of sweet ''comfort food'' access not only depends on the nutritional properties of sucrose, but also appears to require reward signaling through central neural circuits that promote synaptic remodeling within the basolateral nucleus of the amygdala.

In the third section of this report (Emotional consequences of prolonged high-fat feeding), Dr Stephanie Fulton presents her laboratory's findings using an experimental model in which mice consuming a high-fat diet (HFD) become obese and display related metabolic derangements that serve to generate a state of stress. These diet-induced obese mice are characterized by a depressive-like behavioral phenotype and a hyper-responsive HPA stress axis. Further, when their HFD diet is replaced with standard chow (in an experimental ''dieting'' condition), the mice display behavioral and endocrine anxiety-like responses accompanied by increased motivation (operant responding) for palatable foods. Dr Fulton also presents evidence that saturated fats in the diet produce a larger effect than unsaturated fats to alter neural processes of emotion and reward.

In the fourth part of this *Symposium* report (Stress-induced eating), Dr Mark Wilson summarizes research using socially housed, non-human primates (female rhesus macaques) to explore the biological bases of stress-induced ''emotional'' over-eating. His research program also considers the role of social status and history of adverse experience on stress-induced eating. Dr Wilson compares and contrasts data from rodent and monkey studies to make the important point that changes in food intake after stress exposure depend critically on history of stress, the type of food available for consumption, and the sex of the animal, and he further suggests that stress-induced reductions in central dopamine signaling, possibly mediated through activation of central corticotropin releasing factor type 1 receptors (CRF-R1), may provide a common thread for increased eating and other goal-directed behaviors as a consequence of stress exposure.

While the initial sections of this Symposium report focus on the neurobiological substrates of increased food intake after stress, the final section (Stress-induced anorexia), prepared by Dr Gorica Petrovich, considers the opposite side of the coin: what are the neural substrates of hypophagic responses to stress? To probe the underlying circuits, Dr Petrovich's research group uses a rat model of conditioned fear in order to suppress food intake in hungry rats during exposure to danger cues that also increase anxiety-like behavior. Dr Petrovich reports striking sex differences in experimental outcomes, such that female rats take much longer to extinguish their conditioned ''fear anorexia'' compared to males. Brain regions that are critical for feeding suppression by conditioned fear cues include the prefrontal cortex, central amygdala and lateral hypothalamus, and she points out that selective neural signaling through the basolateral versus central amygdala may comprise a biological ''fear-or-feeding'' switch.

Stress relief by palatable food reward – Yvonne Ulrich-Lai

''Comfort food''

For most people, stress influences both the amount and types of food consumed. For example, approximately 35–60% of people report eating more total calories when they are experiencing stress, whereas approximately 25–40% of people report eating less (Epel et al., 2004; Oliver & Wardle, 1999; Weinstein et al., 1997). Furthermore, for many people, stress alters food selection towards eating a greater proportion of calories from highly-palatable foods (i.e. tasty, calorically-dense foods containing high amounts of sugars, other carbohydrates and/or fats) (Groesz et al., 2012; Kim et al., 2013; Laugero et al., 2011; McCann et al., 1990; Oliver & Wardle, 1999; Tryon et al., 2013), and this shift can even occur in individuals who reduce their total caloric intake during stress (Oliver & Wardle, 1999). This altered food selection is often referred to as eating ''comfort food'' – a term that reflects the idea that palatable food intake reduces stress responses, thereby providing a potential means for people to ''self-medicate'' for stress relief. Consistent with this idea, the intake of palatable and/or high carbohydrate food is associated with improved mood, decreased perceived stress and reduced plasma cortisol concentration in people (Anderson et al., 1987; Barr et al., 1999; de Castro, 1987; Deuster et al., 1992; Dube et al., 2005; Fernandez et al., 2003; Gibson, 2006; Lieberman et al., 1986; Utter et al., 1999), particularly those with high stress-proneness (Markus et al., 2000).

Similar changes in palatable food intake are observed in rodents during stress. When rats are offered both a highly palatable food (e.g. lard, sucrose) and a less palatable food (e.g. chow), they choose to eat a large proportion of their daily calories as the highly-palatable food (la Fleur et al., 2014; Packard et al., 2014; Pecoraro et al., 2004; Zeeni et al., 2013). When these rodents are then exposed to chronic stress, palatable food intake is generally preserved whereas chow intake is reduced, resulting in a greater proportion of their daily food intake being derived from the palatable food source (Packard et al., 2014; Pecoraro et al., 2004). Moreover, elevated palatable food intake in rodents is associated with reduced stress indices, including anxiety-related behaviors, stress-induced learned helplessness, post-stress plasma corticosterone concentration and reactions to pain and distress (Bell et al., 2002; Francolin-Silva et al., 2006; la Fleur et al., 2005; Minor & Saade, 1997; Prasad & Prasad, 1996; Shide & Blass, 1989; Strack et al., 1997; Suchecki et al., 2003). Based on evidence reviewed by Dr Fulton (see next section), such relief may be transitory/temporary in the face of continued stress exposure, which generally leads to increased HPA activation that, in turn, may sustain palatable food intake and promote obesity. Taken together, however, results from human and rodent studies strongly suggest that palatable food intake blunts acute stress responses, although the mechanisms by which such ''comfort'' foods engender stress relief are largely unknown. In order to explore these mechanisms, we first developed and characterized a paradigm of limited exposure to a sucrose drink, as described below.

Limited sucrose intake paradigm reduces stress responses

To explore the mechanisms by which moderate palatable food intake dampens stress, we have developed a limited sucrose intake (LSI) ''snacking'' model, in which adult male rats with *ad libitum* chow and water available are given additional brief (30 min) twice-daily access to a small amount (4 ml) of 30% sucrose solution (or water as a control) for 2–4 weeks (Ulrich-Lai et al., 2007, 2010). The rats rapidly begin to drink the sucrose solution, but not the water, with intakes approximating the maximum permitted (8 ml per day, ∼9 kcal/d) (Ulrich-Lai et al., 2007). Rats with this LSI modestly decrease chow intake (by ∼9 kcal/d), resulting in no effect on body weight or adiposity (Ulrich-Lai et al., 2007). As a result, this sucrose paradigm allows us to explore the effects of a modest dietary change on stress responses without the additional, and perhaps confounding, effects of increased body weight and adiposity that could alone influence stress systems (see later section by Dr Fulton).

A history of LSI blunts several types of behavioral and physiological responses to stress. For example, LSI reduces indices of anxiety-related behaviors (Figure 1) in social interaction, elevated-plus maze and open field tests of behavioral anxiety (Ulrich-Lai et al., 2010). In addition, both CRF mRNA expression in the hypothalamic paraventricular nucleus (PVN) (Ulrich-Lai et al., 2007) and HPA axis hormonal responses to a subsequent acute stressor (e.g. restraint) are decreased after 14 days of LSI (Figure 2A and B) (Christiansen et al., 2011, Ulrich-Lai et al., 2007, 2010, 2011). The tachycardic response to restraint is also reduced following LSI (Figure 1B), suggesting that the sympathetic response to acute stress is similarly blunted by sucrose ingestion (Ulrich-Lai et al., 2010). These data support the view that LSI provides a general stress relief that impacts multiple components of the stress response.

Role of reward in LSI-induced stress relief

Brain reward pathways are largely responsible for processing information related to the motivation, expectation and pursuit of pleasurable experiences. Palatable food intake is a naturally rewarding behavior, and it is possible that sucrose ingestion may constrain stress system activation, at least in part, via its actions on brain reward circuitry. We addressed this possibility by determining the extent to which the taste, hedonic and/or rewarding properties of sucrose contributes to its stress-relieving effects. The non-caloric sweetener saccharin is highly palatable to rats, and was used to replicate many of the hedonic/rewarding properties of sucrose while minimizing the post-ingestive consequences (e.g. macronutrients, calories, osmolarity) (Collier & Novell, 1967; Smith & Sclafani, 2002). Rats given limited saccharin (0.1%) drink intake showed HPA axis-dampening similar to the effects of sucrose ingestion (Ulrich-Lai et al., 2010), suggesting that the hedonic/rewarding properties of sucrose may be sufficient for stress relief (Figure 2A). In contrast, twice-daily orogastric gavage of 4 ml of sucrose was used to replicate many of the post-ingestive effects of sucrose while minimizing its taste, hedonic and/or reward properties [though likely not completely preventing reward system activation (Sclafani, 2004)]. Rats given twice-daily limited sucrose gavage did not exhibit HPA axis-dampening (Ulrich-Lai et al., 2010), suggesting that the post-ingestive effects of sucrose are not sufficient, and furthermore indicating that hedonic/rewarding properties are likely necessary (Figure 2B). Finally, if the naturally pleasurable and rewarding properties of sucrose are mediating stress relief, then another type of naturally rewarding behavior may replicate these effects. In order to test this possibility, male rats were given limited (up to 30 min) intermittent (once daily) access to a sexually receptive female for two weeks, followed by assessment of restraint-induced increases in plasma corticosterone (Figure 2C). Rats with a history of sexual activity had a reduced HPA response to restraint compared to both undisturbed home cage controls and also to sham-sex males (which were exposed to a female in their cage that was contained within a wire mesh box so the male could not physically access the female) (Ulrich-Lai et al., 2010). Collectively, this work indicates that in this limited access paradigm, the pleasurable and rewarding properties of palatable food, as well as other types of natural rewards, appear to play a major role in attenuating the response to a stressor.

