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Mood, food, and obesity

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Food is a potent natural reward and food intake is a complex process. Reward and gratification associated with food consumption leads to dopamine (DA) production, which in turn activates reward and pleasure centers in the brain. An individual will repeatedly eat a particular food to experience this positive feeling of gratification. This type of repetitive behavior of food intake leads to the activation of brain reward pathways that eventually overrides other signals of satiety and hunger. Thus, a gratification habit through a favorable food leads to overeating and morbid obesity. Overeating and obesity stems from many biological factors engaging both central and peripheral systems in a bi-directional manner involving mood and emotions. Emotional eating and altered mood can also lead to altered food choice and intake leading to overeating and obesity. Research findings from human and animal studies support a two-way link between three concepts, mood, food, and obesity. The focus of this article is to provide an overview of complex nature of food intake where various biological factors link mood, food intake, and brain signaling that engages both peripheral and central nervous system signaling pathways in a bi-directional manner in obesity.

Keywords: mood, depression, anxiety, food, obesity

INTRODUCTION

It is hypothesized that individuals engage in a variety of behaviors to regulate their mood (Morris and Reilly, 1987). Important among mood regulating behaviors is food consumption. The interaction between mood, emotional state, and feeding behaviors is complex and it is hypothesized that individuals regulate their emotions and mood by changing both food choices and quantities. It is also apparent that mood can affect the self-rewarding mechanisms of food consumption (Morris and Reilly, 1987). Specific types of food tend to be preferred under certain psychological conditions due to the influence of foods on the activity of brain reward centers (**Figure 1**) (Rangel, 2013; Jauch-Chara and Oltmanns, 2014; Weltens et al., 2014). Positive feedback loops can result in enhancement of appetite leading to obesity. Interestingly, highly palatable foods activate the same brain regions of reward and pleasure that are active in drug addiction (Volkow et al., 2012), suggesting a neuronal mechanism of food addiction leading to overeating and obesity (Davis et al., 2011, 2014; Dileone et al., 2012; Volkow et al., 2012; Dagher, 2013; Davis, 2013; Ziauddeen and Fletcher, 2013; Pai et al., 2014; Potenza, 2014). Dopamine, which directly activates reward and pleasure centers, affects both mood and food intake (Cantello et al., 1989; Diehl and Gershon, 1992; Fochtmann and Fink, 1992; Black et al., 2002; Cawley et al., 2013), further supporting the link between psychology and eating behaviors.

Mood disorders are often found in association with abnormal feeding behaviors. For example, depression and anxiety are comorbidities of obesity (Novick et al., 2005; Simon et al., 2006; Kloiber et al., 2007). Impairment in central nervous system (CNS) function has been linked to obesity that in turn impacts mental and physical health (Allison et al., 2009; Talen and Mann, 2009; Duarte et al., 2010). Obese individuals are at increased risk of developing depression (25, 26), and this risk is doubled in the presence of diabetes (Anderson et al., 2001; De Groot et al., 2001; Labad et al., 2010). Depressed mood is also associated with abdominal obesity and poor diet (Roberts et al., 2003; Dong et al., 2004; Simon et al., 2006; Luppino et al., 2010; Zhao et al., 2011; Hamer et al., 2012). A link between obesity and depression has been found in animal models of mood disorders (Lombard, 2000; Pawels and Volterrani, 2008; Dallman et al., 2003, 2005; Singh et al., 2007, 2009, 2011; Dallman, 2010; Chuang et al., 2011; Diz-Chaves, 2011; Maniam and Morris, 2012; Spence and Courbasson, 2012; Akubuiro et al., 2013; Kumar et al., 2013), suggesting that a common signaling pathway may underlie these phenotypes in both humans and animals.

There are numerous articles on the regulation of food intake, obesity, and mood. However, further exploration of the interaction among mood, food, and obesity is much needed. The aim of this review article is to highlight the complex interplay among mood, emotional state, and eating behaviors that influence body weight. This review provides an overview of known biological factors and foods that influence appetite and mood *via* brain signaling pathways. Specifically discussed are the foods and biological factors, which override the normal physiological requirements of appetite regulation, and how these factors influence in a bi-directional manner emotion, food, food intake, and obesity (**Figure 1**).

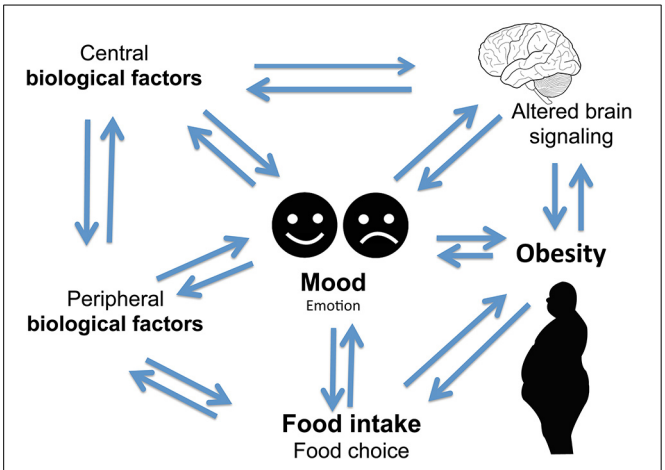

FIGURE 1 | Complex two-way relationship linking food intake, mood, and obesity.

CENTRAL NERVOUS SYSTEM IN REGULATION OF MOOD, FOOD, AND OBESITY

BI-DIRECTIONAL LINK OF FOOD AND EMOTION

In humans, eating behavior is complex and is affected by both mood and emotions (Lyman, 1982; Mehrabian, 1995; Macht, 1999; Macht and Simons, 2000). However, mood and emotions are distinct. Mood is characterized by psychological arousal in the absence of obvious stimuli that can last for several minutes or longer. In contrast, emotions are short-term affective response to reinforcing stimuli. Of all emotions, a study shows that frequent emotions such as, anger and joy have the strongest influence on appetite and food choice (Macht, 1999). Behavior based findings from human studies of questionnaires, field, and clinical studies suggest an integrative five way model that predicts five different aspects of emotional eating. These five aspects include: food choice, food intake, loss of cognitive controls, food modulating emotions, and emotion-congruent modulating eating, see review by Macht (2008). Therefore, depending on the state of negative emotions or distress, emotional eating is triggered where food intake can either increase or decrease within the same individuals (Ouwens et al., 2009). Emotional state has also been connected with addiction (Parylak et al., 2011). Sensory and psychological pathways influence food choice, the quantity, and meal frequency that may not be a part of normal physiological requirement. Many psychosomatic theories of obesity suggests that obese people overeat due to inability to perceive their physiological state, hunger, and satiety and that overeating reduce emotional discomfort and anxiety (Kaplan and Kaplan, 1957; Schachter, 1968; Bruch, 1985). The internal/external theory of obesity predicts that normal eaters alter their food intake to regulate their emotion, while obese people do not (Schachter, 1968; Canetti et al., 2002). Depending on whether an eater is restrained or emotional, stress and negative emotions could be associated with both increased and decreased motivation to eat; and under those circumstances, food choice differs (Herman and Mack, 1975). Thus, emotional distress influences emotional food choice and intake.

