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The contribution of brain reward circuits to the obesity epidemic

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Abstract

One of the defining characteristics of the research of Ann E. Kelley was her recognition that the neuroscience underlying basic learning and motivation processes also shed significant light upon mechanisms underlying drug addiction and maladaptive eating patterns. In this review, we examine the parallels that exist in the neural pathways that process both food and drug reward, as determined by recent studies in animal models and human neuroimaging experiments. We discuss contemporary research that suggests that hyperphagia leading to obesity is associated with substantial neurochemical changes in the brain. These findings verify the relevance of reward pathways for promoting consumption of palatable, calorically dense foods, and lead to the important question of whether changes in reward circuitry in response to intake of such foods serve a causal role in the development and maintenance of some cases of obesity. Finally, we discuss the potential value for future studies at the intersection of the obesity epidemic and the neuroscience of motivation, as well as the potential concerns that arise from viewing excessive food intake as an “addiction”. We suggest that it might be more useful to focus on overeating that results in frank obesity, and multiple health, interpersonal, and occupational negative consequences as a form of food “abuse”.

Keywords

Obesity; feeding; reward; reinforcement; mesolimbic dopamine system; opioids; food addiction; drug addiction; food abuse

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1. Introduction

One of the most alarming public health threats during the past 50 years is the increased prevalence of obesity. According to reports from the Centers for Disease Control, during the past three decades the average prevalence of obesity in the US adult population has risen from below 20% to 35.7% (CDC, 2012). During the same period, childhood obesity has tripled to a rate of 17%. Currently, more than 1/3 of all children and adolescents are overweight or obese. This high prevalence appears to have plateaued in the United States (Flegal et al., 2012; Ogden et al., 2012), and continues to be a major public health concern: The collective medical costs of obesity within the United States were estimated at $147 billion in 2008 (Finkelstein et al., 2009), and continue to increase with the rising cost of health care. Obesity has become a global phenomenon; the World Health Organization estimates that obesity is responsible for up to 8% of health costs in Europe and over 10% of deaths (WHO, 2012).

Obesity is a multifaceted problem, and its rapid increase in societies such as the U.S. is likely to have been brought about by several causes, both physiological and environmental. There has been a substantial change in the food environment over the past half century. In developed nations, the availability of palatable foods that are high in sugar, fat, and calories has transformed the modern food environment into one of abundance. Until the development of modern agricultural practices, food resources have been historically scarce, and thus human physiology evolved in an environment in which significant resources were required to forage for and consume sufficient calories. Physical activity also declined during this period, contributing to obesity. Across vertebrate species, central nervous system control of energy homeostasis includes behavioral regulation by hypothalamic neural circuits that monitor energy balance based upon peripheral endocrine and metabolic signals, and that serve to motivate us to seek food when energy resources are depleted. A subset of this circuitry, including that connected with the mesolimbic dopamine pathway, processes the hedonic and rewarding aspects of food and can promote the predisposition to overeat when presented with palatable and energy dense food sources. Food serves as a strong reinforcer, whether evaluated in controlled behavioral paradigms in the laboratory, or in naturalistic or societal circumstances.

The reinforcing attributes of drugs have always been, either explicitly or implicitly, linked to the reinforcement circuitry that serves to shape and select behavior based upon more natural (or physiologically relevant) rewards such as food, water, and sex. The early use of brain stimulation reward techniques and agents of abuse such as amphetamine in research both targeted and aided understanding of the neural pathways and mechanisms involved in positive reinforcement, broadly defined (e.g., Olds et al., 1971; Phillips and Fibiger, 1973). Subsequent research, including that from the laboratory of Ann E. Kelley, demonstrated that the motivational circuitry that drugs of abuse act upon serves important and distinct roles in regulating the learning and motivation underlying natural reinforcement, particularly food. In two memorable reviews, Dr. Kelley emphasized the insight that basic neuroscience research into the mechanisms of reward (Kelley and Berridge, 2002) and learning and memory (Kelley, 2004) provided in terms of understanding the processes and neural substrates that regulate adaptive behavior, and which are often driven in maladaptive ways by exposure to drugs of abuse and to the current food environment. Her scientific approach of examining the neural pathways, neurotransmitters, and molecular processes underlying learning and food motivation (reviewed elsewhere in this issue; see Andrzejewski et al., Baldo et al.) anticipated the work of many contemporary researchers interested in food and drug motivation and the intersection between the two topics.

Recently, it has been suggested that excess intake of palatable foods may be a problem akin to that of drug addiction. Although overeating is not a psychiatric disorder, like anorexia nervosa or bulimia nervosa, it represents consistently elevated non-homeostatic feeding. The apparent parallels that might be drawn between drug and food intake as "addictive" behaviors may lie, to some extent, in the overlapping neural circuitry that is engaged by both types of motivated behaviors. However, the fact that drugs of abuse activate reinforcement circuitry involved in feeding behavior is not sufficient evidence to deduce that excessive intake of high-calorie palatable food is therefore akin to a "food addiction". For such an argument to be made, there must first be agreement upon what qualifies as an addiction, and evidence must be provided that the "addictive" intake of food parallels the behavioral patterns and physiological processes of other addictive behaviors.

The main goal of this review will be to provide a brief overview of recent research demonstrating the overlap between brain reward/reinforcement circuits as they relate to food- and drug-motivated behavior. Evidence from studies with both humans and animals will be examined. First, we will discuss the interplay between metabolic signals that monitor energy balance and the motivational circuitry that regulates the rewarding value of food and drug reinforcement. We will then discuss the ways in which food and drugs of abuse activate similar neural pathways and affect motivated behavior, how reward/reinforcement circuitry is changed by drug use or the consumption of energy-dense foods, as well as how the brain responds differently to food or drugs of abuse. Finally, we will discuss the implications from this literature review regarding the heuristic value of invoking an addiction process as it relates to overeating and obesity, including the potential insights from viewing overeating patterns as an "addiction", as well as the challenges/problems/social concerns that arise from such a characterization. We suggest instead that it might be more useful to consider overeating that results in multiple negative health, interpersonal, and occupational consequences as "food abuse".

