



Contents lists available at ScienceDirect

## Biological Psychology

journal homepage: [www.elsevier.com/locate/biopsycho](http://www.elsevier.com/locate/biopsycho)

## Role of addiction and stress neurobiology on food intake and obesity

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## ARTICLE INFO

## Keywords:

Addiction  
Stress  
Neurobiology  
Food intake  
Obesity

## ABSTRACT

The US remains at the forefront of a global obesity epidemic with a significant negative impact on public health. While it is well known that a balance between energy intake and expenditure is homeostatically regulated to control weight, growing evidence points to multifactorial social, neurobehavioral and metabolic determinants of food intake that influence obesity risk. This review presents factors such as the ubiquitous presence of rewarding foods in the environment and increased salience of such foods that stimulate brain reward motivation and stress circuits to influence eating behaviors. These rewarding foods via conditioned and reinforcing effects stimulate not only metabolic, but also stress hormones, that, in turn, hijack the brain emotional (limbic) and motivational (striatal) pathways, to promote food craving and excessive food intake. Furthermore, the impact of high levels of stress and trauma and altered metabolic environment (e.g. higher weight, altered insulin sensitivity) on prefrontal cortical self-control processes that regulate emotional, motivational and visceral homeostatic mechanisms of food intake and obesity risk are also discussed. A heuristic framework is presented in which the interactive dynamic effects of neurobehavioral adaptations in metabolic, motivation and stress neurobiology may further support food craving, excessive food intake and weight gain in a complex *feed-forward* manner. Implications of such adaptations in brain addictive-motivational and stress pathways and their effects on excessive food intake and weight gain are discussed to highlight key questions that requires future research attention in order to better understand and address the growing obesity epidemic.

## 1. Multifactorial determinants of body weight and food intake

Obesity is a global epidemic with more than 500 million people worldwide classified as obese (body mass index, BMI  $\geq 30$  kg/m<sup>2</sup>) (2011). The United States is at the forefront of the pandemic with two-thirds of its population classified as overweight or obese (BMI  $\geq 25$  kg/m<sup>2</sup>) (Flegal, Carroll, Ogden, & Curtin, 2010). Thus, most Americans are above the recommended normal weight (lean BMI 18.5–24.9 kg/m<sup>2</sup>) and are predisposed to obesity-related conditions including cardiovascular disease, type 2 diabetes (T2DM), and various cancers (Ogden, Carroll, McDowell, & Flegal, 2007). This serious and worrying pandemic has thrown into question previously believed notions that body weight is regulated by the hypothalamus with homeostatic and physiologic metabolic processes that maintain a balance between energy intake and energy expenditure (Berthoud, 2012; Yeo & Heisler, 2012). There is growing acknowledgment that a number of social factors such as the easy availability and relatively low cost of high calorie foods that are highly palatable (HP), widespread marketing of such HP foods, increased use of sugars, sugar substitutes, preservatives and sugar sweetened beverages, altered eating patterns as well as the

promotion of sedentary lifestyles all contribute to this pandemic (Hill & Peters, 1998; Ogden et al., 2007; Wang, Volkow, Thanos, & Fowler, 2004). In addition, genetic and other social and biological variables may also contribute towards vulnerability to obesity and weight gain (Stice, Spoor, Bohon, Veldhuizen, & Small, 2008; von Deneen, Gold, & Liu, 2009), but these alone do not explain the pandemic levels of obesity. Thus, this review focuses on the dynamic interplay between, (a) environmental variables of overabundance of rewarding foods and food cues (e.g. advertising), (b) the neurobiological effects of consuming such foods on the hypothalamic and extrahypothalamic reward/motivation and stress pathways, and, (c) effects on metabolic hormones, to impact food craving and motivation, excessive food intake and weight gain.

