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STRESS AND FOOD ARE INTERRELATED

Dr. Anil Batta*[1] and Dr. Surjit Singh Mal[2]

[1]*Professor & Head, Dep't of Medical Biochemistry, GGS Medical College / Baba Farid Univ. of Health Sciences, Faridkot.
[2]Vety. Officer,Govt. of Punjab, Faridkot.

***Corresponding Author: Dr. Anil Batta**
Professor & Head, Dep't of Medical Biochemistry, GGS Medical College / Baba Farid Univ. of Health Sciences, Faridkot.

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ABSTRACT
Obesity is a heterogeneous construct that, despite multiple and diverse attempts, has been difficult to treat. One conceptualization gaining media and research attention in recent years is that foods, particularly hyperpalatable (e.g., high-fat, high sugar) ones, may possess addictive qualities. Stress is an important factor in the development of addiction and in addiction relapse and may contribute to an increased risk for obesity and other metabolic diseases. Uncontrollable stress changes eating patterns and the salience and consumption of hyperpalatable foods; over time, this could lead to changes in allostatic load and trigger neurobiological adaptations that promote increasingly compulsively behavior. This association may be mediated by alterations in the hypothalamic-pituitary-adrenal (HPA) axis, glucose metabolism, insulin sensitivity and other appetite-related hormones and hypothalamic neuropeptides. At a neurocircuitry level, chronic stress may affect the mesolimbic dopaminergic system and other brain regions involved in stress/motivation circuits. Together, these may synergistically potentiate reward sensitivity, food preference and the wanting and seeking of hyperpalatable foods, as well as induce metabolic changes that promote weight and body fat mass. Individual differences in susceptibility to obesity and types of stressors may further moderate this process. Understanding the associations and interactions between stress, neurobiological adaptations and obesity is important in the development of effective prevention and treatment strategies for obesity and related metabolic diseases. A study carried out describes the impact of a major school examination on eating behavior in medical students where each student served as his own control. Food eaten was recorded on the day of an examination (D0) and on a control day (D7) identical to the former but without a stressful school event. Results revealed that the total energy intake (2225 ± 49 kcal vs. 2074 ± 48 kcal; $p \leqslant 0.01$) and amount of fat in the diet (38.3 ± 0.5 per cent *vs* 36.8 ± 0.6 per cent; $p \leqslant 0.05$) were significantly increased on the day of the examination. Energy intake in girls was affected by the stressful event (+ 135 kcal; $p \leqslant 0.05$) while the level of fat in the diet was modified in boys (+ 1.9 per cent; $p \leqslant 0.05$) on day D0. The ninetieth and tenth percentiles for the energy variable showed that students who had low-energy intake on the control day increased their intake on the day of the examination while students whose energy input was high on the control day decreased consumption on the day of the examination. These results suggest that a major stressful event in school may induce significant changes in eating habits in high-school students.

KEYWORDS: Obesity, Food Addiction, Stress, HPA axis, Mesolimbic, Dopaminergic System.

INTRODUCTION
There is a well-documented rapid rise in obesity linked to an increase in associated chronic health conditions.[1] Gaining a greater understanding of the underlying physiology and psychology influencing eating behavior is therefore a current and topical research focus. There are many factors influencing feeding behavior and appetite control.[2] However, individuals do not always initiate eating due to (learned) internal physiological symptoms of hunger; it is recognized that psychological and external (environmental) cues can promote overeating, at least in the short term.[3,4,5] Highly palatable food and snacks can contribute to overconsumption of calories, particularly through promotion of hedonic or reward mechanisms. Stress or 'daily hassles' has been shown to increase snacking behavior, particularly for high-fat and high-sugar foods[5], which may contribute to our 'obesogenic environment'. The relationship between stress and eating behavior has been explored from several different domains. In psychology, the relationship between the two has been observed with eating behavior identified as susceptible to change as an emotion coping strategy.[3,6] While it is recognized that the health of people who work is generally better than that of those that do not, it is also recognized that there are circumstances in which the