2. From Motivation to Action: Metabolic influences on reward circuits

That the mesolimbic dopaminergic pathway is involved in the reinforcing and addictive properties of drugs of abuse has been well documented ever since Roberts, Corcoran, and Fibiger (1977) reported that catecholaminergic lesions of the nucleus accumbens reduced self-administration of cocaine in a rodent model. As reviewed below, both the human and rodent literature is replete with examples of how the dopaminergic and opioid systems within the substantia nigra, ventral tegmentum, and their projections to the striatum are affected by drugs of abuse. Natural reinforcers also affect behavior through these same pathways (e.g., Kelley et al., 2005a; Mogenson et al, 1980; Figlewicz et al., 2009). Despite this understanding, it is only recently that food, and hyperpalatable foods in particular, have been posited to be potentially "addictive". This may in part be due to the fact that many early researchers interested in obesity focused upon the dysregulation of metabolic processes that result from gaining excess weight. Obesity is a complex metabolic syndrome that is characterized by energy dyshomeostasis and involves not only the brain, but also basic biochemical reactions within liver, fat, and muscle tissue. Early lines of research evolved, from the 1970s forward, that considered energy homeostasis—the regulation of feeding and regulation of body weight metabolism—as a separate CNS-regulated function from appetitive motivation. However, there has always been evidence that such a dichotomy between metabolic regulation and motivated behavior might be overly simplistic. In 1962, Margules and Olds observed that both feeding and self-stimulation could be induced by electrical stimulation of identical sites within the lateral hypothalamus (LH); self-stimulation is a paradigm by which an animal presses a lever and receives a small, direct electrical stimulation of the site into which a probe is implanted. The LH was identified as a major target for self-stimulation activity and it was concluded that it was part of intrinsic 'reward

circuitry' within the brain. Subsequently, Hoebel (1976) reported that this self-stimulation activity could be enhanced by food deprivation. The extensive research of Marilyn Carroll and colleagues from the 1980s onward (e.g., Carroll and Meisch, 1984), in both animal models and humans, made it clear that the 'addictiveness' of rewarding substances such as drugs of abuse could be modified by metabolic states, including how and whether the subjects were fed.

How is the reward circuitry 'informed' of an animal's nutritional status? Research has revealed that the CNS circuitry, transmitters, and the peripheral signals that inform the CNS of metabolic and nutritional status all impact directly and indirectly on the key substrates of motivation, particularly the mesolimbic dopamine neurons and their projections from the ventral tegmental area (VTA) to the nucleus accumbens (Figlewicz and Sipols, 2010). Teleologically, it makes sense that motivation to seek food would be greater in circumstances of food deprivation, and conversely, food would be less 'rewarding' under circumstances of repletion. This phenomenon, which resides in CNS crosstalk between these circuitries and endocrine/neuroendocrine signals, would of course be dramatically manifest in subjects taking drugs that directly and strongly activate mesolimbic circuitry. Thus, ingestion of calorically dense palatable foods may override the circuitry of energy homeostasis; and they may also override homeostatic restraints on dopaminergic and other components of the reward circuitry.

The key endocrine signals that reflect the acute and chronic energy status of an animal have direct effects on dopaminergic function. For example, the hormones insulin and leptin, which correlate with caloric repletion and energy stores in adipose tissue, not only affect hypothalamic regulation of energy homeostasis but also reduce dopamine release, facilitate its synaptic re-uptake, and can decrease dopamine neuronal excitability (Figlewicz and Benoit, 2009; Mebel et. al, 2012). In contrast, the gut hormone ghrelin, which is elevated in association with caloric deprivation, enhances dopaminergic function (Overduin et al., 2012; Perello and Zigman, 2012). All three of these hormones have predictable effects in animal models on 'reward tasks' in which solid or liquid foods serve as the reward. Insulin and leptin decrease food reward, and ghrelin enhances it. Specifically, ghrelin enhances place preference conditioning and the self-administration of rewarding foods (Overduin et al., 2012; Perello and Zigman, 2012). Both insulin and leptin decrease rewarding self-stimulation behavior; leptin appears effective in animals that are food-restricted, and insulin likewise is effective in both food-restricted and diabetic (hence, insulinopenic) animals, when either are administered directly into the cerebral ventricles. Studies in the 2000s demonstrated that insulin and leptin can decrease food reward in rats assessed by two different tasks: conditioning of a place preference for a food treat (Figlewicz et al., 2004) and self-administration of sucrose solutions (Figlewicz et al., 2006). In the self-administration study, insulin and leptin were ineffective in animals fed a high fat diet, compared with low-fat chow (Figlewicz et al., 2006). This observation of an effect of a high fat background diet is a clue that qualitative changes in the macronutrient composition of the background diet can impact food reward: In addition to the blockade of insulin and leptin effects, the high fat diet-fed animals showed an increase in sucrose self-administration relative to (low fat) chow-fed controls. Additional animal studies have demonstrated that higher fat diets, or longer diet exposures, can result in suppression of dopamine synthesis, release or turnover, and reductions in motivated behaviors, not limited to motivation for food (e.g., Davis et al., 2008). Although the underlying mechanisms for this phenomenon have not been completely elucidated, the involvement of intrinsic CNS circuitry and transmitters has been identified in food reward behavior and function and suggests, indeed, multiple links between feeding, nutritional status, and reward circuitry. Recent research has demonstrated that multiple medial hypothalamic nuclei (the arcuate [ARC], paraventricular [PVN], and ventromedial [VMN]) are active at the onset of sucrose self-administration

(Figlewicz et al., 2011). Further, the ability of the peripheral satiety signal insulin to decrease sucrose self-administration is localized to the ARC (Figlewicz et al., 2008). Recent research from several labs has demonstrated that the ARC-based orexigenic neuropeptide, agouti-related protein (AGRP), can stimulate motivation for food, assessed in multiple paradigms, in the mouse and rat (Aponte et al., 2011; Krashes et al., 2011, Figlewicz et al., in press 2012). Since ARC AGRP neurons project to the PVN, which in turn relays to the LH, this represents a major hypothalamic transmitter system that can enhance motivated, "addictive" behavior.