A pivotal role for the basolateral amygdala in reward and stress processing

The basolateral amygdala (BLA) contributes to brain reward circuitry and is activated by palatable food intake, which increases neuronal firing and cFos expression (Fontanini et al., 2009; Muramoto et al., 1993; Verwey et al., 2007; Yamamoto et al., 1997). Moreover, the BLA is implicated in the control of behavioral and physiological stress responses (Bhatnagar et al., 2004; Coover et al., 1973; Feldman et al., 1983; Goldstein et al., 1996), and stress-induced c-fos mRNA responses in the BLA are reduced by a prior history of LSI (Ulrich-Lai et al., 2007). Taken together, this suggests that the BLA is well-positioned to mediate stress relief by LSI. In order to test this possibility, we assessed whether axon-sparing, ibotenate lesions of the BLA prevent HPA-dampening by sucrose ingestion (Figure 3A and B) (Ulrich-Lai et al., 2010). As a positive control, rats given vehicle
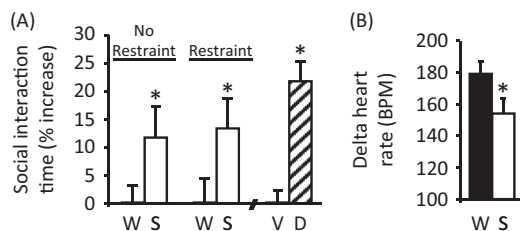

Figure 1. A history of limited sucrose intake reduces behavioral and physiological responses to stress. (A) In a social interaction test of behavioral anxiety, rats with a history of limited sucrose (S) drink spent a greater proportion of time interacting socially with a novel conspecific relative to water (W) controls, regardless of whether they received an acute restraint stress (Restraint) or not (No Restraint) immediately prior to the social interaction test (left). *p < 0.05 versus water controls. This increased social interaction was similar to that which occurs after treatment with the known anxiolytic diazepam (D) versus vehicle (V) (right). *p < 0.05 versus vehicle. (B) The tachycardic response to acute restraint was reduced by limited sucrose drink relative to water controls. *p < 0.05 versus water controls. Data are shown as mean ± SEM. Reproduced from (Ulrich-Lai et al., 2010).
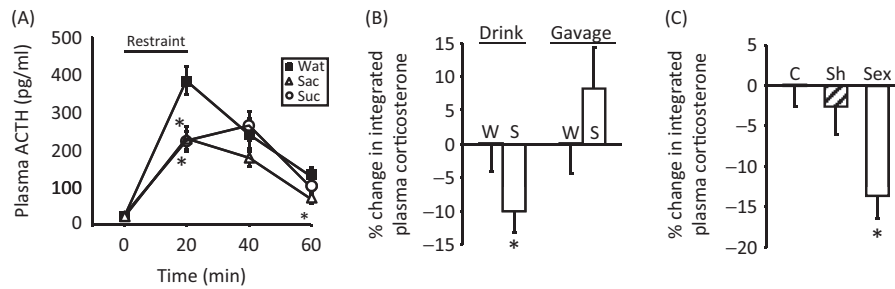
Figure 2. A history of limited sucrose intake reduces hypothalamic–pituitary–adrenal (HPA) axis responses to stress and is largely mediated by the pleasurable and rewarding properties of the sucrose. (A) The plasma adrenocorticotropic hormone (ACTH) response to a 20-min restraint stress is blunted by either limited sucrose (Suc; 30%) or saccharin (Sac; 0.1%; a non-caloric, artificial sweetener) drink intake, suggesting that the pleasurable or rewarding properties of these sweet drinks are sufficient for stress relief. *$p < 0.05$ versus Water (Wat). (B) Rats given twice-daily sucrose (S) drink have a reduced integrated (area-under-the-curve) plasma corticosterone response to restraint relative to water-only controls (left). In contrast, those receiving twice-daily orogastric gavage of 4 ml of sucrose versus water (to replicate many of the post-ingestive effects of the drink while minimizing taste and hedonic properties), do not have a reduced plasma corticosterone response (right), suggesting that sucrose's hedonic/rewarding properties are necessary. *$p < 0.05$ versus Water. (C) Male rats with a history of daily, limited (30 min) access to a sexually responsive female engaged in sexual activity (Sex) and had a reduced integrated plasma corticosterone response to restraint compared to both undisturbed controls (C) and sham-sex rats (Sh; this group received a female rat in their cages, but the female was enclosed in a wire mesh box that prevented physical interactions), suggesting that other types of natural reward provide similar HPA-dampening. *$p < 0.05$ versus control and sham. Data are shown as mean ± SEM. Reproduced from (Ulrich-Lai et al., 2010).
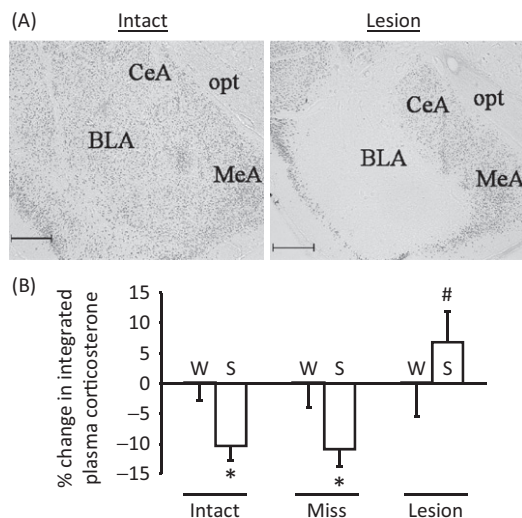

Figure 3. Neuronal activity in the basolateral amygdala (BLA) is necessary for hypothalamic–pituitary–adrenal (HPA) axis-dampening by limited sucrose intake. The plasma corticosterone response to restraint stress was assessed after sucrose (S) versus water (W) intake in rats with bilateral vehicle-injected, intact BLA (Intact) or bilateral ibotenate infusion that produced lesions that either missed (Miss) or hit (Lesion) the BLA. (A) Representative images of neuron-specific nuclear protein (NeuN)-immunolabeling in the BLA of Intact and Lesion rats. CeA = central amygdala, MeA = medial amygdala, opt = optic tract. Scale bar = 500 um. (B) Sucrose reduced the integrated (area-under-the-curve) plasma corticosterone response to restraint stress (relative to water control rats) in Intact and Miss rats, while this HPA-dampening did not occur in rats with bilateral BLA lesion (Lesion). *$p < 0.05$ versus water controls, #$p < 0.05$ versus Intact-Sucrose and Miss-Sucrose. Data are shown as mean ± SEM. Reproduced from (Ulrich-Lai et al., 2010).

injection into the BLA, and hence with an intact BLA, showed typical HPA-dampening by LSI. In contrast, LSI did not result in HPA-dampening in rats with confirmed bilateral BLA lesions (using NeuN-immunolabeling to characterize the lesion extent), despite equivalent sucrose intake. Finally, rats with ibotenate lesions that missed the BLA showed typical HPA-dampening by LSI. As a whole, this work suggests that neuronal activity in the BLA is necessary for LSI-mediated stress relief.

In order to identify potential intra-BLA mechanisms for stress relief by sucrose, we collected BLA tissue after LSI (versus water controls) and performed a microarray analysis of mRNA expression (Ulrich-Lai et al., 2010). This procedure identified 145 genes whose expression was altered by LSI. Functional clustering analyses indicated that these genes were significantly enriched in members of the intracellular calcium signaling and long-term potentiation (LTP) pathways, suggestive of synaptic plasticity (Ulrich-Lai et al., 2010). Subsequent neuroanatomical studies showed that LSI increased BLA immunolabeling for synaptophysin (Ulrich-Lai et al., 2010), a marker of pre-synaptic terminals (Tominaga-Yoshino et al., 2008; Wiedenmann & Franke, 1985), indicating an increased synaptic density in the BLA. Furthermore, LSI increased the number of phospho-cAMP response element-binding protein (pCREB)-, phospho-calcium/calmodulin-dependent protein kinase II alpha (pCamKII)- and FosB/deltaFosB-positive cells in the BLA (Christiansen et al., 2011; Ulrich-Lai et al., 2010), all of which are post-synaptic indices that are linked with synaptic strengthening and plasticity (Huang et al., 2000; Lisman et al., 2002; Rodrigues et al., 2004; Silva et al., 1998). Taken together, these data indicate that LSI induces synaptic remodeling in the BLA. Consistent with this inference, both LSI-induced HPA-dampening and elevated BLA FosB/delta FosB levels persist for at least 21 days following cessation of LSI (Christiansen et al., 2011) – these long-lasting effects of sucrose are suggestive of enduring changes in synaptic remodeling. Collectively, this work indicates that LSI-mediated stress relief may result, at least in part, from sucrose ingestion-induced plasticity and remodeling in the BLA. Future work will be directed towards understanding the phenotype of this plasticity and the defining role that it plays in this process.

Summary

Evidence reviewed in this section indicates that a modest amount of sucrose intake can reduce collective (behavioral,

HPA axis and cardiovascular/sympathetic) stress responses, in the absence of clear changes in body weight and adiposity. These stress effects are primarily mediated by the pleasurable and rewarding properties of the sucrose drink, and the BLA, a key reward- and stress-regulatory brain region, is necessary for sucrose-induced stress relief. Finally, the BLA undergoes synaptic remodeling following sucrose intake, which may enable stress relief to persist beyond the cessation of sucrose intake. Importantly, this work suggests that individuals may not need to consume large amounts of palatable food to achieve relief from acute stress. Moreover, the ability of other types of natural rewards to provide similar effects may be a useful strategy to diminish the contribution of life stress to obesity and other stress-related disorders.