burden of work may contribute to unhealthy behavior(s).[9] The workplace could be the origin of various health inequalities since working conditions are associated with employees' health behavior. Unfortunately, stress is a feature of everyday modern life, particularly so in the workplace. A recent survey conducted by the UK Trade Union Congress estimated at 62% of workers experience feelings of stress in their workplace with 1 in 10 seeking support from their general practitioner for work-related stress.[10] It is increasingly recognized that the economic cost of workplace stress is significant. Aside from the financial impact, stress has been causally linked to many negative health outcomes, including heart disease, diabetes and obesity.[11,12] The role of the employee and employer can influence stress levels, since 'demand' and 'control' both play important roles in perceived stress levels in the workforce.[13] Individuals who experience high demand and low control may be at greater risk of stress. However, the degree to which one is susceptible to stress also depends on the individual's personality phenotype. There have been a few studies conducted within workplaces in order to assess the impact of specific work-related stress on eating behavior. Wardle et al.[6] assessed the association between work stress and eating behavior in 90 workers, and the results indicated that high work stress was associated with elevated energy, saturated-fat and sugar intake in comparison to individuals with low work stress. In this instance, however, high and low work stress was defined by hours worked, rather than specific work-induced stressors. O'Connor et al.[7] examined the effect of hassles and stressors in the workplace on eating behavior in a large sample (n = 422) of workers from one organization. Results revealed that increased daily hassles were associated with increased snacking on high-energy, high-fat sugar snacks. In particular the increased snacking occurred in response to ego-threatening, interpersonal and work-related hassles only. Research investigating workplace stress and eating behavior has thus far primarily focused on day workers. However, compared to individuals who work during the day, shift workers have been identified to be at greater risk of metabolically related disorders. One in 5 workers in Europe is employed on shift work involving night work, and more than 1 in 20 have extended work hours.[14]

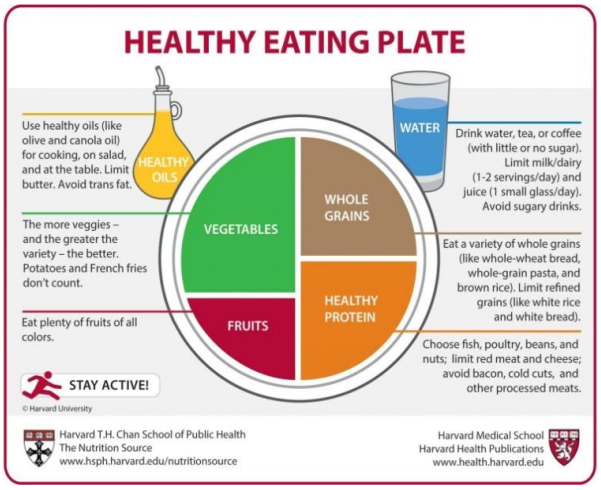

Figure 3

OBSERVATION

When an organism encounters a stressful event, a number of steps occur to divert resources appropriately and to assist coping mechanisms (reviewed in, Sapolsky Papadimitreou, 2009). In terms of acute appetite regulation, corticotrophin-releasing hormone (CRH) is released from the medial parvocellular (mp) paraventricular nucleus of the hypothalamus (PVN) in response to the stressor. In addition to stimulating adrenocorticotropic hormone (ACTH) release from the pituitary and the cascade of events leading to glucocorticoid release, CRH is also released into the arcuate nucleus of the hypothalamus (ARC) to inhibit neuropeptides Y (NPY)/agouti-related peptide (AGRP) neurons there (Heirich & Curie, 2009). This population of cells is normally responsible for stimulating feeding behavior and suppressing energy expenditure; thus CRH released after acute stress inhibits appetite (Heinirchs and Richards, 1999).