STRESS AND FOOD INTAKE

There is a close interaction between food, mood, and stress (Benton and Donohoe, 1999; Oliver and Wardle, 1999; Gibson, 2006; Dallman, 2010; Bast and Berry, 2014). Stress can affect feeding behavior (Greeno and Wing, 1994; Yau and Potenza, 2013), resulting in either increased or reduced food intake depending on the types of external or psychological stressors (Oliver and Wardle, 1999; Gibson, 2006; Dallman, 2010; Yau and Potenza, 2013). Similarly, chronic stress can lead to either increased consumption of palatable and rewarding foods leading to obesity or a diminished appetite leading to weight loss (Cartwright et al., 2003; Adam and Epel, 2007; Tryon et al., 2013). Furthermore, following exposure to a stressor, studies show that intake of palatable foods reduce signs of stress and anxiety (Pecoraro et al., 2004; La Fleur et al., 2005; Maniam and Morris, 2010, 2012; Ulrich-Lai et al., 2010; Finger et al., 2011, 2012). Interestingly, stress-induced preference for palatable food is often seen in humans (Souquet and Rowland, 1989; Epel et al., 2004; Pecoraro et al., 2004; Christiansen et al., 2011; Gibson, 2012; Merali et al., 2013; Sharma et al., 2013; Sharma and Fulton, 2013; Meye and Adan, 2014; Park et al., 2014; Rho et al., 2014). Notably, this behavior is extended to animals (Dallman et al., 2003, 2005; Cottone et al., 2009). This suggests that a common neurobiological pathway maybe involved in food choice and patterns of eating behavior during stress.

MOOD AND FOOD INTAKE

Mood states such as anxiety and depression affect food choice and energy metabolism. Overeating and obesity is often associated with depression and anxiety in humans which has also been reported in animal models (Novick et al., 2005; Simon and Von Korff, 2006; Kloiber et al., 2007; Singh et al., 2007, 2009; Akubuiro et al., 2013; Patterson and Abizaid, 2013; Sharma and Fulton, 2013). Both endocrine and metabolic conditions are exacerbated in major depression (Mcelroy et al., 2004; Simon et al., 2006; De Wit et al., 2010; Luppino et al., 2010; Marijnissen et al., 2011). Individuals experiencing depressed moods show preference for and consume palatable "comfort foods" as a mean to alleviate their negative feelings (Macht, 2008). Although on a short-term basis, palatable foods can provide some relief from negative emotions and mood states, chronic consumption of calorically-rich foods ultimately leads to obesity which in turn promotes vulnerability to depression and anxiety (Novick et al., 2005; Simon et al., 2006; Kloiber et al., 2007; Sharma and Fulton, 2013). Conversely, there are findings showing that prolonged high-fat feeding leads to negative emotional states, increased stress sensitivity, and altered basal corticosterone levels (Sharma et al., 2012). Thus, negative emotion impacts food choice and intake that in turns affects mood in a bi-directional manner.

Interestingly, other behaviors of reduced pleasure/reward experience, anxiety-like behavior, and heightened stress-induced hypothalamic pituitary adrenal axis (HPA) activation have been found in mice. Furthermore, after exposure to chronic high-fat diet and then switching to normal chow diet, mice showed craving for sucrose, high-fat foods, and displayed enhanced anxiety-like behavior (Sharma et al., 2012). Similar findings of increased behavioral and physiological signs of depression and anxiety have been reported in humans when switched from a high-fat sugar

diet to regular diet (Avena et al., 2008; Teegarden and Bale, 2008; Cottone et al., 2009; Pickering et al., 2009; Iemolo et al., 2012; Sharma et al., 2012; Blasio et al., 2013). All together, these findings suggest that chronic high-fat feeding promotes negative emotional states and potentiates condition for enhanced sensitivity to stress that leads to continuous repetitive cycles of overeating, weight gain, and depressed mood.

FOOD PREFERENCE AND MOOD

Hippocrates, father of modern medicine, said: "Let your food be your medicine, and your medicine be your food" (Prasad, 1998). Research from human trials and animal studies have shown that foods directly influence brain neurotransmitter systems which in turn has effects on mood and performance by altering the brain structure, chemistry, and physiology. Mood can also influence our food choices and expectations on the effects of certain foods can influence our sapiens. Some of those foods impacting mood are discussed below and summarized in **Table 1** (Spring et al., 1982-1983; Rogers and Lloyd, 1994).

Chocolate has a strong effect on mood, generally increasing pleasant feelings and reducing tension (Osman and Sobal, 2006; Parker et al., 2006b; Cartwright et al., 2007; Fletcher et al., 2007). Chocolate contains psychoactive chemicals such as andamines that stimulate the brain and result in good mood (Ottley, 2000). However, negative feelings are also associated with chocolate in some women on weight loss regimes who experience guilt after eating chocolate. The unique taste and feel from chocolate in the mouth leads to chocolate craving due to sensory factors associated with chocolate eating (Macht and Dettmer, 2006; Osman and Sobal, 2006; Parker et al., 2006b; Cartwright et al., 2007; Fletcher et al., 2007).

Caffeine, mostly consumed in the form of coffee and tea, not only has stimulant effects on enhancing alertness, vigilance, and reaction time but also increases anxiety in susceptible individuals (Acquas et al., 2002; Rossi et al., 2010). Caffeine blocks adenosine receptors in the brain and can relieve headaches, drowsiness, and fatigue. Short-term caffeine deprivation in regular users results in withdrawal symptoms (Rogers, 1995).

Omega-3 fatty acids, found in various foods can influence, mood, behavior, neuroticism, and impulse control (Van Strater and Bouvy, 2006; Conklin et al., 2007; Stahl et al., 2008). Omega-3 fatty acids play a role in major depressive disorder, bipolar disorder, schizophrenia, substance abuse, and attention deficit disorder (Young and Martin, 2003; Parker et al., 2006a; Van Strater and Bouvy, 2006; Stahl et al., 2008). Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), both members of the omega-3 fatty acid family, contribute to the fluidity of the cell membrane, and thereby play an important role in brain development and function (Pawels and Volterrani, 2008). Low blood levels of polyunsaturated omega-3 fatty acids are associated with depression, implying a role in mood disorders (Lombard, 2000; Sanchez-Villegas et al., 2007; Antypa et al., 2012; Moranis et al., 2012; Kang and Gleason, 2013; Grosso et al., 2014).

Micronutrients, such as thiamine (vitamin B1), iron, and folic acid, play a role in emotion. Thiamine containing foods influence mood states (Benton et al., 1995). Improved thiamine status increases well-being, sociability, and overall energy levels. Insufficient amounts of thiamine are associated with impaired mood and cognitive functioning (Benton et al., 1997; Benton and Donohoe, 1999).

Iron deficiency represents one of the most common nutritional problems worldwide. Iron deficiency anemia can result in depressed mood, and problems with attention and lethargy (Benton and Donohoe, 1999).

Folic acid plays an important role in the brain. Folic acid deficiency is associated with depressed mood (Coppen and Bolander-Gouaille, 2005; Young, 2007). Psychiatric patients often run the risk of developing folic acid deficiency due to loss of appetite from anticonvulsant drugs that inhibit folic acid absorption (Ottley, 2000). Collectively, these findings suggest foods influence mood.

Mood can influence food preference (Christensen and Brooks, 2006). Choice of eating palatable foods can either lead to comfort feeling or disgust. A good example of behavioral change that is observed after taking a meal is altered mood. A general effect of meal on behavior is observed from animals to humans where hunger leads to irritability and meal intake leads to arousal and alertness. Thus, a search for food is cultivated. Once satiety sets in, sedentary and calm behaviors most likely have positive rather than negative effect on mood (Macht and Simons, 2000; Macht et al., 2003; Macht and Dettmer, 2006; Macht, 2008). A potential internal information route on emotional behavior was first recognized in 2001 where nutrients from gut were relayed to the brain by the vagus nerve affecting emotions (Zagon, 2001). However, the relationship of emotions, physiological arousal, and mood in a given situation is significantly dependent upon on the subject's motivational state (Reid and Hammersley, 1999) and the individual's personality trait of neuroticism that interacts with mood and response to emotional stimuli (Dess and Edelheit, 1998).