Emotional consequences of prolonged high-fat feeding – Stephanie Fulton

Strong ties exist between the ingestion of foods rich in fat and/or sugar and the modulation of emotional states. As previously described, palatable food intake can relieve negative emotions by dampening signs of stress and anxiety following exposure to stressors or conditions of chronic unpredictable stress (Finger et al., 2011, 2012; la Fleur et al., 2005; Maniam & Morris, 2010; Pecoraro et al., 2004; Ulrich-Lai et al., 2010). Moreover, individuals experiencing depressed mood show increased preference and consumption of ''comfort foods'' and report the use of these foods as a means by which to alleviate adverse feelings (Macht, 2008). Such positive emotional reactions to tasty, energy-dense food, including their rewarding and hedonic actions, are considered to play a significant role in overeating and the development of

obesity (Fulton, 2010). While intake of palatable foods can attenuate negative emotions and mood states in the short term, their excessive consumption leading to increased adipose tissue mass and obesity can heighten vulnerability to depression and anxiety (Hryhorczuk et al., 2013). Mood disorders are now well recognized as a significant risk factor for obesity and associated metabolic pathologies such as type 2 diabetes mellitus. Obesity elevates the odds of depression by about 55% (Luppino et al., 2010), whereas it is estimated that as many as 1 in 3 individuals with diabetes experience depressed mood at a level that diminishes overall functioning, disrupts glycemic control, and increases the risk of diabetic complications (Anderson et al., 2001). Indeed, apart from impairing quality of life and everyday functioning, depressed mood presents additional threats by counteracting adherence to treatment and lifestyle changes and increasing the risk of complications associated with metabolic diseases.

Diet-induced obesity elicits depressive-like behavior

Emerging findings are beginning to uncover the mechanisms that promote depressed mood in obesity, including the contribution of diet and abdominal adiposity. Using the diet-induced obesity (DIO) model, we demonstrated that adult C57Bl6 mice consuming a diet high in trans-fat (as 58% of kcal in diet) for 12 weeks develop depressive-like features characterized by greater immobility in the forced swim task and reduced time spent in open areas of the elevated-plus maze and open field tests (Sharma & Fulton, 2013) (Figure 4). These behavioral indices of despair and anxiety were accompanied by elevated basal HPA activity and increased corticosterone secretion in response to stress.
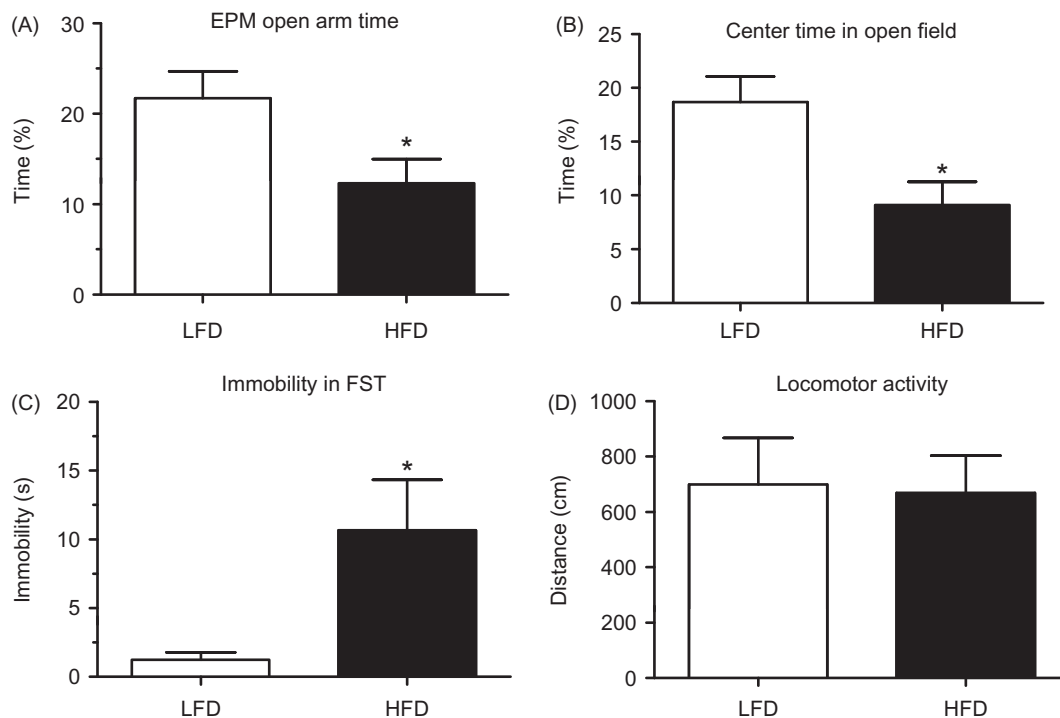

Figure 4. Diet-induced depressive-like behavior. (A) Percentage of time spent in open arms of the elevated plus maze (EPM) was significantly reduced in high fat diet (HFD)-fed mice as compared to control low fat diet (LFD)-fed mice. (B) Significant increase in time spent in center of open field in HFD mice compared to control LFD mice. (C) Effect of chronic consumption of HFD on depressive behavior expressed as immobility time in the forced swim test (FST) conducted in a separate cohort of mice. (D) Spontaneous locomotor activity expressed as total distance traveled during 15 min in a metabolism cage in C57Bl6 LFD and HFD mice ($n = 6$ each group). Mean ± SEM *$p < 0.05$. Figure from Sharma & Fulton (2013).

Analysis of the neuroadaptive changes in brain nuclei controlling motivation and emotional regulation in response to excess dietary fat is essential to understand the pathogenesis of diet-induced depression. The nucleus accumbens (NAc) is a limbic region that is strongly implicated in motivation, food-seeking and the hedonic deficits associated with depression. The NAc is highly interconnected with other brain areas important for mood regulation, including the prefrontal cortex, hippocampus and amygdala (Russo & Nestler, 2013). The significance of the NAc in the etiology of depression is underscored by the success of deep brain stimulation targeting the NAc to improve mood ratings in depressed individuals (Bewernick et al., 2012). The well-characterized reduction in brain monoamine levels in depression is posited to be linked to neuroplastic adaptations that include transcriptional and translational changes generated by signals such as brain-derived neurotrophic factor (BDNF) and CREB (Russo & Nestler, 2013). Depressive-like responses can be triggered by stress-induced increases in pCREB activation and BDNF expression in the NAc, whereas antidepressant-like actions are linked to their downregulation in this region (Martinowich et al., 2007; Nestler & Carlezon, 2006). Diet-induced depressive behavior was associated with decreased NAc protein expression of the rate-limiting enzyme for dopamine biosynthesis, tyrosine hydroxylase (TH), and by increases in ΔFosB, pCREB and BDNF (Sharma et al., 2013a). Increases in BDNF and pCREB protein levels in the NAc correlated positively with the magnitude of behavioral despair in the forced swim test, suggesting that prolonged high-fat feeding may promote depressive symptomatology via the neuroplastic changes elicited by these signaling molecules.

Diets high in saturated fat and relatively low in monounsaturated and polyunsaturated fatty acids (PUFA) may contribute to the pathogenesis of mood disorders during obesity. The consumption of foods rich in saturated and/or trans-fat are associated with an increased risk of depression, while a diet consisting of mostly unsaturated fats, such as the Mediterranean diet, is largely protective. Interestingly, elevated dietary consumption of trans-fatty acids, such as that implemented in studies described above, has been shown to reduce brain docosahexaenoic acid, an omega-3 PUFA with described antidepressant actions (Phivilay et al., 2009). Indeed, insufficient dietary PUFA augments depression risk (Peet et al., 1998), whereas increasing dietary omega-3 PUFA has been shown to be protective (Lin & Su, 2007; Moranis et al., 2012; Oddy et al., 2011) and to prevent inflammation-induced depression (Su et al., 2014). Diets rich in saturated fatty acids are associated with increases in overall adiposity and bias visceral fat accumulation (Rosqvist et al., 2014). Adipose accumulation in abdominal stores is more effective than total body fat in predicting the risk of several complications of obesity, including insulin resistance and the metabolic syndrome (Tchernof & Despres, 2013). In a similar manner, central adipose depot mass is a better predictor of developing depression than body weight or body mass index (BMI) (van Reedt Dortland et al., 2013a). Consistent with these findings, Sharma and colleagues recently demonstrated that male adult mice consuming a saturated high-fat diet (50% kcal palm oil) for eight weeks develop greater visceral obesity and metabolic impairments, including elevated levels of plasma

corticosterone and cytokines, along with increased anxiety and depressive-like behaviors, as compared to mice consuming an isocaloric monounsaturated fat diet (Sharma et al., 2013a). These effects could be related to the actions of saturated fats to stimulate pro-inflammatory signaling. Obesity is characterized by a state of prolonged low-grade inflammation, and several gene markers of neuroinflammation are upregulated in the brain of rodents by chronic high-fat feeding (De Souza et al., 2005; Thaler et al., 2012). Correspondingly, several lines of evidence implicate immune responses in the pathophysiology of depression (Miller et al., 2009). In agreement with a role for inflammation, a recent study demonstrated that elevated circulating levels of the pro-inflammatory signal C-reactive protein accounts for most of the association between depression severity with lipid and obesity levels (van Reedt Dortland et al., 2013b). Collectively, these data suggest that abdominal obesity and associated circulating inflammatory signals contribute to the etiology of depression; however, the neural mechanisms underlying this functional link remain unknown.