Insulin is another appetite-regulatory hormone that is influenced by glucocorticoids, although the role of glucocorticoids here is more complex. Insulin usually acts at the hypothalamus to reduce food intake and at the ventral tegmental area (VTA) to reduce the dopaminergic neuron-mediated rewarding nature of food (Figlewicz et al., 2008). Acutely, glucocorticoids stimulate insulin secretion from the pancreas (Strack et al., 1995), having an appetite-suppressant effect. However, chronically activated glucocorticoids also contribute to insulin resistance. Thus, as is seen with leptin, glucocorticoids contribute to a reduced ability of insulin to inhibit NPY/AGRP neurons in the ARC, which has the converse effect of lessening appetite suppression (Asensio et al., 2004). The intermediate role of glucocorticoids in the connection between insulin sensitivity and increased appetite is typically observed in patients with Cushing's syndrome. Glucocorticoid excess in these patients leads to an increase in appetite, weight gain and insulin resistance (Anagnostis et al., 2009). Glucocorticoids also influence food intake by enhancing the preference for "comfort foods." Insulin's suppressive effect on reward pathways likely means the food needs to be more

"rewarding" to achieve the same effect; hence under stressed conditions rats prefer foods that are high in fat and sucrose when a choice is available (la Fleur et al., 2004; Warne et al., 2006, 2009). Chronically stressed animals thus prefer calorically dense foods (Pecoraro et al., 2004; Foster et al., 2009). This enhanced caloric intake has been proposed to correspond with the increased brain energy demand and thus preferential glucose allocation to the brain under the conditions of stress (Peters et al., 2011). Remarkably, this highly palatable food also leads to a reward-mediated negative feedback onto the hypothalamic-pituitary-adrenal (HPA) axis to suppress it. In this way, a junk food diet or a stress-induced ice-cream binge may actually alleviate the symptoms of stress (Pecoraro et al., 2004; Foster et al., 2009). Rats given chronic restraint stress for 3 h per day for 5 days voluntarily eat more lard and sucrose than control rats and the plasma ACTH and glucocorticoid response to this restraint is suppressed in those rats that were given free access to these "comfort" foods. Unsurprisingly, these rats also become heavier than their restraint-stressed counterparts given normal chow (Pecoraro et al., 2004). Another mechanism by which glucocorticoids can influence appetite during stress is via its interaction with ghrelin. Ghrelin is a peptide derived principally from the gut. It is released as a signal of hunger or just prior to the usual meal time to stimulate feeding (Hosoda et al., 2006). Circulating ghrelin is increased in response to stress (Kristenssson et al., 2006) and probably acts at the level of the anterior pituitary as well as higher brain regions, such as the centrally projecting Edinger Westphal nucleus (EWcp), to modulate ACTH release from the pituitary and regulate glucocorticoid negative feedback (Spencer et al., 2012.

Figure 2

DISCUSSION

Lifetime experience, whether acute or chronic, clearly shapes both HPA axis and eating behavior. However, how an individual responds to each experience can be influenced at times outside the immediately pertinent event. It is now well accepted that the early life period is one of significant vulnerability to programming influences. For instance, central pathways governing feeding and metabolism start to develop at specific stages of early life and, at this time, the animal is particularly vulnerable to influences from the environment. An initial critical window of vulnerability occurs in prenatal life, when HPA axis and feeding-regulatory pathways begin to develop. For instance, both stress (or synthetic glucocorticoids) and poor nutrition *in* utero*can* have significant long-term consequences for feeding and behavior. Excessive stress during pregnancy can lead to HPA axis dysfunction (Henry et al., 1994; Rossi-George et al., 2009) and a long-term susceptibility to mood disorders in the offspring (Vallee et al., 1997), as well as impaired learning and memory (Lordi et al., 1997; Entringer et al., 2009), changes to reward pathways that lead to addictive behaviors (Morley-Fletcher et al., 2004; Thomas et al., 2009) and also, obesity (Li et al., 2010). The effects of prenatal stress on long-term feeding biology have been elegantly reviewed in (Entringer et al., 2012; Entringer and Wadhwa, 2013). Conversely, obesity during pregnancy, or even a pregnancy diet high in fat and sugar, can influence metabolic phenotype long-term as well as central reward processing, altering the way the rewarding aspects of food are perceived throughout life, leading to a preference for fatty, sugary foods (Ong and Muhlhausler, 2011). This type of vulnerability in the developing individual continues postnatally.In the rodent the hypothalamic connectivity involved in feeding develops during the second week Postnatally (Bouret et al., 2004a,b). Leptin is one critical trophic factor in stimulating this growth. Thus, insufficient leptin available in the dam's milk while these pathways are developing can disrupt the formation of these connections (Bouret and Simerly, 2007). A premature leptin surge or excessive leptin, such as can occur with*in* utero growth restriction or with obese or hyperleptinemic dams, can also disrupt this connectivity and result in a subsequent insensitivity to satiety signals (Yura et al., 2005; Kirk et al., 2009). Similarly, ghrelin normally counteracts leptin's trophic effects on these regions and a change in the timing or magnitude of the expected progressive elevation in plasma ghrelin can also disrupt this development (Grove and Cowley, 2005). The ultimate effect of such developmental influences on the animal is a disruption of central responses to nutritional status and disrupted feeding behavior. It is interesting to note that development of the HPA axis occurs in the rodent at similar times to the development of feeding-regulatory pathways. An animal's ability to respond to stress is immature at birth and the lifespan is characterized by a stress-hyporesponsive period that lasts from approximately the first to second weeks of life (Sapolsky and Meaney, 1986). Excessive stress, exposure to glucocorticoids, or prolonged absence from the dam can permanently terminate this stress hyporesponsive period, leading to life-long hypersensitivity to stress (Lehmann et al., 2002a, b; Barna et al., 2003; Xu et al., 2011). Certainly, early life stressful events such as maternal separation in the rodent, or child abuse/loss of a parent in humans can