## 2. Highly palatable (HP) foods and related cues, food seeking and intake

Highly palatable (HP) foods are more liked, preferred and found to be rewarding in taste. These include foods high in sugar and sweet taste, highly processed foods high in saturated fats or high carbohy-

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<http://dx.doi.org/10.1016/j.biopsycho.2017.05.001>

Received 9 December 2016; Received in revised form 20 February 2017; Accepted 1 May 2017  
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drates making up savory tastes and combination of food groups prepared in ways that enhance taste and value or 'salience' of such foods. These foods are ubiquitous in our current obesogenic environment and their related sensory (including both discrete and context related) and autobiographical associations such as sights, smells, tastes, place where eaten, with whom, when and time and other context factors serve as conditioned cues that may increase liking and preference for such foods, tendency towards seeking them, thereby resulting in facilitating food craving and intake of these foods. For example, in a cross sectional study with a large community sample, we found higher food craving for these HP foods. Furthermore, higher food craving was significantly associated with greater intake of these foods, and those with higher body mass index (BMI) reported greater levels of food craving (Chao, Grilo, White, & Sinha, 2014). In other population-based research, fast foods such as potato chips, processed meats, sugar sweetened beverages all predicted long term weight gain in large prospective cohorts of US men and women (Mozaffarian, Hao, Rimm, Willett, & Hu, 2011). Such highly palatable and processed foods and their related associations or 'cues' stimulate the brain reward and motivation pathways just as reinforcing drugs of abuse and via learning/conditioning mechanisms increase the likelihood of HP food seeking and consumption (Alsio, Olszewski, Levine, & Schioth, 2012; Avena, Rada, & Hoebel, 2009; Berthoud, 2012; Coelho, Jansen, Roefs, & Nederkoorn, 2009; Lutter & Nestler, 2009; Weingarten, 1983). The conditioned properties of these HP foods and related increases in their intake promotes their heightened salience, and, in turn, results in greater 'wanting' and seeking of HP foods, similar to the incentive salience processes that occur with increasing alcohol and drug intake (Robinson & Berridge, 2008; Sinha & Jastreboff, 2013). Research with animals and humans has documented activation of brain reward regions and increased dopaminergic transmission with HP food cue exposure, along with concomitant increases in food craving and motivation (Kelley, Schiltz, & Landry, 2005; Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001; Wang et al., 2001), with greater responsibility of brain reward regions and food craving among individuals with higher BMI (Pelchat, Johnson, Chan, Valdez, & Ragland, 2004; Saelens & Epstein, 1996; Simansky, 2005; Stice et al., 2008; Stice, Spoor, Ng, & Zald, 2009; Tetley, Brunstrom, & Griffiths, 2009).

### 3. Overeating of HP foods and metabolic and stress hormone responses

Intake of balanced meals with healthy foods or even small amounts of HP foods in healthy individuals will lead to food-related rise in plasma glucose that stimulates insulin secretion and enables glucose uptake into peripheral tissues. Previous evidence indicates that in lean healthy individuals, peripheral and even central infusion of insulin suppresses appetite and feeding (Kahn, Hull, & Utzschneider, 2006; Konner et al., 2011; Schwartz, Woods, Porte, Seeley, & Baskin, 2000; Sherwin, 2008; Woods, Lotter, McKay, & Porte, 1979). However, interesting new evidence suggests that with greater consumption of HP foods, the concomitant changes in carbohydrate and fat metabolism, insulin sensitivity and appetite hormones may influence neural reward regions involved in increasing salience and motivation for food intake, that, in turn, may alter energy homeostasis (Alsio et al., 2012; Chuang et al., 2011; DiLeone, 2009; Dossat, Lilly, Kay, & Williams, 2011; Farooqui, 2009; Figlewicz & Sipols, 2010; Malik, McGlone, Bedrossian, & Dagher, 2008). For example, chronic high levels of peripheral insulin and insulin resistance, as is observed in many individuals with obesity, may promote rather than suppress food craving and intake as well as increase brain activation in dopamine-rich reward regions such as the ventral tegmental area (VTA), nucleus accumbens and dorsal striatum (Anthony et al., 2006; Chechlacz et al., 2009; Jastreboff et al., 2013; Konner et al., 2011; Kullmann et al., 2012). Similar adaptations are noted with leptin in obesity, with evidence indicating that leptin and ghrelin influence dopaminergic