As noted, the lateral hypothalamus (LH) is a key site within reward circuitry. The effect of food restriction or fasting on increased self-stimulation activity can be reversed by direct CNS administration of the satiety hormones insulin and leptin. Although identification of the precise mechanisms for these effects is not yet clear, it should be noted that within the LH are, first, projections to the VTA dopaminergic neurons, and, second, populations of orexin neurons. Orexin is known to stimulate feeding, and also arousal, and functional anatomy has determined that the LH orexin neurons are not only critical for arousal but are important modulators of motivational function and circuitry. There are reports of orexin involvement in feeding of palatable foods and reward-based paradigms (food self-administration and sucrose seeking). These effects of orexin appear to be substantially influenced by the paradigm used and the nutritional state of the animal (Mahler et al., 2012).

Thus, homeostasis-regulating factors co-modulate motivational circuitry and function, both directly and indirectly (for a summary of the relevant neural pathways involved, see Figure 1). These findings have, for the most part, been elucidated in non-obese rodents, although numerous studies have evaluated rodents after consumption of a high fat diet. One notable study accomplished with humans found that administration of leptin to two obese human patients with congenital leptin deficiency modulated neural striatal response to palatable food images (fMRI measurement), providing direct support for a role of basal leptin in blunting reward circuitry (Farooqi et al, 2007). This finding was extended by evidence that blocking the expression of leptin receptors in the VTA (the site of dopaminergic cell bodies) resulted in increased sucrose self-administration in rodents (Davis et al., 2011b). The advantage of carrying out such studies in rodents is that the time course and other stimulus aspects of high fat diet exposure, during pre-obesity or at established obesity, allow for the study of development or adaptation to diet effects, ultimately at the level of the mesolimbic dopaminergic circuitry. For the purpose of this article, the important point is that high fat diet and diet-induced obesity are known to modulate efficacy of peripheral endocrine signals, as well as hypothalamic signaling systems (Figlewicz and Benoit, 2009). Animal studies allow us to find out about initiating events in this process. The use of functional CNS imaging approaches in humans also provides a powerful tool for determining how the human brain changes as a result of diet experience and obesity. Given that diet and obesity can have dramatic effects on homeostatic circuitry, it is to be expected that diet and obesity likewise have substantial effects on the functioning of motivational circuitry, both when it comes to patterns of feeding or drug intake.

3. Food and Drug Effects within Reward Circuitry

3.1. Effects of Drug Use and Palatable Food Intake on Mesolimbic Circuitry

In both animal and human models, several parallels have been shown between the effects of use of drugs of abuse and palatable foods intake on mesolimbic circuitry. First, acute administration of abused drugs causes activation of the VTA, nucleus accumbens, and other striatal regions according to studies with humans and other animals (Volkow et al., 2002; Koob and Bloom, 1988). Consumption of palatable food likewise causes increased activation in the midbrain, insula, dorsal striatum, subcallosal cingulate, and prefrontal

cortex in humans and these responses decrease as a function of satiety and reduced pleasantness of the foods consumed (Small et al., 2001; Kringelbach et al., 2003).

Second, humans with, versus without, various substance use disorders show greater activation of reward regions (e.g., amygdala, dorsolateral prefrontal cortex [dlPFC], VTA, prefrontal cortex) and attention regions (anterior cingulate cortex [ACC]) and report greater craving in response to substance use cues (e.g., Due et al., 2002; George et al., 2001; Maas et al., 1998; Myrick et al., 2004; Tapert et al., 2003). Craving in response to cues correlates with the magnitude of dorsal striatum dopamine release (the latter being inferred from the measure of ^{11}C-raclopride uptake; Volkow et al., 2006) and with activation in the amygdala, dlPFC, ACC, nucleus accumbens, and orbitofrontal cortex (OFC; Childress et al., 1999; Maas et al., 1998; Myrick et al., 2004). In a similar fashion, obese versus lean humans show greater activation of regions that play a role in encoding the reward value of stimuli, including the striatum, amygdala, orbitofrontal cortex [OFC], and mid-insula; in attention regions (ventral lateral prefrontal cortex [vlPFC]); and in somatosensory regions, in response to high-fat/high-sugar food images relative to control images (e.g., Bruce et al. 2010; Martin et al., 2009; Nummenmaa et al., 2012; Rothemund et al., 2007; Stoeckel et al., 2008; Stice et al., 2010). These findings in humans closely parallel regions that are activated by cues associated with drugs and palatable food in rats (Kelley et al., 2005b). There is also some evidence that obese versus lean humans show reduced activation in inhibitory control regions in response to palatable food images versus control images (e.g., Nummenmaa et al., 2012; Stice et al., 2008). Obese versus lean humans likewise show elevated activation in reward valuation and attention regions in response to cues that signal impending high-fat/high-sugar food receipt versus control cues that signal impending receipt of tasteless solution (Ng et al., 2011; Stice et al., 2008). A meta-analytic review found considerable overlap in the reward valuation regions activated in response to palatable food images in humans and brain reward regions activated by drug cues among drug dependent humans (Tang et al., 2012).

These data confirm that drugs of abuse and palatable foods, as well as the cues that predict drug and food reward, activate similar regions that have been implicated in reward and reward learning. The circuits involved include the mesolimbic dopamine system, which projects from the VTA to the medial ventral striatum. The following sections emphasize the overlapping nature of the effects of food and drug reward on dopaminergic and opioid signaling within this critical reward pathway.

3.2. Effects of Drug Use and Palatable Food Intake on Dopamine Signaling

In addition to the parallels observed across food and drug intake on neuronal activity, there are also striking parallels in terms of the effects of drugs of abuse and palatable food intake on dopamine signaling. First, intake of commonly abused drugs causes dopamine release in the striatum and associated mesolimbic regions (Dayas et al., 2007; Di Chiara, 2002; Heinz et al., 2004; Kalivas and O'Brian, 2008; Volkow et al., 2002, 2008). Palatable food intake likewise causes dopamine release in the nucleus accumbens in animals (Bassareo and Di Chiara, 1999). Consumption of high-fat and high-sugar palatable food is similarly associated with dopamine release in the dorsal striatum and the magnitude of release correlates with ratings of meal pleasantness in humans (Small et al., 2003). Second, dopamine is released in the dorsal striatum of the rat during drug seeking behavior (Ito et al., 2002). Similarly, responding to earn palatable food is also associated with increased phasic dopamine signaling (Schultz et al., 1993). Third, exposure to cues that signal the availability of the administration of commonly abused drugs, such as tones or a light, cause phasic dopamine signaling after a period of conditioning in rodents (Schultz et al., 1993). However, visual and olfactory exposure to palatable food has not been shown to change availability of D2 receptors in the striatum in two separate studies (Volkow et al., 2002; Wang et al., 2011),

suggesting that food cue exposure does not produce detectable effects on extracellular dopamine in the striatum, at least in human studies with very small samples.