cause disruption of the HPA axis in this way (Koch et al., 2008; D'Argenio et al., 2009). However, neonatal developmental influences can also be fairly subtle and still have pronounced effects. For instance, Meaney's group has shown rat pups given high-intensity nursing and grooming by their dams grow up to have attenuated HPA axis responses to psychological stress and reduced vulnerability to anxiety (Liu et al., 1997;Champagne and Meaney, 2001). In addition to, or perhaps as a result of, disarupting the HPA axis, the parental influence at this time is also crucial for establishing feeding patterns long-term. Thus, maternal separation can lead to the offspring having lower voluntary food intake and a preference for foods low in carbohydrates (Penke et al., 2001), while social isolation in previously maternally separated rats elevates food intake and weight gain (Ryu et al., 2009). It is likely this effect of the early environment on feeding patterns long-term is somewhat adaptive for the animal. Thus, early maternal separation in the wild rat likely occurs when food is scarce and foraging difficult. Thus, the offspring is brought into a world of food scarcity and high stress and its physiology adjusts accordingly to become hypersensitive to the effects of stress and to overeat. Essentially the neonatal environment thus imposes a drive to make the most of feeding opportunities when they are available (Meaney, 2001).

RESULT

Early life events are able to disrupt HPA axis function in a variety of ways. Prior to birth, the fetus is remarkably well protected from the effects of stress. The placenta produces 11β hydroxysteroid dehydrogenase 2 (11βHSD2), which converts active glucocorticoids from the mother into the inactive form, ensuring maternal glucocorticoids are prevented from reaching fetal circulation (Lucassen et al., 2009). Central changes also occur in the mother to ensure she responds to stress by secreting less glucocorticoids; for instance, allopregnanolone-mediated inhibition of the noradrenergic input to the PVN is enhanced as progesterone levels increase with pregnancy, meaning HPA axis activation is suppressed (Brunton et al., 2005, 2009). However, severe or prolonged stress or synthetic glucocorticoid exposure can over-ride these protective mechanisms and influence the development of the fetal HPA axis. For instance, excess maternal glucocorticoids can increase fetal circulating glucocorticoid levels and can alter fetal 11βHSD2 (Clifton et al., 2006) and glucocorticoid receptor (GR) expression (Edwards et al., 1993). Excess fetal glucocorticoids can also interfere with normal brain growth and development at this time, with restraint stress to the dam during pregnancy leading to reduced levels of proteins such as growth-associated protein of 43 kDa (GAP-43) that are involved in synaptic pruning (Pfenninger et al., 1991; Larsson, 2006; Jutapakdeegul et al., 2009).