Stress, anxiety and craving responses to high-fat diet removal

Is the onset of depressive-like behavior that is induced by prolonged high-fat feeding secondary to metabolic impairments produced by obesity? To begin addressing this question, we examined whether high-fat feeding could provoke behavioral depressive-like symptomatology and neurobiological changes even before the onset of severe obesity and associated metabolic dysfunction (Sharma & Fulton, 2013). HFD consumption for 6 weeks resulted in moderate weight gain (∼11% increase versus controls), enhanced stress-induced HPA activation and sucrose anhedonia (reduced ability to experience pleasure/reward from sucrose drink), but did not increase anxiety-like behavior. Similarly, others have shown that high-fat feeding independent of obesity (using a pair-feeding paradigm) can dampen mesolimbic dopamine turnover and reward responses (Davis et al., 2008). However, returning high-fat fed mice to a normal chow diet (i.e. akin to ''dieting'') increased anxiety-like behavior (Figure 5) and physiological stress responses (Figure 5B and C), and also increased motivation to access both sucrose and fatty food (Figure 5D) (Sharma et al., 2013b). Similarly, several groups have shown that removal of a high-fat/sugar diet following prolonged intermittent or regular intake can increase behavioral and physiological signs of depression and anxiety akin to withdrawal symptoms (Avena et al., 2008; Cottone et al., 2009a,b; Teegarden et al., 2008). Thus, not only can chronic high-fat feeding provoke signs of anhedonia and attenuate mesolimbic dopamine function prior to development of severe metabolic dysfunction, it appears to augment sensitivity to stress, including stress triggered by dieting, which may further perpetuate overeating, weight gain and depressed mood.

In order to isolate potential neurobiological mechanisms contributing to increased anxiety and palatable food craving following withdrawal from high-fat feeding, we analyzed protein expression of several neuroplasticity markers in the NAc and amygdala. The 6-week period of high-fat feeding (not associated with anxiety or HPA stimulation) increased pCREB in the BLA and central nucleus of the amygdala
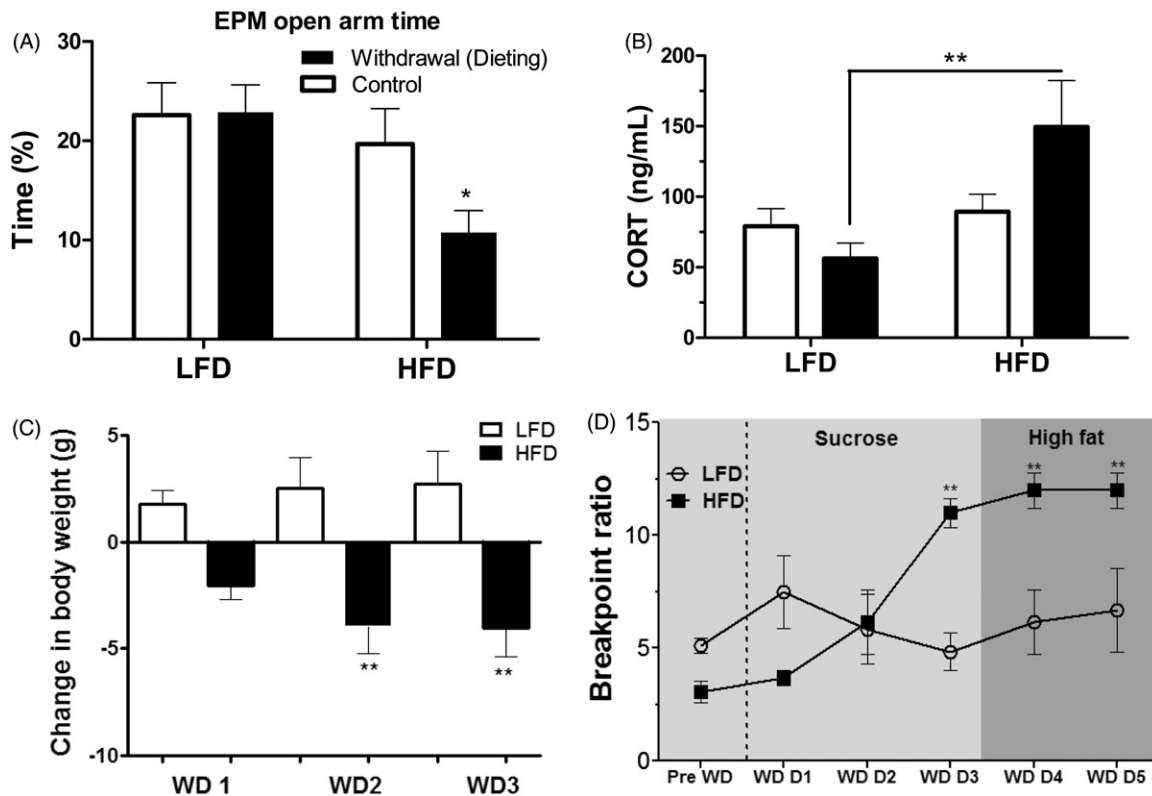
Figure 5. High-fat diet (HFD) withdrawal (dieting) increases anxiety, stress and palatable food craving. (A) Elevated plus maze (EPM) open arm time was significantly reduced in mice withdrawn from HFD as compared to mice withdrawn from low fat diet (LFD). (B) Elevated basal plasma corticosterone (CORT) concentration in HFD withdrawn mice as compared to LFD withdrawn mice. (C) Body weights decreased post-withdrawal in mice subjected to HFD withdrawal (WD: day of withdrawal). (D) Withdrawal from HFD, but not LFD, significantly increased breakpoint thresholds for sucrose rewards (indicating increased motivation for sucrose reward) as of day 3 of withdrawal (WD D3). Breakpoints remained elevated on day 4 and 5 of withdrawal when sucrose rewards were replaced by high-fat food rewards. Mean ± SEM; $*p \leq 0.05$, $**p \leq 0.001$. Figure from Sharma et al. (2013b).

(CeA), similar to findings reported for the BLA following the LSI paradigm (Ulrich-Lai et al., 2010) (see previous section), and elevated ΔFosB in the NAc as previously documented (Sharma & Fulton, 2013; Teegarden et al., 2008). However, several days after removal of the HFD, heightened anxiety and stress responses and elevated motivation for palatable food were associated with lower pCREB and NAc ΔFosB levels in the amygdala. At the same time, NAc BDNF protein levels were increased, similar to findings in the diet-induced depression model described above. Thus, even prior to the development of severe obesity and metabolic dysfunction, chronic high-fat feeding provokes signs of stress, anxiety and food craving in response to dieting in a manner inversely related to neuroplastic adaptations that are associated with stress relief. These neurobiological and behavioral responses to dieting may reinstate palatable food-seeking and thereby foster overeating, weight gain and the development of depression that accompanies diet-induced obesity.

Summary

It is increasingly evident that the amount and quality of the nutrients consumed over the long run can impact the neural circuits controlling emotions, motivation and mood. Findings on several fronts tie the development of depressed mood in obese individuals to poor dietary lifestyle, central adipose mass and associated metabolic disturbances. Studies in mice indicate that weight gain and to a greater extent obesity produced by excessive intake of dietary fats can generate depressive-like symptomatology and several neuroplastic adaptations in brain reward circuitry. Chronic high-fat feeding may affect neural processes of emotion and reward via actions on energy metabolism, endocrine function and immunity, or perhaps through the direct actions of free fatty acids on the central nervous system. Recent research findings implicate the nature of the dietary fat as an important element, with saturated fats being more deleterious than unsaturated fats. Trans- and saturated fats favor central fat deposition and are linked with cardiometabolic and neurological diseases (Barnard et al., 2014; Kanoski & Davidson, 2011; Micha & Mozaffarian, 2010). Our knowledge of the mechanisms contributing to diet-induced depression can be advanced by building upon our understanding of the metabolic disturbances associated with abdominal obesity, and how they influence central signaling mechanisms that regulate emotion. It also is imperative to understand the neurobehavioral processes by which sensitivity to stressors, including dieting, is enhanced by prolonged high-fat feeding. Improved understanding of these mechanisms may suggest novel ways to avert the self-defeating cycle of depressed mood promoting the intake of comfort foods as a means to achieve stress relief.

Research by Dr Ulrich-Lai and Dr Fulton also indicates that palatable food intake can have opposing effects on physiological and behavioral responses to stress. Stress

responses are decreased in chow-fed rats with a history of intermittent intake of small amounts of sweetened drink (LSI), and this effect appears to be mediated primarily by the rewarding (versus macronutrient/energetic) properties of the food (see previous section). In contrast, unlimited and prolonged access to high dietary fat in mice increases stress responses in a manner that is modulated by the type of fat. Several key differences between these two palatable food paradigms likely influence the valence of stress effects. These factors include the amount and type of palatable food offered (small amounts of sugar versus large amounts of fat), the duration of exposure (2 weeks for LSI versus 12 weeks for HFD), whether the paradigm altered either body weight or adiposity (no effects for LSI versus increase in body weight with HFD), whether the food was offered as a choice (choice with LSI versus no choice with HFD), whether food intake was limited (intake limited with LSI versus unlimited with HFD), as well as the species tested (rat for LSI versus mouse for HFD). Indeed, some evidence suggests that stress relief is associated with increased carbohydrate intake and also with the presence of food choice, whereas exacerbated stress is associated with reduced dietary carbohydrate, lack of dietary choice and increased adiposity (Anderson et al., 1987; Barr et al., 1999; de Castro, 1987; Deuster et al., 1992; Markus et al., 2000; Utter et al., 1999). We refer readers to the ''Concluding remarks'' section for additional discussion of this intriguing topic.