The pathogenesis of both mood and metabolic disorders during obesity can be triggered by certain diets (Wallin and Rissanen, 1994; Sanchez-Villegas and Martinez-Gonzalez, 2013). Diets like Western diets that are rich in saturated fat and low in poly-unsaturated and mono-unsaturated fatty acids tend to increase the incidences of depression (Peet et al., 1998). On the other hand, diet like the Mediterranean diet appears to reduce depression (Sanchez-Villegas and Martinez-Gonzalez, 2013; Sanchez-Villegas et al., 2013). Furthermore, many reports show the increased incidence of depression on diets that lack omega-3 polyunsaturated fatty acids (PUFA) and that depression is reduced when intake of PUFA is increased in both humans (Lin and Su, 2007; Sanchez-Villegas et al., 2007; Oddy et al., 2011; Park et al., 2012a) and rodents (Moranis et al., 2012; Park et al., 2012b). Besides mood changes, high fat diets promote increased weight gain, visceral adipose tissue, larger waist circumference, and more cardiovascular disease mortality (Schulze et al., 2006; Molenaar et al., 2009; Romaguera et al., 2009, 2010; Mozaffarian et al., 2011; Estruch and Salas-Salvado, 2013; Nazare et al., 2013). The accumulation of adipose tissue in abdominal stores leads to several complications of obesity including insulin resistance leading to metabolic syndrome (Despres et al., 2006; Tchernof and Despres, 2013). These changes also lead to neurobiological impairments affecting mood disorders such as depression and anxiety (Weber-Hamann et al., 2002; Van Reedt Dortland et al., 2013a,b). It is believed that increased circulating plasma fatty acids such as

Table 1 | Summary of biological factors and food influencing mood, emotions, food intake, and brain signaling pathways.

Foods and biological factors	Influence on mood, emotion, food intake, and brain signaling pathways	References
Chocolate	Increases pleasant feeling, reduce tension, and results in good mood via serotonin and cannabinoid receptors signaling	Ottley, 2000; Osman and Sobal, 2006; Parker et al., 2006b; Cartwright et al., 2007; Fletcher et al., 2007
Caffeine	Enhances alertness and increases anxiety and results in withdrawal symptoms in some individuals *via* cannabinoid CB1 receptor signaling pathway	Rogers, 1995; Acquas et al., 2002; Rossi et al., 2010
Omega-3 fatty acids	Influences neuroticism, mood, behavior, and plays a role in mood disorders. Omega-3 fatty acids in receptor functioning, neurotransmitters levels, and monoamine metabolism are all implicated in depression (see review Parker et al., 2006a)	Lombard, 2000; Young and Martin, 2003; Parker et al., 2006a; Van Strater and Bouvy, 2006; Conklin et al., 2007; Sanchez-Villegas et al., 2007; Stahl et al., 2008; Antypa et al., 2012; Moranis et al., 2012; Kang and Gleason, 2013; Grosso et al., 2014
Micronutrients	Thiamine plays a role in emotion, mood states, and cognitive functioning. The pathway is unknown	Benton et al., 1995, 1997; Benton and Donohoe, 1999
Iron	Iron deficiency results in depressed mood and lethargy. The pathway is unknown	Benton and Donohoe, 1999
Folic acid	Folic acid deficiency is associated with depressed mood. The pathway is unknown	Coppen and Bolander-Gouaille, 2005; Young, 2007
Ghrelin	Linked to stress mediated food reward behavior, depression, and anxiety via ghrelin receptor signaling pathway	Schanze et al., 2008; Barim et al., 2009; Kluge et al., 2009, 2011; Perello et al., 2010; Chuang et al., 2011; Diz-Chaves, 2011; Kumar et al., 2013
Serotonin	Linked to food intake, depression, and anxiety via serotonin receptor signaling pathway	Wurtman and Wurtman, 1989; Benton and Donohoe, 1999; Pepino et al., 2009; Shabbir et al., 2013
Dopamine	Linked to food reward behavior and mood via dopamine receptor signaling pathway	Cantello et al., 1989; Diehl and Gershon, 1992; Fochtmann and Fink, 1992; Berridge, 1996; Black et al., 2002; Davis et al., 2009; Cawley et al., 2013
Leptin	Linked to food intake, depression, anxiety, and mood disorder via leptin receptor signaling pathway	Collin et al., 2000; Asakawa et al., 2003; Lu et al., 2006; Finger et al., 2010; Liu et al., 2010; Sharma et al., 2010; Yamada et al., 2011; Guo et al., 2012, 2013
Adiponectin	Linked to depression and mood disorder. May involve adiponectin-induced inhibition of GSK-3β pathway	Arita et al., 1999; Maeda et al., 2001; Milan et al., 2002; Cnop et al., 2003; Delporte et al., 2004; Ryo et al., 2004; Leo et al., 2006; Narita et al., 2006; Hanley et al., 2007; Weber-Hamann et al., 2007; Ye et al., 2007; Yilmaz, 2008; Zeman et al., 2009; Jeong et al., 2012; Wilhelm et al., 2013
Resistin	Indirect link to depression. The pathway is unknown	Krsek et al., 2004; Silha et al., 2004; Weber-Hamann et al., 2007; Lehto et al., 2010
Insulin	Linked to mood, depression, anxiety and negative emotion via insulin receptor signaling	Gustafson et al., 1999; Benedict et al., 2004; Koponen et al., 2008; Akbaraly et al., 2009; Almeida et al., 2009; Benoit et al., 2009; Kleinridders et al., 2009; Marks et al., 2009; Pulkki-Raback et al., 2009; Grillo et al., 2011; Chapman et al., 2013; Platt et al., 2013

palmitic acid enters the brain and impairs neurological function (Tsuboi et al., 2013). Palmitic acid impairs leptin and insulin receptor signaling in the hypothalamus and promotes weight gain (Benoit et al., 2009; Kleinridders et al., 2009). Under these circumstances, obesity is promoted, as well as a negative emotional state. In addition, leptin and insulin have been noted to influence mood (Gonder-Frederick La et al., 1989; Lu et al., 2006; Lu, 2007; Zeman et al., 2009; Ryan et al., 2012).

Furthermore, several studies have shown humans on high fat diet manifest mood disorders like depression that correlates positively with high serum palmitate (Tsuboi et al., 2013). Similarly, rats on high fat diet display increased anxiety-like

behavior, altered body weight, plasma insulin, leptin, and glucose levels when compared to rats on iso-caloric olive oil high fat diet that show no changes in body weight, glycaemia, leptin, and insulin levels (Hryhorczuk et al., 2013). Thus, saturated fats stimulate HPA disturbances and/or inflammation, leading to anxiogenic-like behavior in animals and depression in humans. All together these findings suggest an association between certain foods and improved mood.

