Published in final edited form as:

Psychosom Med. 2015 ; 77(6): 664–670. doi:10.1097/PSY.0000000000000146.

MODULATION OF FOOD REWARD BY ENDOCRINE AND ENVIRONMENTAL FACTORS: UPDATE AND PERSPECTIVE

Dianne P. Figlewicz, PhD

BSR&D Program, VA Puget Sound Health Care System, Seattle, Washington; and the Department of Psychiatry & Behavioral Sciences, University of Washington School of Medicine, Seattle, Washington

Abstract

OBJECTIVE—Palatable foods are frequently high in energy density. Chronic consumption of high energy density foods can contribute to the development of cardiometabolic pathology including obesity, diabetes, and cardiovascular disease. This paper reviews the contributions of extrinsic and intrinsic factors that influence the reward components of food intake.

METHODS—A narrative review was conducted to determine the behavioral and central nervous system -related processes involved in the reward components of high energy density food intake.

RESULTS—The rewarding aspects of food, particularly palatable and preferred foods, are regulated by central nervous system circuitry. Overlaying this regulation is modulation by intrinsic endocrine systems and metabolic hormones relating to energy homeostasis, and developmental stage or gender. It is now recognized that extrinsic or environmental factors including ambient diet composition, and the provocation of stress or anxiety, also contribute substantially to the expression of food reward behaviors such as motivation for, and seeking of, preferred foods.

CONCLUSIONS—High energy density food intake is influenced by both physiological and pathophysiological processes. Contextual, behavioral and psychological factors and central nervous system-related processes represent potential targets for multiple types of therapeutic intervention.

Keywords

Insulin; leptin; glucocorticoids; stress; sucrose; rats; motivation; fat

Introduction

Over a decade ago, medical and health professionals began to focus intently on the persistent increase in obesity rates in adult and pediatric populations. This has occurred in the U.S. (1), but also across the globe (2,3), with increased rates being found in circumstances of improved socioeconomic status or in societies that have access to “Westernized” diets, soft

Address correspondence and reprint requests to: Dianne Figlewicz Lattemann, Ph.D. VA Puget Sound Health Care System (151), 1660 So. Columbian Way, Seattle WA 98108, latte@uw.edu.

Conflicts of Interest

There are no conflicts of interest.

drinks and fast foods (4). Soft drinks, in particular, are ubiquitous in availability across cultures and continents and represent a source of calories that are high in fructose-containing sweeteners (5). Fast foods and prepared foods can contain high amounts of added sugars (e.g., salad dressings, pasta sauces, as well as dessert items), and high or unbalanced mixtures of fats. Because markets respond to demand, it is clear that the purchase and consumption of these foods drives the presence and expansion of the market for them. Thus, understanding the biological and sociocultural factors which underlie the drive for sweet and calorically-rich foods is critical for guiding individual behavioral choices in the face of omnipresent food offerings. Importantly, my lab has shown the primacy of sweet reward in driving motivated intake of nutrient mixes (6), and this observation has been supported recently by human brain imaging research (7). Research from my lab and others has made it clear that motivation for food reward can be substantially modified by brain biology, with contributions from both intrinsic and extrinsic or environmental factors. The implications of this for human behavior are that individuals should accept the liking and wanting of tasty foods as reflecting normal brain function, but also that identification of ‘pseudo-hard-wired’ modulators or influences on food reward serves as a point for behavioral intervention. The focus of this update is to briefly summarize what we know about these factors currently, based upon studies in animal models, and a perspective will be offered as a guide for future directions for the field.

Reward behaviors

“Reward” is a broad term when considered in the light of quantitative and qualitative behavioral observation. Thus, numerous rather specialized behavioral paradigms have been developed to test for the ‘rewarding’ value of an experience. Rather than add to the extensive discussion of definitions for reward vs. motivation vs. reinforcement, I will use it operationally based upon the specific behavioral task under discussion. Thus lick-rate tasks and free-feeding of certain foods assess immediate hedonic value of these foods, and the lick rate task in particular can examine this hedonic valuation unencumbered by secondary physiological changes (assessed within seconds to minutes) (8). Operant behavior tasks, such as lever presses or nose pokes, or a runway task, assess motivation to obtain a food reward (9). Conditioning of a place preference reflects learning about attributes of a reward (10,11), such as the strength or quality of the reward and its physical localization (a human analogy would be individuals learning which office in their building has a candy jar, and which candy jar has the best candy). These tasks engage overlapping but not identical circuitries in the CNS, and use some common but also some unique neurotransmitters. The range of specific behaviors under the rubric of ‘reward’ suggests that there are potentially multiple behavioral or therapeutic intervention points for adjusting human food choices.