Stress-induced eating – Mark Wilson

Diet-induced obesity (DIO) resulting from the persistent consumption of a calorically dense diet is a well-accepted strategy to study the consequences of obesity in animal models (Hariri & Thibault, 2010; Panchal & Brown, 2011). However, some animals show resistance to developing this phenotype (Archer & Mercer, 2007). While a number of genetic factors could account for this variance in susceptibility to DIO (Levin, 2000; Yazbek et al., 2010), accumulating data indicate a history of adverse experience resulting from chronic stressor exposure may also be important (Dallman et al., 2007; Tamashiro et al., 2011). It must be noted, however, that the effects of stressor exposure on food intake are complex and may be bidirectional, with the specific effect dependent on a number of factors such as whether the experience is severe (see later section by Dr Petrovich), and/or whether it is acute or chronic (Maniam & Morris, 2012). Furthermore, macronutrient content of the diet is also likely important for the directionality of effect, as a large literature from rodent models suggests that stressor exposure to animals fed a typical low calorie, laboratory chow diet produces a state of inappetence (Harris et al., 1998; Tamashiro et al., 2006), an effect reversed by the central administration of a CRF receptor antagonist (Smagin et al., 1999). Indeed, acute central administration of CRF to adult macaques has immediate and lasting suppressive effects on food intake (Glowa & Gold, 1991). However, an extensive literature in rodent models indicates that chronic exposure to stressors is a mitigating factor in the preference for and excess consumption of high-caloric diets containing fats and sugars (Tamashiro et al., 2006; Warne, 2009). These data underscore the importance of considering diet composition

when assessing the consequences of stressor exposure on appetite.

Increased stress-induced intake of calorically dense diets in rodents is consistent with the notion of comfort food ingestion in people (Adam & Epel, 2007; Epel et al., 2000) (see previous section by Dr Ulrich-Lai). With the exception of a few reports (Solomon et al., 2011), the majority of studies in rodent models have used males (Tamashiro et al., 2005; Warne, 2009), despite the growing evidence highlighting significant bias towards stress-induced eating and obesity in women (Grunberg & Straub, 1992; Kitraki et al., 2004; Soulis et al., 2005, 2007). Socially housed female macaques provide an opportunity to further define mechanisms for stress-induced emotional feeding in women. A large body of data shows that social subordination in established macaque groups produces a number of stress-related phenotypes in females (Michopoulos et al., 2012a), including a dysregulation of the HPA axis (Kaplan et al., 2010; Michopoulos et al., 2012a; Shively et al., 1997a) and an upregulation of a number of proinflammatory genes (Tung et al., 2012). In a dietary environment where a typical low fat, high fiber laboratory chow diet is available (''low caloric diet'' or LCD), subordinate female rhesus monkeys consistently have lower body weights and lower serum concentrations of leptin than more dominant group mates (Michopoulos & Wilson, 2011). By employing automated feeding stations that detect food intake by free-feeding individuals in these social groups (Wilson et al., 2008), the reduced body weight in subordinate females was shown to be associated either with periodic mild inappetence (Michopoulos et al., 2009) or with calorie intake that was similar to intake by dominant females (Michopoulos et al., 2012a). What is not known is whether there is a social status-related difference in energy expenditure in these socially housed monkeys.

A different pattern emerges when animals are maintained in a rich dietary environment and given the choice between the LCD and a high fat, high sugar diet. This dietary choice environment, where animals have access to both the LCD and high caloric diet (HCD), which better models the human dietary environment, sustains stress-induced consumption of HCDs (Warne, 2009) and promotes obesity more effectively than HCD alone (Rolls et al., 1983). Under these conditions, all animals prefer the HCD (Arce et al., 2010; Michopoulos et al., 2012c). However, dominant females consume a similar number of calories in this rich dietary environment as they do when only the LCD is available (Arce et al., 2010; Michopoulos et al., 2012c). In contrast, subordinates consume significantly more calories in this dietary choice environment compared with dominant females (Figure 6) (Arce et al., 2010; Michopoulos et al., 2012c). This status difference in caloric intake is the result of increased meal size by subordinates compared with dominant females, and is not due to more frequent meals or calories consumed outside of defined meals (snacks) (Figure 7) (Moore et al., 2013). Interestingly, these statistically defined meals were significantly more often comprised of calories from both diets rather than either diet alone (Moore et al., 2013). While these short-term studies were focused on changes in appetite rather than the long-term consequences on body composition, the data

Figure 6. Average (±SEM) daily caloric intake for dominant and subordinate female rhesus monkeys from both a low caloric (LCD) and high caloric diet (HCD). Redrawn from Arce et al. (2010) and Michopoulos et al. (2012c).
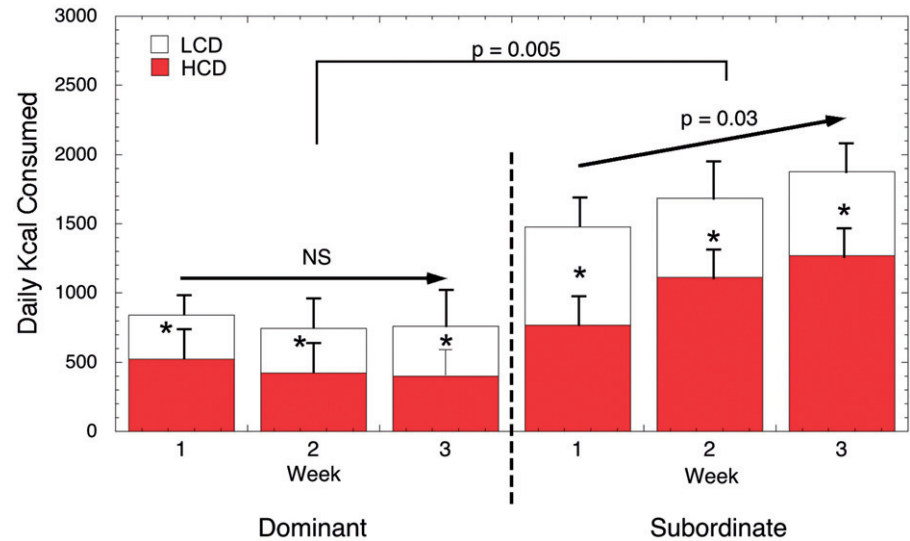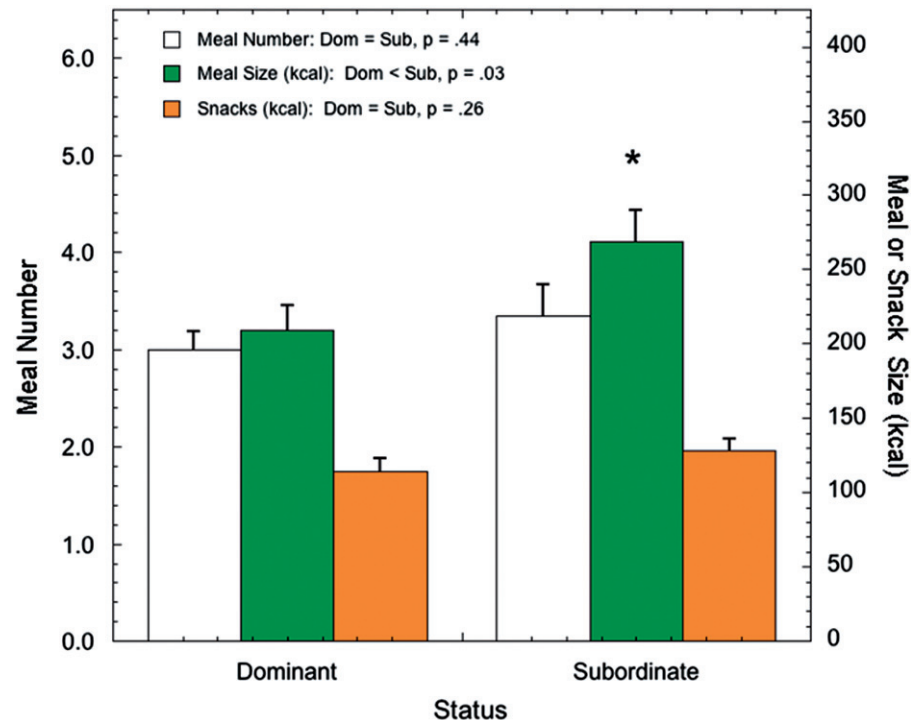
Figure 7. Comparison of average (± SEM) meal size (kcal), meal number and calories from snacks for dominant and subordinate female rhesus monkeys maintained in a dietary environment where both a low caloric (LCD) and high caloric diet (HCD) are available. Redrawn from Moore et al. (2013).

Possible mechanisms for stress-induced emotional feeding

It is still unclear how chronic stressor exposure increases susceptibility to DIO in female monkeys. One possibility is that subordinate females may be more sensitive to orexigenic signals. Although acute ghrelin administration increases intake of a LCD in subordinate but not dominant females (Michopoulos et al., 2010), it has no effect on consumption of a HCD. In contrast, a number of studies in rats have confirmed that glucocorticoids dose-dependently increase the

nonetheless suggest that female rhesus monkeys provide a useful model to better understand how psychosocial stressor exposure may account for variance in DIO in females.

intake of diets high in fat and sugar (Dallman et al., 2005; Warne, 2009), supporting the well-established notion that these steroids promote food intake (Sominsky & Spencer, 2014). Although prospective studies assessing the direct effects of stress-like glucocorticoid levels on diet preference and caloric intake have not been performed in monkeys, serum cortisol concentrations following a dexamethasone suppression test positively predict consumption of a HCD but not a LCD in female rhesus monkeys (Michopoulos et al., 2012c). These data suggest that female monkeys with reduced glucocorticoid negative feedback will consume more calories from a palatable, calorically denser diet.