3.3. The Role of Opioids in Food Reward

Research has revealed that opioid peptides and their receptors play a role in the regulation of food intake, and that the mu opioid system appears to be particularly involved in mediating food reward (see Bodnar, 2004; Gosnell and Levine, 1996, 2009; Kelley et al., 2002; Le Merrer et al., 2009 for reviews). Evidence for this involvement includes findings that opioid agonists and antagonists generally are more effective in increasing and decreasing, respectively, the intake of palatable foods or fluids than that of standard chow or water. Human studies suggest that opioid antagonists generally decrease ratings of taste pleasantness without affecting taste perception (Yeomans and Gray, 2002). In animal models, the mu opioid agonist DAMGO will stimulate food intake when microinjected into several brain sites, including the nucleus of the solitary tract, parabrachial nucleus, various nuclei within the hypothalamus (notably the paraventricular nucleus), the amygdala (notably the central nucleus), nucleus accumbens, and VTA (see Bodnar, 2004; Gosnell and Levine, 1996; Le Merrer et al., 2009). Finally, several studies indicate differences in brain opioid peptides and receptors in rats exposed to highly palatable food (when compared to rats fed chow; Alsio et al., 2010; Barnes et al., 2003; Colantuoni et al., 2001; Kelley et al., 2003; Olszewski et al, 2009; Smith et al., 2002).

Generally, the ingestion of highly palatable food is associated with increased mu opioid receptor gene expression in multiple brain areas, and changes (increases or decreases) in opioid peptide precursor mRNA in many of the same areas. It has been suggested that increases in mu opioid receptors may reflect reduced peptide release (Smith et al., 2002) and that reduced enkephalin expression may be a compensatory down-regulation (Kelley et al., 2003). There is also some evidence of differences in opioid peptide or receptor gene expression that can be attributed to preferences for a given diet rather than to actual consumption of that diet. For example, Chang et al. (2010) selected rats with a high or low preference for a high fat diet based on intake measures over a 5-day period. After a 14-day period of maintenance only on rat chow, there was increased proenkephalin expression in the PVN, nucleus accumbens and the central nucleus of the amygdala in the rats with a high preference for the high fat diet. The authors suggest that this effect represents an inherent characteristic of the fat-preferring rats, as opposed to an effect due to intake of the diet. Similarly, Osborne-Mendel rats, known to be susceptible to diet-induced obesity, when compared to rats of a strain known to be resistant to diet-induced obesity (S5B/Pl) showed an increased level of mu opioid receptor mRNA in the hypothalamus (Barnes et al., 2006).

The complex role of opioids in the control of feeding has great significance for the understanding of eating disorders and obesity. Opioid antagonists, particularly naloxone and naltrexone, have been shown to reduce food intake in normal-weight and obese participants in short-term trials (Yeomans and Gray, 2002; de Zwaan and Mitchell, 1992). Unfortunately, these antagonists have adverse side effects (e.g., nausea and elevation of liver function tests) that have precluded their widespread use in the treatment of obesity and eating disorders; it was suggested that newer opioid antagonists may offer a more favorable risk/benefit ratio (de Zwaan and Mitchell, 1992). One compound that shows promise in this regard is GSK1521498, a mu opioid receptor inverse agonist. This drug, which is reported to have a favorable safety and tolerability profile, has been shown to reduce hedonic ratings of high-sugar and high-fat dairy products, to reduce caloric intake of snack foods, an to reduce fMRI-assessed activation of the amygdala induced by palatable food (Nathan et al., 2012; Rabiner et al., 2011). Finally, recent genetic analyses indicate that variants in the human mu opioid receptor gene (OPRM1) are associated with variability in preference for sweet and fatty foods. Humans with the G/G genotype of the functional A118G marker of this gene

reported higher preferences for foods with high fat and/or sugar than humans with the G/A and A/A genotypes (Davis et al., 2011a). It was also observed that, in obese humans, a subgroup with binge eating disorder had an increased frequency of the G allele at the A118G marker of the mu opioid receptor gene compared to obese subjects without binge eating disorder (Davis et al., 2009). Thus, human genetic analyses support the results of pharmacological studies that indicate a role for opioids in mediating food palatability and reward, and suggest that variations in mu opioid receptors are associated with disordered eating. It addition to the role of opioids in mediating food reward, they may also facilitate eating by attenuating satiety and/or aversion. This effect may be mediated via the inhibition of a central oxytocin (OT) system. OT reduces food intake, and OT neuronal activation is greater toward the end of feeding than at the initiation of feeding (Sabatier et al., 2006; Olszewski and Levine, 2007). The opioid agonist butorphanol reduced this OT activation (Olszewski and Levine, 2007). In what may be a related action, OT is thought to contribute to the formation of a conditioned taste aversion, and pretreatment with various opioid receptor ligands inhibited activity of OT neurons precipitated by lithium chloride in a conditioned taste aversion (CTA) procedure (Olszewski et al., 2010; Olszewski et al., 2000). This opioid-induced decrease in OT neuronal activity was associated with a diminished aversive responsiveness in rats. In line with a proposed relation between opioid-driven feeding reward and the OT system, long-term exposure to a high-sugar diet caused a down-regulation of OT neuronal responsiveness to a food load, an effect that may contribute to elevated intakes of rewarding tastants (Mitra et al., 2010). This idea is supported by a report that OT knockout mice over-consume carbohydrate solutions, but not lipid emulsions (Sclafani et al., 2007).