transmission in brain reward regions and food seeking behavior in animals, and activate brain reward regions in humans (Chuang et al., 2011; DiLeone, 2009; Farooqui, 2009; Malik et al., 2008). Interestingly, we have also shown that higher leptin levels (associated with obesity) predicted blunted ventromedial prefrontal cortex and rostral anterior cingulate (VmpFC/rACC) activation to high fat food images and to glucose and fructose intake in adolescents, suggesting a role for leptin in central control of food intake (Jastreboff et al., 2014; Jastreboff et al., 2016). Furthermore, higher activity in the insula and dorsal striatum correlated with higher insulin levels, insulin resistance and with food craving when participants were placed in their favorite food contexts via imagined exposure (Jastreboff et al., 2013). Together, these findings support the notion that there may be parallel and related adaptations in metabolic and neural reward and motivation circuits that closely interact to dynamically influence hunger, food motivation and choice and subsequent overeating of HP foods.

In other evidence, we found in a recent longitudinal study of community volunteers that higher ghrelin was associated with greater food cravings, while higher chronic stress, insulin and cortisol responses predicted greater weight gain at a future 6-month follow-up assessment (Chao, Grilo, White, & Sinha, *in press*). There is also evidence that laboratory chow and specific macronutrients such as carbohydrates, fats and proteins stimulate autonomic and cortisol responses in animals and humans (Dallman, 2010; Stimson et al., 2014). The source of cortisol increases appears to be via both adrenal and extra-adrenal production (Stimson et al., 2014). These findings suggest that cortisol rise with macronutrient intake may serve to promote gluconeogenesis underscoring the critical role of glucocorticoids in energy homeostasis. On the other hand, there is also basic science evidence in laboratory animals that sucrose and palatable snack foods dampen HPA axis stress responses (Christiansen, Dekloet, Ulrich-Lai, & Herman, 2011; Ulrich-Lai et al., 2010). These findings suggest that specific types of foods may significantly affect both hypothalamic and extrahypothalamic peripheral sources of cortisol and may modulate stress responses to promote food motivation and intake.

Overconsumption of HP food intake is also known to reduce reward thresholds along with an upregulation of the extrahypothalamic Corticotrophin Releasing Factor (CRF) in the amygdala and related limbic striatal pathways, which, in turn, may promote food craving and associated greater neural reactivity to food cues in these brain regions thereby increasing risk of overeating of HP foods (Cifani, Polidori, Melotto, Ciccocioppo, & Massi, 2009; Cottone et al., 2009; Ghitza, Gray, Epstein, Rice, & Shaham, 2006). Thus, exposure to high fats diets, yo-yo dieting and withdrawal from such diets, may alter extrahypothalamic CRF pathways involved in the regulation of stress responses and also disrupt brain reward motivation responses to increase compulsive food seeking and stress-induced HP food seeking (Cifani et al., 2009; Cottone et al., 2009). Such findings are consistent with the Koob allostasis model of addiction (Koob & Le Moal, 1997) which posits that binge or heavy substance use results in allostatic load and adaptations in brain reward pathways, which, in turn, increases compulsive reward seeking and intake, suggesting similar effects with overconsumption of rewarding drugs and HP foods.

On the basis of evidence cited above, it is possible that higher intake of HP comfort foods may alter cortisol responses to such food intake, with glucocorticoid-related alterations that not only influence homeostatic functions of glucocorticoids in energy balance, but also affect hypothalamic and extrahypothalamic regulation of food intake. For example, it is well known that binge and heavy alcohol use, but also high nicotine and other psychostimulant use, reduces the well-known increased cortisol responses observed with acute alcohol/drug intake (Koob & Kreek, 2007; Lee & Rivier, 1997; Richardson, Lee, O'Dell, Koob, & Rivier, 2008; Sinha, 2001). These HPA axis adaptations with binge levels of alcohol and drug abuse have been identified as "neuroendocrine tolerance" (Lu & Richardson, 2014; Richardson et al., 2008), and raise the possibility that such blunted HPA axis responses

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