PSYCHIATRIC AND EATING DISORDERS

The Diagnostic and Statistical Manuals of Mental Disorders (DSM-5), which was developed by the American Psychiatric Association in 1994, reported disturbed eating behaviors in psychiatric disorders (American Psychiatric Association, 2013). In humans, melancholic depression is associated with hypercortisolism, anhedonia, hypophagia, and weight loss (Fisher et al., 1997; Krishnan and Nestler, 2008; Ulrich-Lai and Herman, 2009; Hammack et al., 2010; Carroll et al., 2012; Hryhorczuk et al., 2013; Patterson and Abizaid, 2013; Schellekens et al., 2013b). In contrast to atypical depression, the most common forms of depression are characterized by reduced hypothalamic pituitary adrenal axis (HPA) activity, increased appetite, carbohydrate craving, and weight gain (Juruena and Cleare, 2007). Those with abdominal obesity are associated with hyperactive HPA axis due to an elevated response to corticotrophin releasing hormone (CRH) stimulation and increased stimulated response to stress (Pasquali, 2012).

Altered serum cortisol level is associated with depression (Parker et al., 2003; Raison and Miller, 2003; Stetler and Miller, 2011). Altered cortisol, HPA axis, and food intake have been associated with depression (Ulrich-Lai and Herman, 2009; Dallman, 2010; Schellekens et al., 2012a). The neuronal pathways that regulate food intake, and circuitries that act *via* the HPA axis are implicated in a complex two-way relationship of three concepts between mood, food, and eating behavior (**Figure 1**) (Kyrou and Tsigos, 2009; Ulrich-Lai and Herman, 2009; Dallman, 2010; Schellekens et al., 2012b, 2013b). It is noted that there is an overlap in neural circuitry of food intake and stress that likely reinforces a link between stress and feeding behavior (Maniam and Morris, 2012). These overlapping circuitries of HPA axis modulating feeding behavior and stress converge on corticosterone hormone producing neurons in the paraventricular nucleus (PVN). Thus, elevated glucocorticoid and a dysfunctional HPA axis are common to both depression and obesity.

Glucocorticoids exert multiple effects on metabolic, endocrine, immune, and behavioral functions. Glucocorticoids regulate reward and emotional processes *via* their receptors in midbrain and limbic circuits (Arnett et al., 2011; Solomon et al., 2012; Hryhorczuk et al., 2013; Patterson and Abizaid, 2013; Wang et al., 2013). Glucocorticoids not only act peripherally to maintain energy homeostasis but also centrally to modulate HPA activity, emotional, and behavioral effects of stress (Fedoroff et al., 2003; Figueiredo et al., 2003). Under physiologic acute stress, the HPA axis is activated, and glucocorticoids are released. This leads to a major restoration of energy balance by increasing insulin, increasing motivation for palatable food (Piazza and Le Moal, 1997; Dallman et al., 2006; Dallman, 2010), and mobilizing stored energy toward central stores that leads to obesity (Mann and Thakore, 1999). Thus, obesity and mood disorder are linked *via* the HPA axis. In rodents, chronic corticosterone exposure leads to increased glucocorticoid receptor (GC) expression in fore-brain and basolateral amygdala that results in depressive-like, anxiety-like behaviors, and increased locomotors (Wei et al., 2004; Boyle et al., 2005, 2006). Therefore, these findings suggest that a deficit in glucocorticoid signaling in distinct brain regions may play a role in affective disorder.

OBESITY AND MOOD

Obesity increases incidence of anxiety and mood disorders (Simon et al., 2006). Stress induced overeating and obesity is also associated with major depression in humans (Novick et al., 2005; Simon et al., 2006; Kloiber et al., 2007). Individuals under chronic stress tend to have more visceral fat due to excessive systemic cortisol levels (Brown et al., 2004; Adam and Epel, 2007; Kyrou and Tsigos, 2009). In all, there appears to be a good association between hypercortisolemic depression, abdominal fat accumulation (Weber-Hamann et al., 2002), decreased glucocorticoid-mediated negative feed back, and increased corticotropin releasing hormone (CRH) release from the paraventricular nucleus (PVN) (Holsboer, 2000). Furthermore, major depression in adolescence is linked to a higher risk for obesity in adulthood (Richardson et al., 2003). It is also noted that metabolic conditions are exacerbated in depression and vice versa (Mcelroy et al., 2004; Simon et al., 2006; De Wit et al., 2010; Luppino et al., 2010; Marijnissen et al., 2011). Like-wise, stress significantly impacts food intake in both humans and animals, thereby promoting metabolic disturbances (Block et al., 2009; Dallman, 2010; Maniam and Morris, 2012). Overeating can also be considered to be analogous to drugs of use because it reflects an addiction where individuals become physically and psychologically dependent on foods rich in fat and sugar (Avena et al., 2008, 2009; Barry et al., 2009; Parylak et al., 2011; Allen et al., 2012; Davis, 2013). Reports also show that with intake of palatable rewarding food, acute stress responses are reduced (Dallman et al., 2003; Lutter and Elmquist, 2009; Chuang et al., 2011; Kumar et al., 2013), thereby showing the potential of "comfort eating" in stress relief. All together these findings suggest that there is a reciprocal link in mood disorder and obesity.

RODENT MODELS OF MOOD AND EATING DISORDERS

Rodent studies have provided the best insight into dopamine-mediated food intake. Dopamine deficient mice die quickly due to decreased food intake (Hnasko et al., 2004). Dopamine when given in the striatum rescues deficient food intake by restarting feeding behavior. Further, when dopamine is given to the nucleus accumbens, a food preference for pleasant food vs. non-pleasant food is observed. Altered dopamine receptor expression is also associated with feeding behavior (Clifton et al., 1991; Zeng et al., 2004; Wang et al., 2009) (18). Post-transcriptional modification such as RNA editing could also play a role in altered reward circuitry mediating overeating behavior (18). It is noteworthy that altered serotonin 2C receptor ($5HT_{2C}R$) editing has been associated with dopamine production, reward, mood, feeding, and

recently obesity (Burns et al., 1997; Sodhi et al., 2001; Gurevich et al., 2002; Higgins and Fletcher, 2003; Iwamoto et al., 2005; Rosenzweig-Lipson et al., 2007; Berg et al., 2008; Olaghere Da Silva et al., 2010; Hayes and Greenshaw, 2011; Schellekens et al., 2012a). Intriguingly, both serotonergic and dopaminergic system are altered in transgenic mice with dysregulated RNA editing enzyme, ADAR2 (Singh et al., 2007, 2009, 2011) (18). These transgenic mice show significantly hyperactive brain regions implicated in reward and also behaviorally display goal oriented behavior toward food in a competitive rewarding environment (Akubuiro et al., 2013). Furthermore, altered dopamine receptor expression, food preference for high fat diet are also observed in ADAR2 transgenic mice (Akubuiro et al., 2013). Interestingly, co-morbidities of depression and anxiety behaviors and altered $5HT_{2C}R$ editing are observed in ADAR2 transgenic mice (Singh et al., 2007, 2009, 2011). Collectively, these results suggest that co-morbidities of affective disorder, overeating, and obesity could be linked *via* the modified $5HT_{2C}R$ in ADAR2 transgenic mice. However, more studies are required to provide a better understanding of the post-transcription modification of the $5HT_{2C}R$ linking to mood, food, and obesity in ADAR2 transgenic mice.

Dysfunctional serotonergic signaling has been associated with mood and obesity (Wurtman and Wurtman, 1989; Benton and Donohoe, 1999; Sodhi et al., 2001; Iwamoto and Kato, 2003; Schmauss, 2003; Kawahara et al., 2008; Morabito et al., 2010; Singh et al., 2011; Schellekens et al., 2012a; Silberberg et al., 2012; Shinozaki et al., 2013). In another rodent model of depression brain derived neurotropic factor (BDNF) was shown to have an antidepressant-like effect (Siuciak et al., 1997). BDNF has been shown to be a neurotropic factor on serotonergic neurons in BDNF heterozygous mice where dysfunctional serotonergic signaling is associated with aggression, hyperphagia, and weight gain is rescued (Lyons et al., 1999). Further exogenous BDNF application enhances serotonin signaling and modifies several behaviors regulated by serotonin feeding, body weight homeostasis, and analgesia (Siuciak et al., 1994; Pelleymounter et al., 1995). Thus, these studies suggest that dysfunctional serotonergic and dopaminergic systems play a critical role in mood, food intake, and obesity.