Importantly, the consumption of palatable HCDs in male rats subsequently reduces their response to acute stressors (Foster et al., 2009; la Fleur et al., 2005; Pecoraro et al., 2004;

Ulrich-Lai et al., 2011). However, a different pattern emerges in female monkeys. Both dominant and subordinate females respond similarly to an acute separation from their social group with a robust increase in serum cortisol concentration. However, this response is significantly greater when monkeys are maintained in a rich dietary environment, with access to both a HCD and LCD, compared to a condition when only the LCD is available (Arce et al., 2010; Michopoulos et al., 2012b). These data are consistent with results showing that intake of calorically dense foods increases HPA axis activity in rodents (Kamara et al., 1998; Tannenbaum et al., 1997) and in humans (Pasquali et al., 2002). Furthermore, data indicating that glucocorticoids can alter food salience and increase caloric intake (Dallman et al., 2005; Warne, 2009) are consistent with the idea that emotional feeding is sustained by activation of the HPA axis, and that acute stress superimposed on chronic stress may promote continued intake of HCDs. While these observations in female monkeys are similar to those reported by Dr Fulton in the previous section, i.e. that HFD consumption enhances stress responsivity, they contrast with those summarized above by Dr Ulrich-Lai, which clearly show that comfort food intake diminishes the acute response to a stressor in male rats. It is unclear what accounts for these differences in HPA responsivity in animals maintained on palatable diet, but important factors may include the nature of the stressor and/or the history of comfort food intake. It is tempting to suggest that these differences may reflect sex differences in HPA axis regulation (Handa et al., 1994; Toufexis & Wilson, 2012; Viau et al., 2005), and in how HPA axis responses are modified by dietary environment. However, results from the different experimental paradigms using rats and mice described above by Drs. Ulrich-Lai and Fulton were obtained only from males.

Additional observations from rodents indicate that chronic activation of central CRF-R1 receptors are likely important for stress-induced overconsumption of palatable diets. In these rodent models, chronic diet cycling (intermittent dietary restriction of a palatable diet) functions as a mild stressor, and immunohistochemistry reveals elevated CRF-positive cells in the CeA among diet cycled versus control rats (Cottone et al., 2009a; Iemolo et al., 2013). Importantly, microinfusion of a CRF-R1 antagonist, Antalarmin, into the CeA of diet cycled male rats fully blocks hyperphagia of a palatable food, with no effect on standard chow intake (Iemolo et al., 2013). Our data in female rhesus monkeys are consistent with these findings: during placebo administration, subordinate females consume significantly more calories than non-subordinate females within a dietary environment that includes a choice between a LCD and HCD. However, acute peripheral administration of Antalarmin significantly reduces average daily caloric intake in subordinate female monkeys to amounts comparable to those consumed by dominant group mates (Figure 8) (Moore et al., 2015). As Antalarmin penetrates the blood brain barrier and this dose and route of administration does not affect peripheral cortisol secretion (Herod et al., 2011a,b), the data suggest that activation of central CRF-R1 may be important for sustaining this emotional feeding phenotype across species.
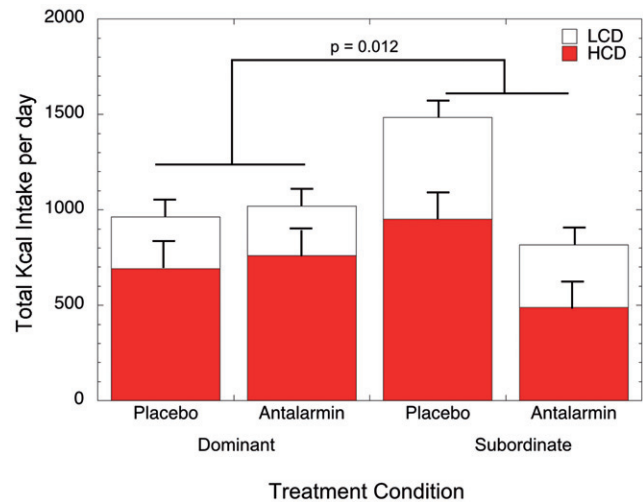

Figure 8. Average (± SEM) daily caloric intake of both a low caloric (LCD) and high caloric diet (HCD) in dominant and subordinate female rhesus monkeys during two days of placebo and two days of treatment with the corticotropin releasing factore receptor type 1 (CRF-R1) antagonist, Antalarmin. Subordinate but not dominant females showed a significant attenuation in caloric intake during Antalarmin treatment. Reprinted from Moore et al. (2015).

An emerging hypothesis is that excess food consumption and resulting obesity is a form of addiction involving the same corticostriatal circuitry engaged by drugs of abuse (Tomasi & Volkow, 2013). Assuming this hypothesis is viable, the question remains as to what accounts for differential vulnerability to the addictive properties of food. Because chronic stressor exposure, possibly mediated through central CRF signaling, is a risk factor for psychostimulant abuse in people (Sinha & Jastreboff, 2013) and for drug self-administration in experimental animals (Goeders, 2002; Koob & Kreek, 2007), including monkeys (Morgan et al., 2002), it is possible that exposure to chronic stressors increases vulnerability to food addiction (Dallman et al., 2005). As highlighted in previous sections by Dr Ulrich-Lai and Dr Fulton, evidence from rodents and humans suggests that changes in dopamine activity are at least part of the mechanism linking stress to comfort food ingestion (Bassareo & Di Chiara, 1999; Martel & Fantino, 1996a,b; Pelchat, 2002; Rada et al., 2005). Based on studies in rodents, it is well established that signals from the stress axis, including glucocorticoids and CRF, target dopamine neurons in mesolimbic regions (Ambroggi et al., 2009; Burke & Miczek, 2013; Koob et al., 2014). This apparently produces a dysregulation of dopamine neurotransmission (Izzo et al., 2005) that increases the expression of anhedonia and the risk for developing an addictive phenotype (Anisman & Matheson, 2005; Koob & Kreek, 2007; Koob & Le Moal, 2001). This stress-induced dopamine dysfunction has been referred to as a "reward deficiency syndrome", characterized by reduced dopamine activity, notably including reduced availability of dopamine type 2 receptors (D2R) (Blum et al., 1996) that is both predictive of an addictive phenotype (Volkow & Wise, 2005; Volkow et al., 2003) and observed in human obesity (Wang et al., 2001). Whether the imposition of chronic stress in the monkey model of social subordination leads to such a reward deficiency syndrome that

predicts stress-induced consumption of calorically dense diets remains to be determined. We do know that social subordination in female macaques produces widespread reduction in D2R binding potential throughout the dopamine-rich reward network (Grant et al., 1998; Shively et al., 1997a), including the striatum and prefrontal cortex, which is critical for regulating reward- and goal-directed behaviors and responses (Haber & Knutson, 2010). Studies of obese humans indicate the presence of disrupted connectivity within cortico-striatal pathways (Tomasi & Volkow, 2013). Preliminary data suggest that social subordination in female macaques reduces functional connectivity within the cingulo-opercular/limbic network, which includes the NAc, amygdala and prefrontal cortex, and has been linked to stimulus salience (Godfrey et al., 2013). As stressor exposure affects structural and functional connectivity of the prefrontal cortex and other regions regulating reward (Govindan et al., 2010; Kaufman & Charney, 2001; Sanchez et al., 1998; Teicher et al., 2002), it is possible that exposure to chronic stress compromises dopamine modulation of prefrontal cortical regulation of the striatum, thereby increasing vulnerability for food addiction.

Summary

Identifying the mechanisms by which chronic stress increases the preference for and consumption of palatable, calorically dense foods may provide insights into possible treatment strategies for overeating and obesity. While results from studies in female macaques show many similarities to results from studies of male rodents, further investigation is needed to determine if sex differences in stress responsivity lead to differences in vulnerabilities to food addiction, as they do for psychostimulant addiction (Bobzean et al., 2014). Given that a history of stressor exposure can have lasting effects on biological signaling and behavior (Zorrilla et al., 2014), an important question is whether the alleviation of chronic stress – by experimentally manipulating social rank so that formerly subordinate females are now dominant (Shively et al., 1997b) – reverses the preference for, and consumption of, palatable, calorically dense diets. Such a finding would be critically important for people attempting to make life style changes to improve their health. The use of female macaque monkeys provides a translational animal model for women that complements the use of rodent models to understand the causal relationship between chronic stress and risk for obesity.

Stress-induced anorexia – Gorica Petrovich

Stress has profound and multifaceted effects on food intake and body weight, which often are stimulatory (see previous section) (Meye & Adan, 2014; Tamashiro et al., 2011). Fear of anticipated stress, however, inhibits food intake (Cannon, 1915; Schachter et al., 1968), and sustained stress, fear and anxiety have been linked to prolonged cessation of eating, including anorexia nervosa (Hotta et al., 1999; Kaye, 2008; Klein & Walsh, 2004; Vallés et al., 2000). Anticipation of aversive events also suppresses food approach and consummatory and instrumental actions towards food (Petrovich, 2013). This suppression of feeding is adaptive and promotes survival

when fear is triggered by real danger (i.e. avoiding imminent danger takes priority over feeding), but could become maladaptive when sustained fear interferes with feeding despite an energy-depleted state, such as in anorexia nervosa. The neural mechanisms controlling the balance between hunger and fear are therefore important in normal function and in disease. Nevertheless, the brain substrates mediating anorexigenic effects of stress anticipation (i.e. fear) on food consumption have been largely unexplored. Here, a behavioral model for short-term fear anorexia[1] will be described, along with functional and anatomical evidence supporting a critical role for a prefrontal–amygdala–hypothalamic circuitry.