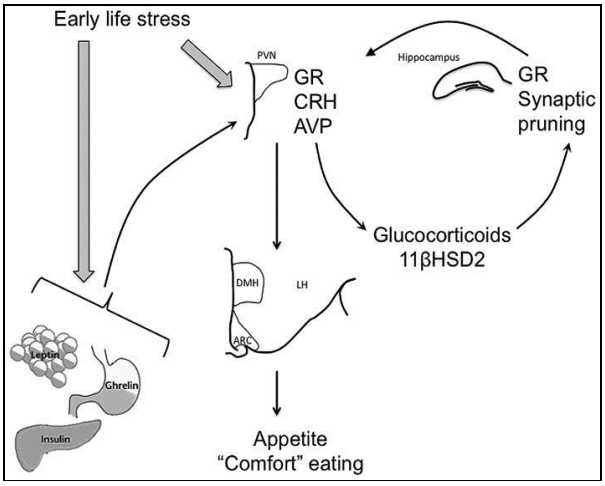

FIGURE 1

Early life stress can influence development of the HPA axis, as well as regulation of satiety-related hormones, leptin, insulin and ghrelin to alter feeding behavior long-term

Thus, early life stress can lead to epigenetic modification of glucocorticoid receptor (GR) expression in the hypothalamus and hippocampus and arginine vasopressin (AVP) and corticotropin-releasing hormone (CRH) in the hypothalamus, resulting in suppressed GR and increased AVP and CRH activity in response to stress later in life. Synaptic pruning in the hippocampus and circulating 11βHSD2 are also affected leading to elevated circulating glucocorticoid (GC) concentrations both under basal conditions and in response to stress. These effects of early life stress are ultimately seen in altered outputs from the paraventricular nucleus of the hypothalamus (PVN) to feeding-related nuclei such as the arcuate nucleus (ARC) and the dorsomedial nucleus of the hypothalamus (DMH). Early life stress can also potentially induce increased release of trophic/satiety hormones such as leptin, insulin and ghrelin, again influencing appetite, feeding behavior and metabolism throughout life. Arginine vasopressin (AVP) regulation of the HPA axis response to stress is also subject to epigenetic modification by early life events. Thus, in the mouse, early separation from the dam leads to changes in DNA methylation, resulting in increased PVN AVP expression and changes in coping responses to stress (Murgatroyd et al., 2009; Murgatroyd and Spengler, 2011). While the early life period is one of particular vulnerability to environmental influences, epigenetic modification can occur in response to the environment at any time. Thus, chronic social stress in adult mice can induce lasting demethylation of the CRH gene, resulting in heightened anxiety-like behavior (Elliott et al., 2010). In addition to the early influence of stress and glucocorticoids directly on the HPA axis, stress and glucocorticoids can also independently influence development of the feeding circuitry discussed above. For instance, perinatal glucocorticoids, in rodents and humans, can lead to elevations in plasma leptin (Bruder et al., 2005; Marinoni et al., 2008). Given what we know about the sensitivity of the developing hypothalamic

connectivity to circulating leptin at this time, it is highly likely this glucocorticoid-mediated increase in leptin interferes with the normal leptin-induced establishment of connections between the ARC, PVN, dorsomedial nucleus of the hypothalamus (DMH), and lateral hypothalamus (LH). Glucocorticoids can also influence levels of other crucial trophic hormones at this time, increasing insulin release from the pancreas (Moyer-Mileur et al., 2011) and ghrelin release from the gut (Hosoda et al., 2006; Kristenssson et al., 2006). There is even recent evidence maternal insulin sensitivity during pregnancy can influence fetal brain activity and may contribute to prenatal programming of long-term insulin sensitivity (Linder et al., 2014). Again, it is likely these changes are able to interfere with appropriate establishment of feeding-related circuitry in the hypothalamus. It is also worth noting these trophic factors may also contribute to HPA axis development, further consolidating the link between the HPA axis and feeding. Thus, elevated neonatal leptin levels (independent of other environmental stimuli) can lead to an increase in GR in the hypothalamus and hippocampus and resulting changes in HPA axis sensitivity to glucocorticoid negative feedback (Proulx et al., 2001).