PSYCHOBIOLOGICAL RELATIONSHIP OF BRAIN REWARD LINKING HUNGER, ADDICTION, OVEREATING, AND OBESITY

Continuous overeating can be viewed as an addictive behavior that involve reward circuitry (Davis, 2013). Reward circuitry involved in addiction spans two key brain regions, (1) the prefrontal region and the amygdala and, (2) the limbic system integrating amygdala with hypothalamus and septal nuclei (Elliott et al., 2000; Schultz, 2000, 2002; Tzschentke, 2001; Baxter and Murray, 2002; Rolls et al., 2002; Koob and Volkow, 2010). The neural mechanism of disrupted dopamine signaling pathways being central to overeating and drugs of use and the overwhelming hallmarks of urge to seek and consume, thereby presents an addiction behavior. Another common phenomenon of compulsive intake of drugs and overconsumption of food intake seen in obesity is the loss of control due to impairments in circuits involved in decision making, self control, interoception, and regulation of mood and stress (Volkow et al., 2010).

Two hormones: ghrelin and leptin interact with the hypothalamus to regulate food intake, energy homeostasis, promote satiety, and hunger. Interestingly, both hormones have been implicated in craving behavior, eating disorder, and mood and have also been associated with the reward pathway (Kiefer et al., 2001; Opland et al., 2010; Dickson et al., 2011). Thereby, suggesting that both ghrelin and leptin are linked to mood and food intake.

There are several neurotransmitter systems involved in feeding such as serotonin, dopamine, opioids, and GABA, of which serotonin and dopamine have been the most closely linked to feeding behavior. Dopamine mediates reward specifically the "wanting" or approach behaviors toward a biologically relevant goals more so than "liking" or enjoyment aspect (Berridge, 1996; Davis et al., 2009). Opioids have been implicated more so in the "liking" or the hedonic aspect of reward processing and both neurotransmitter pathways work together in the perception of reward (Davis et al., 2009). The "wanting" behavior toward a biological relevant goal that is mediated by dopamine is probably due to how dopamine neurons receive signals and the way they are organized in the brain. Dopamine neurons are found in the midbrain region of the ventral tegmental area (VTA) and substantia nigra pars compacta projecting to striatal limbic and cortical regions. Dopamine neurons receive information from; hypothalamus and brain stem regions involved in autonomic responses, hippocampus involved in memory, amygdala involved in emotional reactivity, thalamus involved in arousal and prefrontal cortex and cingulate involved in emotional reactivity *via* neuropeptides and neurotransmitters. Neurochemistry and neuroanatomical reward circuitry involved in addiction to alcohol and drugs translate to an addiction model of overeating and obesity. Certain studies show that hunger can influence memory for food-related stimuli where the orbitofrontal cortex is specifically involved in food-related stimuli in hunger state (Morris and Dolan, 2001). In rodent studies, dopamine has been shown to play a role in feeding by determining a meal size to meal duration, and obesity (Clifton et al., 1991; Schwartz, 2000). Dopamine in the nucleus accumbens has been associated with reinforcement aspects of food and while in the hypothalamus, dopamine plays a role in initiation and duration of feeding (Wang et al., 2004b). Leptin and insulin also help to regulate dopamine production (Leinninger et al., 2009). Dopamine regulates food consumption involving the mesolimbic pathway and the hypothalamus (Volkow et al., 2011). Since dopamine levels in addiction change in these brain regions, it is conceivable that a similar mechanism of reinforcement of food may also be involved in food addiction (Wang et al., 2004b).

FOOD REWARD, ADDICTION, AND OBESITY

Food is a natural reward and has both homeostatic and hedonic characteristics (Rada et al., 2010; Volkow et al., 2011). Depending on the specific type of highly palatable food, it has the potential to engage similar brain reward pathways as drugs of abuse (Weatherford et al., 1990; Pitchers et al., 2010; Olsen, 2011). It may also arise from casual eating to compulsive eating that eventually leads to addiction (Davis, 2013). This may be from food-related brain changes that is associated with psychological changes like that seen in drug addiction (Robinson and Berridge, 2003). Both rewarding and hedonic effects of food result in

positive emotional reactions that play a major role in overeating and obesity (Fulton, 2010; Avena et al., 2013; Bongers et al., 2013; Sinha and Jastreboff, 2013; Yau and Potenza, 2013). Theoretical models support food addiction because highly palatable food activates reward pathways that lead to human and animal obesity (Finlayson et al., 2007; Berner et al., 2008; Heyne et al., 2009; Davis et al., 2011; Sampey et al., 2011; Akubuiro et al., 2013; Davis, 2013).

The American Psychological Association in the DSM-5 manual included behavioral addiction and addictions to natural rewards as a new category of "addiction and related behavior" (Volkow and O'brien, 2007). Human and rodent studies suggest that dysregulated brain reward pathways may contribute to increased intake of palatable food leading to obesity (see review by Berthoud et al., 2011). Despite the divergence in eating behavior, there is an overall increase in tasty, energy- rich foods that is independent of stress-induced hyperphagia or hypophagia (Gibson, 2006; Dallman, 2010). One hallmark of food addiction is the food craving where intense desired food consumption only compensates the craving, whereas in hunger various types of food alleviates the hunger (Martin et al., 2011). Advantages of functional magnetic resonance imaging (fMRI) and positron emission topography (PET) paradigms have been used to provide insights of neural correlates in food addiction and obesity (Wang et al., 2004a; Teegarden and Bale, 2007; Volkow et al., 2012). Interestingly, following various types of food presentation to normal healthy patients, activated brain regions of anterior cingulate cortex, orbitofrontal cortex, and insula are observed (Wang et al., 2004a; Teegarden and Bale, 2007). In contrast to obese overeating patients, neurobiological changes in the reward pathways are similar to those observed in drug addicts (Volkow et al., 2012). However, available data in humans on food addiction suggests that there is heterogeneity in the clinical definitions of food addiction, obesity, and binge eating disorder. Nonetheless through neurobiological data obtained from both human and animal studies, food cravings, overeating, and tolerance support an addiction-like model, see reviews (Albayrak et al., 2012; Volkow et al., 2012; Davis, 2013; Hone-Blanchet and Fecteau, 2014).