Fear anorexia

The fear anorexia model utilizes conditioned fear cues to inhibit feeding in hungry rats. A fear cue in these preparations is a signal that predicts danger, which is a tone and/or an environment (context) previously associated with mild, electric foot-shocks through Pavlovian conditioning (Fendt & Fanselow, 1999; LeDoux, 2000; Maren, 2001). After conditioning, discrete (tone) or contextual fear cues can potently inhibit feeding in hungry rats (Petrovich & Lougee, 2011; Petrovich et al., 2009; Reppucci et al., 2013).

During the feeding tests, conditioned fear cues also induce freezing behavior, a species-typical defense response for rodents, characterized by complete immobility, except as necessitated for breathing (Blanchard & Blanchard, 1969; Fanselow, 1984). Importantly, cessation of feeding in the conditioned fear anorexia model is not simply a product of freezing behavior. Rats do not halt eating simply because they are immobile; rather, anorexia and freezing are two separate behavioral outputs driven by the same fear cue (Petrovich and Lougee, 2011; Petrovich et al., 2009; Reppucci et al., 2013). Furthermore, fear anorexia and freezing are supported by dissociable amygdalar substrates. The CeA, but not the BLA, is critical for fear cue anorexia, while both are necessary for fear cue-driven freezing behavior (Petrovich et al., 2009).

This animal model may provide insights into aspects of eating dysregulation in human, particularly the potential contribution of fear in the maintenance of low food intake in anorexia nervosa (AN) (Petrovich & Lougee, 2011). AN is a complex eating disorder characterized by relentless maintenance of extremely low body weight through restricted eating, sometimes combined with excessive physical activity and purging (American Psychiatric Association, 2013; Kaye, 2008; Klein & Walsh, 2004; Treasure et al., 2010). Restricted food intake is maintained persistently, despite emaciation and despite serious health consequences that can be fatal. Hypophagia under these circumstances is paradoxical and occurs despite physiological hunger signals, including – high ghrelin and low leptin baseline circulating concentrations (Jimerson & Wolfe, 2006; Kaye, 2008) and increased central

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[1]In this section, ''anorexia'' refers to inhibition of food consumption in general, while ''anorexia nervosa'' refers to an eating disorder.

amounts of the potent orexigenic neuropeptide, neuropeptide Y (Kaye, 2008).

An intense and persistent fear of weight gain (including fear of food and eating), despite being underweight, is a key symptom and a diagnostic criterion of AN (American Psychiatric Association, 2013). Anxiety, typically associated with sustained fear, is also highly prevalent in AN. Furthermore, individuals with AN have aberrant processing within the key brain fear network regions (the amygdala and medial prefrontal cortex) (Giordano et al., 2001; Seeger et al., 2002; Takano et al., 2001; Uher et al., 2004). Therefore, increased underlying fear, and associated over-activity within the fear network in AN, could be a critical facilitator of eating inhibition. Nevertheless, the effects of fear on food consumption under conditions of chronic food restriction and low body weight remain to be established.

Sex differences in fear anorexia

A recent study compared learning and feeding behavior of adult male and female rats in the fear anorexia paradigm to determine whether there were sex differences (Figure 9A) (Petrovich & Lougee, 2011). Males and females acquired fear cues similarly well, as evidenced by similar freezing behavior during tests (Figure 9B). The extent of fear anorexia also was similar between the two sexes during the first of four tests. However, a pronounced sex difference, emerged during extinction: females showed sustained inhibition of feeding compared to males. Male rats extinguished this fear anorexia during the second test, when rats in the conditioned and control groups ate similar, large amounts of food. It took females in the conditioned group two additional tests to reach the consumption levels of the controls (Figure 9A) (Petrovich & Lougee, 2011). These findings suggest a biological susceptibility of the female sex that is potentially relevant to AN, which afflicts women disproportionately more than men (see discussion on fear and AN, above). This rodent fear anorexia model provides a novel framework for investigating sex differences in the control of feeding and the underlying brain substrates.

Prefrontal–amygdala–hypothalamic circuitry

Extensive work over the last two decades has focused on determining the brain substrates underlying fear and its behavioral sequelae (LeDoux, 2012; Seymour & Dolan, 2008), and similar efforts have been directed towards examining the central substrates of hunger, food intake and energy balance (Berthoud, 2007; Morton et al., 2006). Knowing when to eat and when to halt feeding and attend to danger is essential for survival, and dysfunction of this system could lead to disease. How fear and hunger compete, however, has not been adequately addressed, and the underlying brain substrates are not well understood.

Recent work has begun to identify components of a fear anorexia neural network. One of the key structures in fear acquisition and behavioral expression, the CeA, also was found to be critical for fear anorexia (Petrovich et al., 2009). Neurotoxic, bilateral lesions of the CeA eliminated decreased consumption during tests with fear cues, and Fos induction in the CeA during similar tests corresponded with the amounts of food consumed (Petrovich et al., 2009; Reppucci & Petrovich, 2014). The circuitry through which the CeA acts to inhibit food intake has not been delineated, but connectional and functional evidence strongly implicates the lateral hypothalamus (LHA). The LHA has historically been associated with the initiation of feeding (Elmquist et al., 1999), and recently was conceptualized as a critical integrator of physiological and environmental feeding signals (Berthoud & Münzberg, 2011; Petrovich, 2013). Indeed, the LHA is crucial for cue-induced feeding, which requires integration between physiological and environmental feeding signals (Petrovich, 2013). Cue-induced feeding is driven by food cues and occurs independently of hunger, and the LHA is an integral part of its critical forebrain network, together with the BLA and ventromedial prefrontal cortex (vmPFC) (Petrovich, 2013). The BLA also is necessary for stress relief by palatable food reward, and is a site of plasticity in the LSI paradigm, described by Dr Ulrich-Lai in a previous section. Fear anorexia, similar to cue-induced feeding, requires competition with physiological hunger/satiety signals and the amygdala;
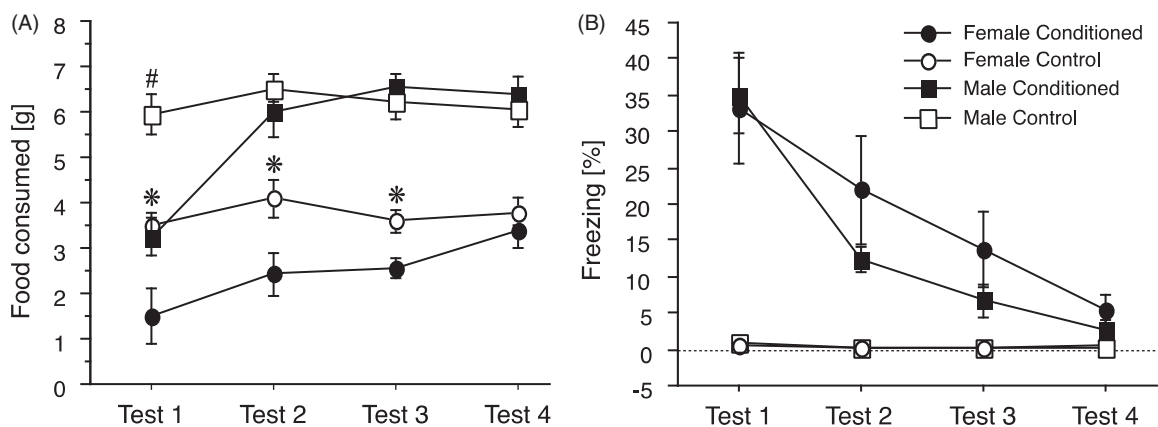

Figure 9. (A) Food consumption (mean ± SEM) of male and female rats during tests with fear cue presentations. During training, rats in the conditioned groups received tones paired with footshocks, while rats in the control groups received tones but no shocks. Tests were conducted on separate days, under acute food deprivation (no footshocks given during tests). Significant differences ($p < 0.05$) between Conditioned and Control groups are indicated by * for females and by the # for males. (B) Conditioned freezing behavior during food consumption tests. Graphs show percentages (mean ± SEM) of the total time spent freezing during the tests. Adapted from Petrovich & Lougee (2011), with permission.