CONCLUSION

The discussed data make it clear that the HPA, stress, axis and feeding regulation are inextricably linked, with the early life developmental environment being critical in establishing both. The challenge now will be to ensure we achieve the appropriate balance when influencing these systems with parental care and neonatal medical treatments. There is no doubt that several current perinatal treatments, while crucial for their immediate purpose, have far-reaching side-effects on systems such as the HPA axis and feeding circuitry. For instance, synthetic glucocorticoid, administered prenatally to assist in lung development, may elevate plasma leptin (Marinoni et al., 2008), stimulate epigenetic modifications in GR and elevate 11βHSD2 (Clifton et al., 2006). Similarly, the current practice of intensively feeding premature and small for gestational age babies to accelerate brain and lung development has the negative side-effect of predisposing these babies to long-term excess weight gain (Ong et al., 2000; Stettler et al., 2005). While these strategies may be essential in the immediate term to ensure the newborn's survival, consideration should be given to how we can mitigate the long-term negative effects. Understanding of the mechanisms by which stress interacts with eating behavior in the developed adult is also essential for behavioral and pharmaceutical treatments to prevent excess weight gain in at-risk patients.

REFERENCES

1. Anagnostis P., Athyros V. G., Tziomalos K., Karagiannis A., Mikhailidis D. P. (2009). Clinical review: the pathogenetic role of cortisol in the metabolic syndrome: a hypothesis. J. Clin. Endocrinol. Metab. 94: 2692–2701 10.1210/jc.2009-0370.
2. Asakawa A., Inui A., Kaga T., Yuzuriha H., Nagata T., Fujimiya M., et al. (2001). A role of ghrelin in neuroendocrine and behavioral responses to stress in mice. Neuroendocrinology, 74: 143–147. 10.1159/000054680.
3. Asensio C., Muzzin P., Rohner-Jeanrenaud F. (2004). Role of glucocorticoids in the physiopathology of excessive fat deposition and insulin resistance. Int. J. Obes. Relat. Metab. Disord. 28(Suppl. 4): S45–S52 10.1038/sj.ijo.0802856.
4. Barna I., Balint E., Baranyi J., Bakos N., Makara G. B., Haller J. (2003). Gender-specific effect of maternal deprivation on anxiety and corticotropin-releasing hormone mRNA expression in rats. *Brain Res. Bull.* 62: 85–91 10.1016/S0361-9230(03)00216-8.
5. Begum G., Stevens A., Smith E. B., Connor K., Challis J. R., Bloomfield F., et al. (2012). Epigenetic changes in fetal hypothalamic energy regulating pathways are associated with maternal undernutrition and twinning. *FASEB J.* 26: 1694–1703 10.1096/fj.11-198762.
6. Bjorntorp P. (1996). The regulation of adipose tissue distribution in humans. Int. J. Obes. Relat. Metab. Disord. 20: 291–302.
7. Bjorntorp P. (2001). Do stress reactions cause abdominal obesity and comorbidities? *Obes. Rev.* 2: 73–86 10.1046/j.1467-789x.2001.00027.x.
8. Bouret S. G., Draper S. J., Simerly R. B. (2004a). Formation of projection pathways from the arcuate nucleus of the hypothalamus to hypothalamic regions implicated in the neural control of feeding behavior in mice. *J. Neurosci.* 24: 2797–2805 10.1523/JNEUROSCI.5369-03.2004.
9. Bouret S. G., Draper S. J., Simerly R. B. (2004b). Trophic action of leptin on hypothalamic neurons that regulate feeding. *Science*, 304: 108–110 10.1126/science.1095004.
10. Bouret S. G., Simerly R. B. (2007). Development of leptin-sensitive circuits. *J. Neuroendocrinol.* 19: 575–582 10.1111/j.1365-2826.2007.01563.x.
11. Bruder E. D., Jacobson L., Raff H. (2005). Plasma leptin and ghrelin in the neonatal rat: interaction of dexamethasone and hypoxia. *J. Endocrinol.* 185: 477–484 10.1677/joe.1.