3.4. Positive Relations Between Food/Taste Preferences and Drugs of Abuse

Behavioral studies with rats indicate that relative propensity to consume (or self-administer) palatable foods is often positively related to drug self-administration. Rats selectively bred for high or low sweet preferences, or selected on the basis of their saccharin or sucrose intake, show corresponding high or low intakes of alcohol, cocaine, amphetamine and morphine (Carroll et al., 2002; DeSousa et al., 2000; Gosnell et al., 1995; Kampov-Polevoy et al., 1999). Sucrose intake also enhances the rewarding and analgesic effects of morphine (D'Anci et al. 1997; Lett 1989), increases behavioral sensitization to the DR2 agonist quinpirole, cocaine, and amphetamine (Foley et al., 2006; Gosnell, 2005; Avena and Hoebel, 2003), and enhances the discriminative stimulus effects of nalbuphine, a mu opioid receptor agonist (Jewett et al., 2005). As noted, intake of sucrose and other highly palatable foods causes an up-regulation of mu opioid receptors; this change may underlie many of the aforementioned behavioral effects.

In humans, an increased preference for sweet solutions has been observed in subjects with alcoholism and/or a family history of alcoholism (Kampov-Polevoy et al, 1997, 2003; Krahn et al, 2006), although this relationship was not observed in other studies (Kranzler et al., 2001; Scinska et al., 2001). Interestingly, a high preference for sweet tastes has been suggested as a possible predictor of non-abstinence in alcohol-dependent subjects (Krahn et al., 2006) and as a possible predictor of efficacy of naltrexone in reducing relapses to heavy drinking (Laaksonen et al., 2011). Opioid dependent subjects also report increases in craving, intake and/or preferences for sweet foods (Morabia et al., 1989; Willenbring et al., 1989; Weiss, 1982; Zador et al., 1996).

3.5. Relation of Reward Region Responsivity to Future Increases in Drug Use and Weight Gain

Emerging evidence suggests parallels in individual differences in responsivity of reward regions to future onset of substance use and initial unhealthy weight gain. A large

prospective study of 162 adolescents found that elevated responsivity in the caudate and putamen to monetary reward predicted initial onset of substance use among initially non-using teens (Stice, Yokum, & Burger, in press). These results dovetail with the well-replicated finding that greater responsivity of reward and attention regions to drug use cues in humans is also associated with increased risk for subsequent relapse (Gruser et al., 2004; Janes et al., 2010; Kosten et al., 2006; Paulus et al., 2005). Although elevated reward region responsivity did not predict initial unhealthy weight gain among healthy weight adolescents in the study by Stice et al., (in press), those data extend prior evidence that found that greater responsivity of a region implicated in reward valuation (orbitofrontal cortex) to a cue signaling impending presentation of palatable food images predicted future weight gain (Yokum et al., 2011).

3.6. Effects of Habitual Drug Use and Palatable Food Intake on Dopamine Circuitry and Signaling

There is also evidence that habitual drug use and palatable food intake are associated with similar neural plasticity of reward circuitry. Animal experiments show that regular substance use reduces striatal D2 receptors (Nader et al., 2006; Porrino et al., 2004) and sensitivity of reward circuitry (Ahmed et al., 2002; Kenny et al., 2006). Data also indicate that habitual psychostimulant and opiate use causes increased DR1 binding, decreased DR2 receptor sensitivity, increased mu-opioid receptor binding, decreased basal dopamine transmission, and enhanced accumbens dopamine response (Imperato et al., 1996; Unterwald et al., 2001; Vanderschuren and Kalivas, 2000). Consistent with this, adults with, versus without, alcohol, cocaine, heroin, or methamphetamine dependence show reduced striatal D2 receptor availability and sensitivity (Volkow et al., 1996, 1997, 2001; Wang et al., 1997). Further, human cocaine abusers show blunted dopamine release in response to stimulant drugs relative to controls (Martinez et al., 2007; Volkow et al., 2005) and tolerance to the euphoric effects of cocaine (O'Brian et al., 2006).

With regard to obesity, three human studies found that obese versus lean individuals showed reduced D2 binding potential in the striatum (de Weijer et al., 2011; Wang et al., 2001; Volkow et al., 2008; though the obese and healthy weight participants were not systematically matched on hours since last caloric intake in the former study and there was some overlap in the participants in the latter two studies), suggesting reduced D2 receptor availability, an effect that also emerged in obese versus lean rats (Thanos et al., 2008). Interestingly, Thanos et al. (2008) also found that as the rats gained weight, they showed a further reduction in D2 binding potential, suggesting that overeating contributes to the reduction in D2 receptor availability. Colantuoni et al. (2001) found that regular glucose intake on a limited-access schedule increases DR1 binding in the striatum and nucleus accumbens and decreases DR2 binding in the striatum and nucleus accumbens, in addition to other CNS alterations in the rat. Interestingly, intake of palatable food resulted in down regulation of striatal D1 and D2 receptors in rats relative to isocaloric intake of low-fat/sugar chow (Alsio et al., 2010), implying that it is intake of palatable energy dense foods versus a positive energy balance that causes plasticity of reward circuitry. These results prompted a study comparing reward region responsivity of lean adolescents (n=152) to their reported intake of ice cream over the past 2-weeks (Burger and Stice, 2012). Ice cream intake was examined because it is particularly high in fat and sugar and was the primary source of these nutrients in the milkshake used in that fMRI paradigm. Ice cream intake was inversely related to activation in the striatum (bilateral putamen: right $r = -.31$; left $r = -.30$; caudate: $r = -.28$) and insula ($r = -.35$) in response to milkshake receipt (> tasteless receipt). Yet, total kcal intake over the past 2-weeks did not correlate with dorsal striatum or insula activation in response to milkshake receipt, suggesting that it is intake of energy dense food, rather than overall caloric intake that is related to reward circuitry activation. These findings are

consistent with the observations of endocrine regulation of sucrose motivation described above--specifically, that effects of insulin and leptin occur at doses that are subthreshold for decreasing overall caloric intake and body weight--and emphasizes the pre-eminent sensitivity of reward circuitry and its plasticity with regards to food rewards.