SOCIETY AND FOOD ADDICTION

Globally about 1 billion adults are overweight of which 475 million are obese (Organization, 2013). Obesity is a complex multifactorial disease. In the United States, increased incidence of adult obesity is on the rise. In the Westernized society, the major cause of obesity is due to reduced physical activity leading to sedentary life style and surplus of food, sodas, variety of fast food, and hyperpalatable foods, all that activate dopamine rewarding centers leading to over consumption of food (Fortuna, 2012; Granados et al., 2012; Ziauddeen et al., 2012). Hyper-palatable foods and their increased availability promote addictive and compulsive eating leading to weight gain. Addictive properties of certain types of food and addiction-like behaviors are observed in both humans and animal models. Animal studies have shown an overview of addiction-like eating behaviors when presented with foods high in sugar and fat (Avena et al., 2008, 2012). In animals, several studies of sugar-binging models support an addiction-like phenotype of tolerance, cross sensitization, withdrawal, and neurochemical changes, but does not induce obesity (Avena, 2007; Avena et al., 2008, 2009). On the other hand, several imaging studies from obese population shows that greater BMI and overeating are associated with neurobiological pathways similar to those observed in drug addicts (Stice and Dagher, 2010; Stice et al., 2010; Volkow et al., 2012, 2013). In humans, feeding behaviors are more complex but pattern of food addiction appears to parallel substance dependence (Gearhardt et al., 2011; Dileone et al., 2012). Some argue that food addiction should be included in the DSM manual (Volkow and O'brien, 2007; Taylor et al., 2010) even though food addiction is not a categorized diagnosis within DSM-5. However, recently Yale Food Addiction Scale (YFAS) has been used as a tool for diagnosis of food addiction in patients with eating disorders (Gearhardt et al., 2009; Clark and Saules, 2013). In one study, using body mass index, body fat percentage by dual-energy X-ray absorptiometry, macronutrient intake, and the YFAS scale has been used as a diagnostic tool to assess food addiction in general Newfoundland population (Pedram et al., 2013). They found that the prevalence of food addiction was significantly associated with obesity in general population. Thus, suggesting that food addiction contributes to severity of obesity in the general population and that food addiction could be a separate etiology of obesity.

In summary, findings of central mediated food intake suggest a complex two-way link between food intake and mood, emotion, reward, food, food choice, and neurotransmitters (**Figure 1**). Food addiction remains as an incomplete described phenomenon due to limited data. Overabundance of food seems to aid in food addiction specifically foods rich in fat and sugar. Although FMRI and PET imaging have been useful in providing some insights into neural correlates in food addiction and obesity, but specific food addiction phenotype in the development of obesity needs to be differentiated. Furthermore, molecular pathways or signatures that link food intake in emotion, mood, food, reward, and obesity are areas that need further investigation. These types of studies in the future will provide further insight into genetic, psychological, neuropsychiatric, and environmental risk factors associated with overeating, food addiction, and obesity.

PERIPHERAL SYSTEM IN REGULATION OF MOOD, FOOD, AND OBESITY

The gut-brain axis mediates the communication between brain and gut when it comes to appetite, satiety, and energy homeostasis (Cummings and Overduin, 2007; Ahima and Antwi, 2008; Blevins and Baskin, 2010; Gibson et al., 2010; Suzuki et al., 2010, 2012). Furthermore, peripheral hormones have also been reported to regulate mood, food intake, and obesity (Tschop et al., 2000; Nakazato et al., 2001; Olszewski et al., 2008; Blevins and Baskin, 2010; Suzuki et al., 2010; Andrews, 2011b; Dickson et al., 2011; Egecioglu et al., 2011; Skibicka and Dickson, 2011; Overduin et al., 2012; Perello and Zigman, 2012; Karra et al., 2013). Gastrointestinal signals such as cholecystokinin (CCK), bombesin, glucagon eneterostatin, insulin, resistin, somatedin, cyclohistiyl-proline, leptin, amylin, and apolipoprotein A-IV are all known to reduce food intake. The exception is ghrelin, which increases food intake. Several peripheral factors that engage the

CNS in a bi-directional manner and influence mood and food intake are summarized in **Table 1** and discussed below.

GHRELIN

A gut orexigenic hormone ghrelin is synthesized in the stomach and acts centrally to mediate increased food intake *via* central pathways (Kojima et al., 1999, 2004; Tschop et al., 2000; Nakazato et al., 2001; Andrews, 2011a; Diz-Chaves, 2011). The hypothalamus in the brain directly senses peripheral ghrelin and modifies the energy status (Schaeffer et al., 2013). Studies support that ghrelin reaches the brain *via* the vagus afferents to the nucleus solitary tract (NST), which further projects to the arcuate nucleus of the hypothalamus (Asakawa et al., 2001; Date et al., 2002; Williams and Mobarhan, 2003). Ghrelin activates downstream signaling *via* the hormone secretagogue receptor (GSH-R1a) where it is ubiquitously expressed in multiple brain regions and in peripheral tissues. Due to multiple sites of GSH-R1a expression, it is not surprising that ghrelin performs many other biological activities of growth hormone secretion, glucose and lipid metabolism, and gastrointestinal motility. However, other properties of GHS-R1a allowing dimerization with multiple G-protein coupled receptors suggest the likelihood of cross talk between many other neuropeptide systems of serotonin and dopamine (Schellekens et al., 2013a,b). Thus, ghrelin has the potential to engage multiple neuropeptide systems in mood, food, and obesity.

The ghrelinergic system also mediates the non-homeostatic hedonic rewarding and motivational aspects of food intake *via* mesolimbic dopaminergic circuitry (Dickson et al., 2011; Egecioglu et al., 2011; Skibicka et al., 2011; Perello and Zigman, 2012). Studies support ghrelin's involvement in stress mediated food reward behavior (Perello et al., 2010; Kumar et al., 2013; Chuang et al., 2011; Diz-Chaves, 2011). Numerous studies provide a link between ghrelin and affective disorders, such as depression and anxiety (Schanze et al., 2008; Barim et al., 2009; Kluge et al., 2009). Ghrelin also alleviates depression (Kluge et al., 2011). All together these studies suggest that the ghrelinergic system is an attractive system to target stress associated metabolic and mood associated eating disorders in obesity.

SEROTONIN

Serotonin has numerous functions besides regulating mood that includes regulation of sleep, appetite, and impulse control (Steiger, 2004; Daubert and Condron, 2010; Nordquist and Oreland, 2010; Mosienko et al., 2012). Serotonin levels from the gut and alimentary canal constitutes about 80–90% of the human body's total serotonin and not in the brain. This is surprising, as serotonin dictates most of our mood and happiness (Wurtman and Wurtman, 1989; Benton and Donohoe, 1999). Central serotonin pathways participate in the regulation of mood and modulate meal patterns in terms of quality and quantity. Neurotransmitter release of serotonin from serotonergic neurons in the brain is governed by food intake (Shabbir et al., 2013). The essential amino acid tryptophan that comes from food is the precursor for serotonin synthesis (Prasad, 1998). Ingestion of carbohydrates increases the plasma ratio of tryptophan to other large neutral amino acids leading to increased serotonin synthesis in the brain and alleviating depression. Such is the case for carbohydrate craving during depression that often leads to obesity and vice versa (Pepino et al., 2009; Shabbir et al., 2013). This is observed during stress, winter depression, or in people trying to give up smoking. Nicotine increases brain serotonin secretion and its withdrawal leads to depression (Wallin and Rissanen, 1994; Wurtman and Wurtman, 1996). Brain serotonin plays a role in the pathophysiology of depression, as treatments with serotonin potentiating drugs alleviates depression in seasonal affective disorder (Wurtman, 1993). Based on these findings it has been suggested that the excessive carbohydrate intake by patients with premenstrual syndrome (PMS) and seasonal affective disorder (SAD) relieves the depressive symptoms *via* an increased central serotonergic activity (Cizza et al., 2005; Miller, 2005). A diet rich in carbohydrates can relieve depression and elevate mood (Wurtman and Wurtman, 1989; Benton and Donohoe, 1999). Furthermore, research has shown that dieters tend to become depressed as the serotonin levels are reduced due to decreased carbohydrate intake (Huether et al., 1997). Thus, these studies imply that certain foods are strong mood regulators.