Figure 10. Summary schematic illustrating the complex inter-relationships between stress and ingestive behavior, and highlighting the overall approach and key findings of each symposium speaker.
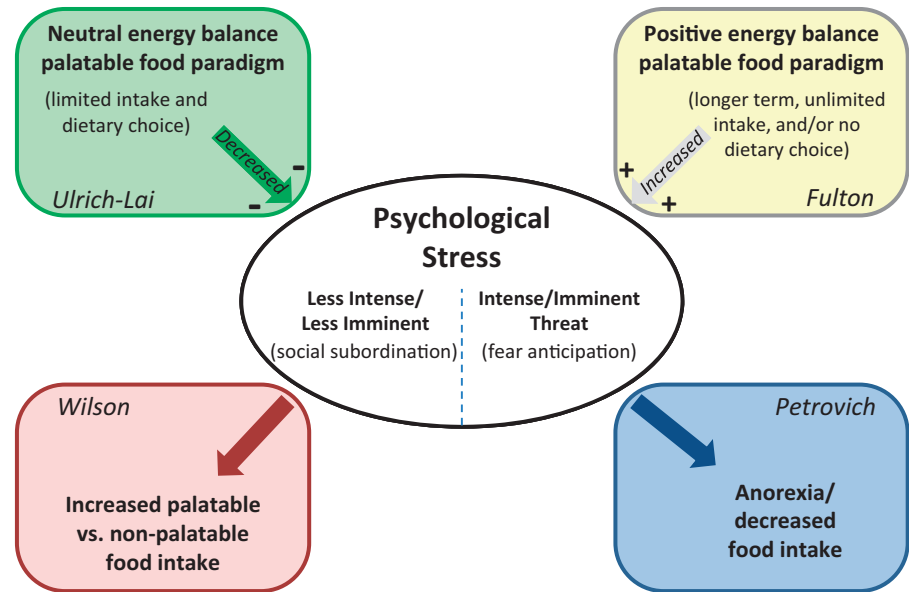
however, the amygdalar component for fear anorexia is the CeA, instead of the BLA.

The CeA is anatomically well positioned to influence LHA processing, via direct and indirect pathways (Petrovich et al., 2001; Yoshida et al., 2006). Its targets within the LHA include the suprafornical region, which is important for ingestive behavior (Hahn & Swanson, 2010), and which contains neurons that express an orexigenic peptide, orexin/hypocretin (de Lecea et al., 1998; Nakamura et al., 2009; Sakurai et al., 1998), which is important in arousal, reward processing and anticipatory feeding motivation (Petrovich et al., 2012). In addition, the CeA sends direct neural projections to brainstem targets that also receive LHA input and are responsible for feeding suppression, the parabrachial nucleus and the nucleus of the solitary tract (Carter et al., 2013; Hahn & Swanson, 2010; Maniscalco et al., 2013; Swanson & Petrovich, 1998).

Another major telencephalic input to the LHA arises from the vmPFC (Petrovich, 2013), an area critical for cognitive processing and executive function, including decision making in goal-directed behaviors (O'Doherty, 2011). The vmPFC and its connections to the LHA support cue-induced feeding (Petrovich, 2013), and are set up to control other forms of feeding. Stimulation of the vmPFC μ-opioid (Mena et al., 2011) and dopamine receptor (Land et al., 2014) systems elicit robust feeding in sated animals, and these effects depend on the LHA (Mena et al., 2013) and amygdala (Land et al., 2014), respectively. In turn, the vmPFC has access to LHA and CeA processing via direct, topographically organized connections (Hahn & Swanson, 2010; Reppucci & Petrovich, 2012; Swanson & Petrovich, 1998). In particular, the infralimbic cortical area sends direct projections to the CeA, as well as to its targets within the LHA and brainstem, including the parabrachial nucleus and the nucleus of the solitary tract (Hahn & Swanson, 2010). This connectional pattern might allow the vmPFC to simultaneously control the CeA and its outputs, which would be an efficient way to regulate feeding under imminent stress.

Summary

Dissociable amygdala substrates participate in stimulatory and inhibitory control of food intake. The BLA, but not CeA, is critical for food cue-driven feeding (Petrovich, 2013) and is recruited during initial cue-food learning (Cole et al., 2013), while the CeA, but not BLA, is critical for fear cue inhibition of feeding (Petrovich et al., 2009). Both amygdalar subregions are connected with the vmPFC and LHA. The vmPFC-BLA-LHA system mediates food cue stimulatory effects on feeding, while a parallel system formed by the CeA, vmPFC and LHA is well positioned to support fear cue inhibitory effects on feeding. Future work should improve our understanding of how these two systems interact in the control of food intake, and reveal the specific neurochemical mediators recruited to control a ''fear-or-feeding'' switch.

Concluding remarks

This research symposium, and each of the contributing authors' research programs, shines a spotlight on the complex physiological and behavioral interactions that link stress, food intake and emotion. Each researcher has his or her own distinct perspective, working hypotheses, experimental models and scientific schema that drive their interest in these issues, but their cumulative efforts promote an increased appreciation and understanding of the myriad biological problems to be addressed.

Effects of palatable food intake on stress responses

As summarized in Figure 10, Dr Ulrich-Lai has applied a rat model incorporating stable energy balance, access to limited amounts of palatable (sucrose) diet and dietary choice to demonstrate improved stress coping via ''comfort food'' exposure. Conversely, Dr Fulton's research uses mice that have become overweight and obese after unlimited, long-term access to a diet high in fat/sugar, without dietary choice, which promotes increased physiological and behavioral stress

responsiveness. Collectively, these and other research findings indicate that intake of highly palatable foods can have opposing effects on stress-regulatory systems, with effect direction dependent upon several factors. First, consistent with the work of Dr Susanne la Fleur's group (la Fleur et al., 2005), dietary choice may promote reduced stress responses, whereas lack of dietary choice may promote increased stress responses. However, while Dr Wilson's approach provides a dietary choice to female rhesus monkeys, his results suggest a facilitation of the stress response under these dietary conditions. Second, the stress-regulatory effects of palatable foods may vary with macronutrient composition. For instance, Dr Fulton's work indicates that some dietary fats can foster increased stress responses (see previous section), whereas dietary carbohydrates may preferentially curb stress responses (Anderson et al., 1987; Barr et al., 1999; de Castro, 1987; Deuster et al., 1992; Markus et al., 2000; Utter et al., 1999). Indeed, the high caloric diet used in Dr Wilson's studies of rhesus monkeys derived 45% of its calories from saturated fats. Finally, weight gain and associated metabolic dysfunction secondary to palatable food intake, as occurs following long-term and/or unlimited access to palatable food, may enhance stress responses. Consistent with this inference, increased adiposity is often associated with increased HPA axis tone (Francis et al., 2013; Lawlor et al., 2011; Lu et al., 2014; Ryan et al., 2014). Notably, results from Dr Ulrich-Lai's limited sucrose paradigm suggest that it may be possible to prevent these stress-promoting effects by limiting the amount and/or duration of palatable food intake.

Effects of stress on food intake

Dr Wilson has used a non-human primate model (female rhesus monkeys) to examine the role of social stress on dietary choice and intake, and the resulting physiological impact of stress-induced food intake. His group has shown that compared to social dominants, social subordinates eat more when offered unlimited access to a rich dietary environment (choice between standard chow and a high fat-high sugar diet). In contrast, Dr Petrovich has used a rat model to examine the neurobiological mechanism by which a more intense and imminent psychological stress, i.e. conditioned fear, promotes hypophagia and anorexia. She has shown that the CeA, likely working with the vmPFC and LHA, is essential for reducing food intake during fear anticipation in otherwise hungry rats. Importantly, the divergent consummatory effects that are observed by these two research groups provide critical insight into the consequences of stress on food intake. For example, the influence of stress on ingestive behavior depends in large part on the type and/or chronicity of stress experienced, with acute, intense and imminent threats of pain/injury being linked with reduced food intake (Bellisle et al., 1990; Popper et al., 1989) (see previous section by Dr Petrovich), while ongoing social stress is associated with increased food intake (Bartolomucci et al., 2009) (see previous section by Dr Wilson). Stress effects also vary with the type of food offered, such that highly palatable food options tend to produce more overeating in response to stress than low palatability foods (Bertiere et al., 1984; Pecoraro et al., 2004; Willner et al., 1998) (see section by Dr Wilson).

Future research priorities

This research symposium closed with an extended group discussion between the contributing authors and workshop participants that was moderated by Dr Rinaman. This lively discussion focused in large part on highlighting future research priorities for the field. More specifically, the group broached several intriguing questions that are ripe for experimental analysis. A few of these questions are posed below.

- How, when, and by what central neural mechanism(s) does palatable food intake transition from promoting stress relief to enhancing stress responsiveness? In other words, how does the apparently adaptive or beneficial effect of consuming rewarding foods become maladaptive and deleterious with regards to stress responsiveness? Important considerations include the type and duration of the stressor, the macronutrient quality of the palatable diet, and subject sex.
- What is the role or importance of timing (with regards to stress exposure) and context (e.g. safe/familiar environment versus novel/challenging environment) in mechanisms that underlie stress-induced overeating versus stress-induced anorexia?
- What is the role of sex hormones in mechanisms that underlie stress-induced overeating versus stress-induced anorexia? Is the female vulnerability to stress-related overeating and stress-related anorexia mediated by a common mechanism?
- Do "comfort foods" provide transitory stress relief by blunting activation of the HPA axis and other stress responses, by stimulating dopamine reward or other systems that counteract or compete with stress, or both? Attention needs to be focused on peripheral signals (e.g. glucocorticoids and inflammatory cytokines) and central neuropeptides (e.g. CRF) as mediators for these effects.
- Is diet important for the bi-directionality of stress on food intake? For example, can prolonged exposure to stress suppress appetite and food intake even when palatable foods are available? Does dietary choice matter and, if so, how does stress-induced disruption of circuits involving prefrontal regions predict diet choice and consumption?
- Is diet-induced obesity linked to a particularly vulnerable stress-responsive phenotype? Are the deleterious effects of stress amplified in individuals who are prone to dietary obesity? Is obesity resistance associated with stress resilience?

As these and other fascinating questions are addressed by ongoing and future work, including thoughtful consideration and integration of data across species and diverse experimental paradigms, the field will move towards an improved understanding of the functional associations and causal links among stress, food intake and emotion.

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Declaration of interest

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