4. Reward Circuits, “Food Addiction”, and Obesity

The above sections have outlined the potential importance of mesolimbic circuitry in regulating food intake, and have examined the parallels between food and drug reward as they relate to the dopamine and opioid systems within reward pathways. Several themes emerge from this review. First, consistent with the pioneering work of Ann Kelley, the overlap in the motivational systems engaged by drugs and food rewards is substantial. Second, to the extent that it has been examined, dietary manipulations and exposure to palatable diets often result in changes in opioid peptides, mu-opioid receptor availability, and D2 receptor expression that parallel those seen after repeated exposure to drugs of abuse. Third, there is evidence to suggest that, in both humans and animal models, individuals that have higher behavioral or physiological responses to palatable foods (due to either experience or genetic variation) are also more likely to have subsequent increases in body weight, and may be more sensitive to the rewarding effects of drugs of abuse.

It should be noted that there is also evidence demonstrating differential signaling of reward types within the brain: even within the nucleus accumbens, individual neurons tend to alter their firing rate in response to tasks that signal natural (water or food) reward or drug (cocaine) reward, but relatively few neurons encode both (Carelli et al, 2000). Further, it has been shown that inactivation or deep brain stimulation of the rat subthalamic nucleus, a separate node within basal ganglia motivational circuitry, reduces motivation for cocaine while leaving food motivation relatively intact (Baunez et al., 2002, 2005; Pratt et al., 2012; Rouaud et al, 2010, but see Uslaner et al., 2005). Other studies that have examined potential pharmaceutical treatments for reducing drug intake in animal models of self-administration have often used self-administration of food reward as the control condition (e.g., Cunningham et al, 2011; Fletcher et al, 2004). Presumably, the desire for pharmacotherapy of drug addiction is to reduce motivation for drug reward without simultaneously suppressing motivation for natural reinforcement. Thus, accumulating evidence suggests that natural rewards and drug rewards are distinguishable within brain reward circuitry, even though the same brain regions are involved in processing them.

Despite these caveats, the brain pathways involved in flexibly directing our behavior towards rewarding stimuli in the environment are similar, regardless of whether the reinforcement is food or a drug of abuse. But what do these findings suggest in terms of using a heuristic of “food addiction” to describe the elevated intake of calories that leads to obesity? First, it is important to note that many humans who consume energy dense foods do not become obese or show persistent overeating in the face of adverse consequences, just as the majority of humans who try an addictive drug like cocaine do not progress to regular use with negative consequences. Within animal models, only 9% of rats that engage in regular self-administration continue to do so in a manner that results in severe adverse health effects (e.g., the neglect of food intake; Cantin et al., 2010). This is fairly similar to the finding that only 12-16% of the general human population aged 15-54 who try cocaine go on to develop cocaine addiction (Anthony et al., 1994; Degenhardt et al., 2008).

As noted, obesity is a systemic metabolic disorder, whereas “addiction” is behaviorally defined. One difficulty in applying “addiction” to food intake is that the current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) does not define addiction *per se* as a mental disorder. It does define substance *abuse* and *substance*

dependence, and there have been attempts to extrapolate from these drug-centered definitions a framework to apply to food and food intake (for critical evaluations of applying these to human obesity, see Benton, 2010 and Ziauddeen et al., 2012). The most successful attempt to do so to date is a report on rats trained to binge on sugar, and then subjected to behavioral tests that examined individual components of dependence, either in terms of examining the behavioral effects of sucrose abstinence, or by precipitating withdrawal symptoms after systemic injections of an opioid antagonist (Avena et al, 2008; Colantuoni et al. 2002). Although those authors argue that an "addiction-like" (dependence) for sugar can be elicited in animal models, the "addiction" was not paired with an increase in body weight versus control animals, suggesting that the sugar "addiction" does not lead to obesity. Further, when rats were exposed to sweetened diets that are high in fat in a similar paradigm, caloric consumption increased, but there was little evidence of behavioral dependence (Avena et al., 2009; Bocarsly et al., 2011). Thus, even in controlled animal models, it has been difficult to argue food dependence for diets high in both fat and sugar that have been shown to increase caloric consumption and body weight beyond that of normal, chow-fed controls. Within humans, evidence has been equivalently difficult to establish in terms of a food "addiction" as it relates to dependence (Ziauddeen et al., 2012).

It should be noted that most drug users do not meet the criterion for dependence, and nonetheless consume drugs of abuse in ways that are harmful to themselves and society. The argument of food "addiction" might be less contentious if the DSM-IV-TR classification of substance abuse were applied, which focuses on use-related negative consequences on the individual and their family rather than on physiologic dependence on the substance (tolerance and withdrawal). Any one of the DSV-IV-TR criteria might be satisfied within this classification scheme to qualify for substance abuse; two notable criteria are:

> "Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; or neglect of children or household)" P. 199.
>
> and
>
> "Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (for example, arguments with spouse about consequences of intoxication and physical fights)." P. 199.

Given that it has been challenging to provide evidence for the key features of *dependence* as applied to food (tolerance and withdrawal), perhaps a more useful heuristic with regard to the behavioral patterns that lead to overconsumption of food might be to apply the DSM criterion for substance *abuse*. We suggest the following provisional definition of "food abuse": a chronic pattern of overeating that results in not only an obese BMI (>30) but also multiple negative health, emotional, interpersonal, or occupational (school or work) consequences. There are clearly many factors that can lead to unhealthy weight gain, but the commonality is that they result in a protracted positive energy balance. There are numerous health consequences that are often associated with obesity, including type 2 diabetes, heart disease, dyslipidemia, hypertension, and some forms of cancer. Negative emotional consequences of overweight/obesity include low self-worth, feelings of guilt and shame, and significant body image concerns. Interpersonal problems might include recurrent conflict with family members about failure to maintain a healthy weight. One example of an occupational consequence from obesity is being discharged from the military services because of excess weight, an occurrence that affects over 1000 military personnel yearly. Some individuals may overeat and not experience unhealthy weight gain; and some individuals might not experience unhealthy weight gain but would be more appropriately

diagnosed with an eating disorder, such as bulimia nervosa (which involves unhealthy compensatory behaviors, such as vomiting or excessive exercise for weight control) or binge eating disorder (which may not be associated with obesity during the initial phase of this condition). We acknowledge that in addition to overeating, other factors (e.g., genetics) contribute to risk for obesity-related morbidity. However, factors other than excessive alcohol and drug use contribute to negative consequences in substance abuse, such as behavioral control deficits for example, which increase risk for use-related legal problems.