LEPTIN

Low leptin levels have been found to be associated with human depression and depression-like behaviors in rodents (Kraus et al., 2001; Lu et al., 2006; Guo et al., 2012; Lawson et al., 2012). Antidepressant-like effect of leptin in leptin insufficiency or leptin resistance suggests the hormone contributes to altered mood (Lu, 2007). Increased visceral fat and dyslipidemia are associated with several endocrine and metabolic changes that link to CNS control of emotional states and mood (Hryhorczuk et al., 2013). As an endocrine gland, adipose tissue secretes numerous peptide hormones that target the brain and peripheral tissues to regulate metabolism and behavior. Leptin circulates in proportion to fat mass (Maffei et al., 1995). Leptin impacts several physiological processes such as appetite, energy expenditure, and neuroendocrine function. The hormone has also been linked to human depression and has been shown in rodents to have antidepressant and anxiolytic effects (Asakawa et al., 2003; Liu et al., 2010; Yamada et al., 2011; Lawson et al., 2012). Nevertheless, there are conflicting findings of leptin levels and depression, which are discussed below.

Major depressive disorder (MDD) has been shown to be associated with lower plasma leptin levels when compared to healthy controls (Kraus et al., 2001; Atmaca et al., 2002, 2008; Westling et al., 2004; Jow et al., 2006). On the other hand, there are reports showing increased plasma leptin levels in depression (Kraus et al., 2002; Esel et al., 2005; Schilling et al., 2013), gender specific increased leptin levels in women with depressive disorder (Rubin et al., 2002; Esel et al., 2005; Zeman et al., 2009), as well as no changes of leptin by antidepressant treatment (Esel et al., 2005). In depressed individuals suffering from loss of appetite, plasma leptin levels do not differ from those of healthy controls (Deuschle et al., 1996). In another study, it was found that higher serum leptin was associated with atypical depressive patients with increased appetite (Gecici et al., 2005). In older men, a combination of elevated visceral fat and high leptin levels was associated with depression (Milaneschi et al., 2012), and high leptin correlated

positively with depressive symptoms in patients with type 2 diabetes (Labad et al., 2012). Thus, these reports suggest more studies are required to draw a better conclusion regarding the role of leptin in human depression.

Interestingly, rodent studies have provided the most conclusive findings. Leptin modulates the HPA axis and mice that lack leptin (obese *ob/ob* mice or its leptin receptor (obese *db/db* mice) show increased depression-like behavior (Collin et al., 2000; Asakawa et al., 2003; Lu et al., 2006; Finger et al., 2010; Liu et al., 2010; Sharma et al., 2010; Yamada et al., 2011; Guo et al., 2012, 2013). Furthermore, leptin deficient *ob/ob* mice have elevated corticosterone that can be reduced by leptin replacement (Garthwaite et al., 1980; Arvaniti et al., 2001). In contrast, chronic unpredictable mild stress in rats activates the HPA axis and leads to depressive-like behaviors that correlate with decreased serum leptin levels (Ge et al., 2013). Leptin receptors (LepRb) in midbrain and forebrain loci that affect emotional processes are targeted by leptin. Genetic deletion of LepRb in the hippocampus results in a depression-like phenotype, which is reduced by leptin administration to the hippocampus thereby showing an antidepressant effects (Asakawa et al., 2003; Lu et al., 2006; Finger et al., 2010; Liu et al., 2010; Guo et al., 2013). Loss of LepRb specifically in glutamatergic neurons of the forebrain elicits depressive-like behavior without affecting anxiety (Guo et al., 2012). Stress-induced dopamine release is also associated with high leptin (Burghardt et al., 2012). Leptin activates dopamine neurons in the VTA of the midbrain reducing dopamine neuronal firing and increases dopamine availability (Fulton et al., 2006; Hommel et al., 2006). Selective deletion of LepRb from midbrain dopamine neurons results in increased anxiety-like behavior, but not depressive-like behavior (Liu et al., 2011). LepRb signaling in limbic and prefrontal nuclei mediates the antidepressant action of leptin. In contrast, leptin in dopamine neurons of the ventral midbrain and in central nucleus of the amygdala leptin signaling exerts the anxiolytic actions of leptin. Thus, leptin signaling in different brain regions exerts different physiological behaviors.

In conditions of central obesity that favors insulin resistance and type 2 diabetes, leptin sensitivity is diminished. Leptin resistance is associated with high plasma leptin levels and defective LepRb signaling. These states are characteristic of obesity and increase the risk for mood disorders (Myers et al., 2012). Mice made obese by a high fat diet intake show reduced sensitivity to effects of leptin and antidepressant actions of leptin when compared to low-fat diet treated controls (Yamada et al., 2011). Further, leptin insensitivity exacerbates HPA dysregulation in obesity (Komorowski et al., 2000; Collura et al., 2009) and thereby enhances the mass of dysfunctional central adipose stores in a cortisol-dependent manner. Leptin resistance has been reported to be associated with the mid brain VTA where mesolimbic DA neurons reside (Matheny et al., 2011). Leptin resistance appears to affect multiple neural and endocrine pathways including hippocampal, mesolimbic dopamine pathways, and HPA activity ultimately affecting emotions and mood. Thus, these studies provide evidence of leptin related mechanisms underlying depression in obesity.

ADIPONECTIN

Low levels of another adipose-derived hormone, adiponectin, has been implicated in energy homeostasis, metabolic disturbances, insulin resistance (Kennedy et al., 2006; Hanley et al., 2007; Turer and Scherer, 2012; Hryhorczuk et al., 2013) and recently, depression in humans (Arita et al., 1999; Cnop et al., 2003; Ryo et al., 2004; Leo et al., 2006; Narita et al., 2006; Hanley et al., 2007; Weber-Hamann et al., 2007; Yilmaz, 2008) and rodents (Maeda et al., 2001; Milan et al., 2002; Delporte et al., 2004; Ye et al., 2007). Changes in adiponectin levels are secondary to metabolic disturbances in obesity (Morrison et al., 2011; Doumatey et al., 2012). There are conflicting reports of either positive or negative associations of adiponectins levels with mood disorder (Yilmaz, 2008; Zeman et al., 2009; Jeong et al., 2012; Wilhelm et al., 2013), or no changes in patients with major depressive disorder or with antidepressants (Lehto et al., 2010; Jeong et al., 2012). Mice exposed to chronic social defeat recapitulate the low levels of adiponectin, stress-induced depressive-like behaviors, and impaired HPA axis (Liu et al., 2012). Interestingly central administration of adiponectin has antidepressant effects (Liu et al., 2012). Thus, a link between plasma adiponectin levels and depression is observed in mice. In contrast, humans show more ambiguous results depending on the type of depressive disorder, sex, and treatment.

RESISTIN

Adipocyte-derived resistin is linked to insulin resistance in rodent models of depression-like behavior while in humans, the role of resistin is less defined (Schwartz and Lazar, 2011; Hryhorczuk et al., 2013). In genetic and diet induced obese mice circulating resistin levels are elevated (Steppan et al., 2001). In contrast, resistin is down regulated in human obesity (Way et al., 2001; Degawa-Yamauchi et al., 2003; Owecki et al., 2011; Sadashiv et al., 2012). However, there is one study that shows a positive correlation between resistin levels and atypical depression (Lehto et al., 2010). In human depression, however, resistin levels positively correlate with salivary cortisol (Krsek et al., 2004; Silha et al., 2004; Weber-Hamann et al., 2007). Conversely, resistin levels are lower in patients receiving antidepressant treatment who have remitted from depression (Weber-Hamann et al., 2007). Thus, these studies imply that resistin plays a role in affecting mood.