Having stated the potential for viewing certain types of food intake as "abuse", there are two additional important points to be made. First, we acknowledge that numerous factors increase risk for entering the prolonged positive energy balance necessary for obesity, which is beyond the scope of this review. Regardless of how obesity is achieved, the disorder becomes a metabolic one, and the new body weight is defended both metabolically and behaviorally through the actions of peripheral metabolic signaling and its interactions with hypothalamic homeostatic regulation of feeding. This is exemplified, for example, by resistance to the satiety-inducing effects provided by insulin and leptin hormone signaling to the brain, which occurs in both the obese and the aging. Secondly, although "food abuse" may be prevalent according to the above definition, the term "addiction" is fraught with intrinsic meaning for the general public. In the absence of a clear clinical definition, the use of the term "addiction" implies that the individual has little control over his/her behavior, and is compelled to make bad decisions in terms of his/her life circumstances. Until the medical and scientific communities agree to a clear definition of addiction, or provide a more compelling case for "food dependence", it may not be in the best interest of society or obese persons to suggest that obese people of any sort are "addicts". More comment regarding the risks of so characterizing obesity, or feeding patterns that lead to obese outcomes, will be discussed below. First, however, we will provide a brief discussion of some of the advantages that we have gained by viewing palatable food intake as a "disorder of appetitive motivation" (Kelley et al, 2005a) that affects reward circuitry in similar manners as drugs of abuse.

4.1 Lessons applied from drug addiction research

Despite the potential for negative consequences in defining the feeding patterns that lead to obesity as "addiction-like", there have been positive developments that have resulted from the noted behavioral and physiological parallels that exist between feeding (particularly on palatable foods) and the intake of drugs of abuse. During the past 50 years, the drug abuse field has developed and/or refined a substantial number of animal models and behavioral paradigms that have recently been utilized by researchers interested in motivated behavior more broadly. For example, there are numerous labs now examining the food intake equivalents of bingeing on palatable diets when such diets are restricted (as is commonly the case in drug abuse studies; e.g., Corwin et al., 2011). Additionally, models of "craving" that were initially developed in drug intake studies have been adopted to examine craving for sucrose and other palatable foods (e.g., Grimm et al., 2005, 2011). In both animal models and humans, relapse to drug-seeking behavior can be caused by exposure to cues that predict the drug, by stressful life circumstances, or by priming with a single unexpected dose of the drug. Similar reinstatement can be observed in animal models of food-seeking behavior, and such reinstatement paradigms are being used to examine the role of brain reward circuitry in promoting the relapse that is often experienced in humans who are trying to maintain a diet (Floresco et al., 2008; Nair et al., 2009; Pickens et al., 2012; Guy et al., 2011). As food motivation can be argued to have anticipatory "appetitive" components as well as a consummatory feeding component, different behavioral paradigms have been developed that can dissociate the impact of pharmacological treatments on these separable components (see Baldo et al, this issue; Berridge, 2004; Kelley et al., 2005a). Further experiments, utilizing

these and other paradigms, may provide insight into the circumstances and neural mechanisms that contribute to regular overconsumption of food, that may in some cases lead to obesity.

With regards to contemporary human studies, the acknowledgement of the role of basal ganglia circuitry in reward processes that contribute to food intake, particularly in the face of palatable foods, has led to an exciting era of examining the role of this circuitry in the processing of food reward and the cues that predict it. Additionally, many of the recent neuroimaging experiments have utilized similar methodology, in terms of cue and stimulus exposure, as has been previously done within the drug abuse literature. Thus, in both animal and human models, the heuristic of viewing both overconsumption of palatable foods, and drug addiction as "disorders of appetitive motivation" (whether it is classified as an "addiction", or something else) has led to new approaches and insight regarding how reward circuits may contribute to the onset and maintenance of unhealthy feeding habits in the presence of densely caloric food sources.

4.2 Problems with viewing obesity as an "addictive" disorder

Few lay people are likely to recognize obesity and the food intake patterns that may contribute to obesity as distinct phenomena, the former being a metabolic disorder and the other potentially a "food addiction" (and potentially not). Thus, as noted, even if it is established that some foods have abuse potential, it is likely that individuals with obesity may be labeled as "food addicts", when that may or may not be the case. There are some potential dangers to such a characterization. Implying that individuals have a disease or mental illness may result in social stigmatization (and obese individuals already are subject to societal stigmas and biases), a sense of lack of control or choice over their behavior, or excusing behavior on a disease label ("I can't help myself, I'm addicted"). Understanding the limits of research findings in this field is as important as the research findings themselves, and these caveats need to be publicly communicated.

Another caution for the field is that anthropomorphic interpretation of animal studies— and ascribing motives to animals that obviously cannot be validated—should be avoided. A further limitation of animal studies is that issues of control and choice, which play a major role in human feeding from an early age forward, are not and frequently cannot be addressed. Certainly, the complexity of the human environment is not simulated in the majority of animal studies to date, and thus represents a challenge and opportunity for future animal studies. To provide a direct comparison, the after-school U.S. teenager may have choices between sports, playing video games, doing homework, or 'hanging out' and eating snacks. All of these choices may have an equivalent cost value and eating snacks may not necessarily be the default. In animal studies, the animal may have a choice of eating or not eating a palatable food, but has no control over what that food is, has limited behavioral options, and has little or no control over when that food is available.

Moreover, suggesting that foods are "addictive" is likely to lead to questions of "which foods are addictive?" From the standpoint of the obesity epidemic, such questions shift the focus away from promoting healthy diet and exercise habits and onto the avoidance of specific foods. As has been previously suggested (Rogers and Smit, 2000), to label the affinity for a particular type of food (even one that is caloric and highly palatable) as an "addiction" trivializes the serious and disruptive nature of the condition in those suffering from drug dependence or addiction. Very few humans are driven to violent criminal behavior due to a craving for chocolate.

4.3. Final thoughts and future directions

Given that eating food is necessary for survival and that reward circuitry presumably evolved to drive this survival behavior, the criticism of eating activity (even abundant quantities of palatable but unhealthy foods) would seem to be a misplaced societal target. As alluded to above, a more appropriate focus would seem to be the elucidation of why individuals engage in overeating or drug use to the point that neural circuitry is altered in a manner that keeps them engaged in the behavior for extended periods of time. However, a second focus for research, education, and perhaps therapy could be upon nutritional choices and balance with an emphasis not on behavior ("addiction"), but on the downstream pathophysiological consequences, which are manifest to a greater degree in the current population, and at a younger age (pediatric population). A great deal of emphasis has been placed upon fructose which has unique metabolic consequences, although some findings are based upon consumption of very large amounts of fructose, in animal or clinical studies (see recent review from Stanhope, 2012). The generically motivating contribution of sucrose to intake of tasty beverages, and the enhancement of sucrose motivation by a background diet high in fat (Figlewicz et al., 2006, 2008, 2012) suggests that research and education about the metabolic consequences of these macronutrients should be a continued focus, and approaches for effective messaging in different target groups need to be developed.

Additional research in humans is also not only desirable but very necessary. Now that the initial 'generation' of studies have been carried out confirming the expected activation of reward circuitry, it is time for the second and third generation studies which are much more difficult: the examination of the neural basis of choices in addition to the underlying motives. Equally challenging and necessary will be the extension of within-subjects' studies across time, as well as identifying vulnerable populations for study prior to the onset of unhealthy eating habits, frank obesity, or both. Stated another way, the field must move from observational studies to studies that begin to address causality (i.e., whether CNS changes mediate behavioral changes, or are a concomitant or a result of behavioral changes) using both prospective and experimental designs.

Further evaluation of obesity-related changes versus palatable food-related changes, as highlighted by new findings from Stice and colleagues, is also needed. As mentioned above, studies in rodents demonstrate a high fat diet effect to increase motivation for sucrose, independent of obesity or metabolic changes, emphasizing the effect of nutrients or macronutrients per se to modulate CNS reward circuits. Thus, this represents another research direction where translational animal studies and human/clinical research may converge. Finally, although there may be some common events that trigger overeating under circumstances of high food availability, there are likely key 'vulnerability factors' that may play a role in the individual expression of eating patterns. This hypothetical begs for further studies combining genetics, and perhaps epigenetics, with brain imaging and clinical psychological studies. Identification of 'vulnerability' genes could lead to 'reverse translational' studies in animals, using appropriate designed models or paradigms to ascertain the role of such genes in, for example, simple food choices. Clearly, this area of study is at a point where contemporary research findings, as well as tools and technologies for human and animal research, can be put into service.

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- The brain circuitry that processes drug and natural reward are similar
- We review evidence of overlapping brain processing of food and drug rewards
- We discuss the implications of viewing food overconsumption as a “food addiction”

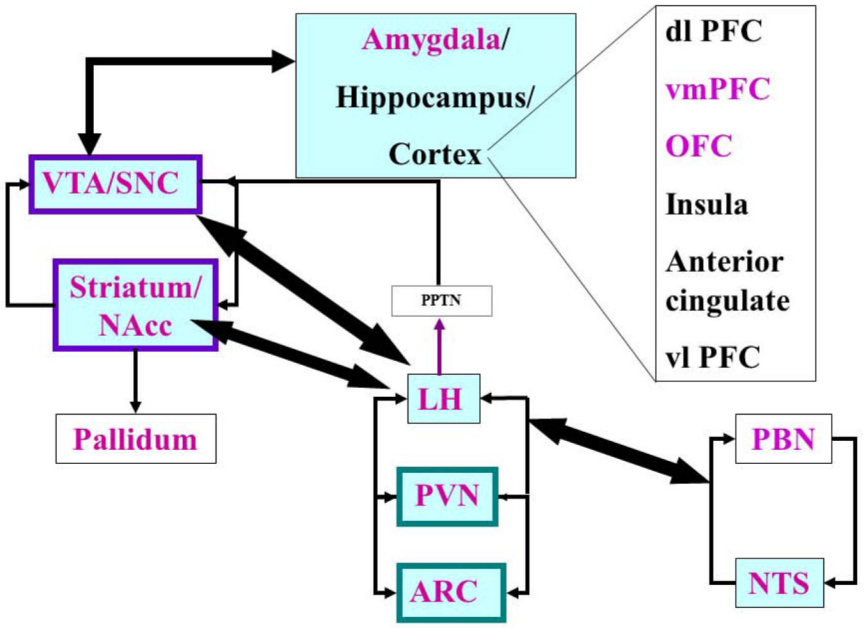

Figure 1.

Integrative signaling of homeostatic and hedonic feeding in the CNS. Major monosynaptic connections are shown, emphasizing the extensive anatomical interconnectivity of functional sets of circuitry that mediate aspects of feeding. Green-framed boxes represent medial hypothalamic sites (PVN, ARC) that had historically been considered key sites for energy homeostasis, coordinating the regulation of body weight, metabolism, and short- and long-term feeding. Blue-framed boxes represent the central dopaminergic cell bodies (VTA/SNC) and mesolimbic projections (striatum/NAcc), historically considered the major regulatory sites of motivated behaviors. The dopaminergic circuitry is connected with hypothalamic circuitry as well as limbic circuitry (amygdala/hippocampus/cortical areas). All regions shaded in pale blue represent CNS sites that are direct receptive targets of the endocrine signals of caloric abundance (insulin, leptin) and caloric need (ghrelin). These include brainstem (PBN/NTS: key relay nuclei for sensory and motor aspects of feeding [Grill, 2010]); hypothalamic, dopaminergic, and limbic regions. Brain regions highlighted in magenta are direct target regions for mu opioid stimulation of feeding (Bodnar, 2004; Gosnell and Levine,1996; Kelly et al., 2002; Mena et al., 2011; Smith and Berridge, 2007). Cortex areas are a major focus of current animal and clinical studies (see text narrative for details) and contributing sub-regions differ between rodents and humans; however the OFC and subareas of the PFC are implicated for both.

ARC, arcuate nucleus; PVN, paraventricular nucleus of the hypothalamus; LH, lateral hypothalamic area; NAcc, nucleus accumbens; VTA, ventral tegmental area; SNC, substantia nigra pars compacta; NTS, nucleus of the tractus solitarius; PBN, parabrachial nucleus; dlPFC, dorsolateral prefrontal cortex; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex; PPTN, pedunculopontine tegmental nucleus; OFC, orbitofrontal cortex.