INSULIN

From a recent systematic review and meta-analysis there appears to be a significant cross-sectional association between depression and insulin resistance (Kan et al., 2013) and there is a bi-directional association between diabetes and depressed mood. Depression is associated with pre-diabetes insulin resistance (Anderson et al., 2001; Kan et al., 2013) and obesity (Hamer et al., 2012). However, there exists a weak association of insulin resistance and depression (Adriaanse et al., 2006; Platt et al., 2013; Shen and Bergquist-Beringer, 2013). High fat diet intake impairs the hypothalamic insulin receptor signaling (De Souza et al., 2005; Kim and Feldman, 2012) and reduced hypothalamic insulin signaling promotes weight gain and negative emotional states (Gustafson et al., 1999; Koponen et al., 2008; Akbaraly et al., 2009; Almeida et al., 2009; Benoit et al., 2009; Kleinridders et al., 2009;

Pulkki-Raback et al., 2009; Platt et al., 2013). Intranasal insulin ameliorates self-reported mood, reduce cortisol levels, and visceral obesity (Benedict et al., 2004; Chapman et al., 2013). Further treating patients with major depressive disorder and abdominal obesity, the insulin-sensitizing drug pioglitazone shows reduced sign of depression, anxiety, and reduced insulin resistance (Kemp et al., 2012).

In rodents, reduced insulin receptor signaling impacts mood when placed on a long-term 30%kcal fat diet that shows anxiolytic effects (Marks et al., 2009). Similarly, rosiglitazone administered to normal chow-fed mice and rats show an antidepressant action in behavioral despair tests (Eissa Ahmed et al., 2009; Ryan et al., 2012). Antisense RNA targeting the insulin receptor in rats results in increased depression-like behavior and anxiety-like behavior (Grillo et al., 2011). By and large, these results suggest that insulin signaling is involved in mood. However, further studies are required to determine whether intranasal insulin has antidepressant effects in depressed individuals and, if so, whether this action is maintained in obesity.

To summarize, food intake is regulated by the peripheral and central system that are engaged in a bi-directional manner. Peripheral signals mostly modulate satiety and indicate adiposity signal to the brain. Ghrelin is the only peripheral hormone that induces hunger but interestingly it is also involved in mood and hedonic aspects of food intake. There are several brain regions involved in food intake that overlaps brain areas involved in drugs of abuse and reward. Overlapping brain regions of reward, mood, and food intake suggests that molecular changes in these regions may provide further insights in to distinct and overlapping pathways that could aid in understanding clinical treatments of comorbidity of mood disorder, overeating, and obesity.

EPIGENETICS, MOOD, AND EATING DISORDER

Interaction of genes and environment has been associated with mood disorders, see review Archer et al. (2013), and eating disorders, see review Pjetri et al. (2012). Exposure to highly palatable foods rich in fat and carbohydrate induces craving. In an obesogenic environment, repetitive exposures to highly palatable food options increase the likelihood of food addiction, overeating, and obesity. There appears to be a complex interaction between genetics and environmental factors such as nutrition with neuropsychiatric, neurodevelopmental, and neurodegenerative disorders. Individual variability in numerous protein coding and non-coding regions in the genome could be related to eating disorders and affective disorders. Epigenetics mechanisms of DNA methylation, RNA editing, post-translational modification of histones, and non-coding RNAs regulate gene regulation without changing DNA sequence in response to changes in internal and external environmental variables. Epigenetics in the context of eating disorders is interesting as it has the potential to answer numerous questions including potential risk factors such as maternal nutrition and stress that alter the risk of eating disorders in the offspring. Unknown questions like how epigenetic modification responds to acute changes like malnutrition or exposure to highly palatable food needs to be answered. Furthermore, epigenetics in learning and memory could also play a critical role in development and maintenance of eating disorders. RNA editing of the $5HT_{2C}R$ has been implicated in affective disorder, stress, maternal separation, Prader Willi Syndrome, hyperphagia, and obesity (Iwamoto and Kato, 2003; Englander et al., 2005; Iwamoto et al., 2005; Bhansali et al., 2007; Kawahara et al., 2008; Morabito et al., 2010; Singh et al., 2011; Schellekens et al., 2012a, 2013b,c). RNA editing of the $5HT_{2C}R$ alters many facets of serotonin signaling *via* 24 different receptor isoforms. These edited $5HT_{2C}R$ isoforms are in a distinct ratio in different brain regions suggests an important role in linking mood, food intake and obesity *via* the $5HT_{2C}R$. Therefore, future research in defining the role of different isoforms in different brain regions is much needed to understand the regulation of RNA editing and mood disorder by the serotonergic system.

CONCLUSION

More than a third of adults and 17% of children and teenagers in the United States are obese (Ogden et al., 2014). Obesity is the second-leading cause of preventable death in the U.S. contributing to 300,000 deaths each year. In addition, the health care burden in obesity-related diseases in the U.S. could reach at staggering $861–957 billion by 2030 (Go et al., 2013a,b, 2014). This article points to biological factors engaging both central and peripheral system in a bi-directional manner linking food intake, mood, and obesity. Food intake is complex due to influence of several factors. The influence of food choice includes biological determinants of hunger, appetite, and taste. Besides these, other factors of cost, income, and availability also influence food choice. Other determinants of social and psychological factors of mood, stress, and emotion also play a critical role in food choice. Many people find it hard to stop eating a particular food even though they are not hungry. Such behaviors activate the brain reward center and alter the brain structure. Willpower has been speculated in the past to control overeating. Through neurobiological data, presence of food cravings, over eating, and tolerance support an addiction-like model by numerous signals that are involved in engaging both the central and peripheral nervous system in a bi-directional manner to regulate food intake. Genes, environment, various emotions also influence food intake, and mood states that trigger eating of palatable foods for comfort in negative emotional states. This repetitive eating of comfort foods, rich in carbohydrate, high-fats and sugar, leads to obesity. Obesity in turn regulates mood due to metabolic disturbances. Metabolic disturbances further alter brain-signaling systems leading to a bi-directional vicious cycle of mood, food, and obesity (**Figure 1**). Furthermore a complex regulation of mood and eating disorders are implied from emerging studies of epigenetics in mood and eating disorders.

FUTURE DIRECTIONS

It is recognized that animal and human findings do not entirely overlap, but animal studies have provided the most compelling neurobiological findings of addictive nature of food, overeating, food addiction, and obesity. In the future, using molecular studies toward an effort to understand the environment of plentiful food leading to obesity rather than food restriction in animal models will provide a valuable insight into the molecular mechanism of overeating and food addiction. Further, using animal models

and molecular studies in the area of withdrawal induction model in highly palatable diet are needed. Understanding how brain regions are altered with various nutrients, in depression, anxiety state may elucidate a common overlapping brain region in co-morbidities of affective and eating disorders. Epigenetic progress in relation to eating disorder has been slow. Molecular pathways of regulated non-coding RNAs in gene regulation involved in affective disorders and overeating may provide novel pathways involved in the pathogenesis. Epigenetic regulation of primary brain signaling and factors governing their metabolism needs further investigation where animal studies are likely to guide psychiatric analysis of epigenetic modification. Furthermore, next generation sequencing can be useful in finding novel long and small non-coding RNAs, alternative spliced RNAs, expression levels of coding RNAs, and RNA editing changes in the clinical treatment responders vs. non-treatment responders. It is anticipated these future studies will aid in the development of more targeted and effective therapies for preventing and treating comorbidities of mood disorder and obesity.

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