The chemical anatomy of food reward

‘Food reward’ and the sub-constructs or behaviors that are included, are mediated via activation of brain reward circuitry, which is known to be important in mediating the rewarding or reinforcing attributes of many classes of stimuli, and is not unique for food (12–14). This includes lateral hypothalamic neuronal populations (15), and the mesocorticolimbic dopaminergic circuitry (DA cell bodies in the ventral tegmental area/substantia nigra, and projections to the striatum and cortical regions) (16–18). Both

endocannabinoids (19,20) and the peptide transmitter orexin (21,22) are key synaptic contributors to the activity of this circuitry. Numerous detailed and contemporary reviews and discussion of this circuitry are available (see [23]); the interested reader is directed to the cited references, with apology to many colleagues for the inability to cite all pertinent studies. However, a point to be emphasized is that medial hypothalamic structures also contribute substantially to the mediation of food reward, including the arcuate nucleus (ARC) and ventromedial nucleus (VMN) (24,25). Research from my lab and others has shown that the neurotransmitter agouti-related peptide (AGRP) is important for motivational behaviors assessed in the mouse and rat (26–29). These findings emphasize the uniqueness of food as a rewarding stimulus in terms of the CNS circuitries that are engaged. To summarize, key intrinsic CNS neurotransmitter systems which support or mediate food reward include dopamine, mu-opioids (30–35), orexin, AGRP, and striatal melanocyte-concentrating hormone (MCH) (36). Anatomically-specific roles for the more ubiquitous CNS transmitters, GABA and glutamate, and for serotonin and norepinephrine, have been identified but will not be discussed here (as examples, [37–42]). A recent focus has been upon interactions of these transmitter systems (e.g., DA/orexin [43]; DA/opioids [44]; DA/endocannabinoids [45]; DA/MCH [46,47]) emphasizing both the robustness and the complexity of the neural system that underlies food reward. Other CNS limbic structures including the subthalamic nucleus (48,49), subregions of the amygdala, and several subregions of the cerebral cortex (e.g., [50]) are also important for mediating aspects of food reward.

Endocrine influences on food reward

Modulation of reward circuitry and food reward behavior has been extensively documented now for several hormones that regulate energy homeostasis and metabolism (51,52). The hormones insulin and leptin, secreted from the pancreatic beta cell and adipose, respectively, are elevated in the circulation in association with ‘nutritional abundance’ in the form of postprandially absorbed calories or stored calories in adipose tissue. Both of these hormones act to decrease food reward. Both have been shown to decrease ‘brain self-stimulation’ activity (a paradigm thought to reflect generic activation of reward pathways) (53,54), the conditioning of a place preference with food treats (55,56), free-feeding of sucrose pellets (39), and sucrose self-administration behaviors (57). Insulin synergizes with dopamine receptor antagonism to decrease sucrose lick rates in rats (58), and insulin increases the synthesis and activity of the dopamine re-uptake transporter (DAT) at DA cell bodies, and terminals in the striatum (51). The effects of insulin on the DAT are of both physiological and pathophysiological relevance, as we have observed changes of DAT expression in association with acute fasting or streptozotocin-diabetes. Effects of diabetes have been confirmed by research from Galli, Daws, and colleagues (59,60). The functional synaptic relevance of this, is that insulin acts to enhance the clearance of, and terminate the signaling of, synaptic DA. This action (modulation of DAT function) at the DA cell body also results in modulation of the firing activity of DA neurons (61). Leptin decreases baseline and stimulated DA release (62,63). Thus, in the non-obese animal, insulin and leptin can act coordinately to decrease DA release and enhance its synaptic clearance: multiple mechanisms to turn down DA signaling. The acute, short-term, and long-term effects may contribute fine-tuning to allow shifts in DA signaling relevant to orexigenic status and

metabolic need. More recently parallel types of studies have been carried out evaluating the influence of the 'hunger hormone' ghrelin on parameters of food reward. Ghrelin does not shift sucrose preference but does increase sucrose motivation in rats (64). Meticulous studies from Zigman and colleagues have expanded upon this (65), and collectively, studies suggest that ghrelin increases food reward and motivation, which would be predicted for a neuroendocrine factor that increases in association with the development of caloric deprivation. In addition to the well-documented effects of insulin, leptin, and ghrelin upon midbrain dopaminergic neurons, interaction with other intrinsic CNS modulators has been observed, including mu- and kappa-opioids, endocannabinoids, and AGRP. Finally, emerging evidence supports a role for the brain-gut peptide glucagon-like peptide-1 (GLP-1) to inhibit food reward, involving not only brainstem signaling (66) but also by acting at midbrain reward circuitry (67). GLP-1 agents modulate activation of brain reward circuitry in humans (68). Collectively these new studies confirm the integration of homeostatic and hedonic feeding mechanisms and add a new metabolic hormone to the list of endocrine regulators.

Lifestage and gender (intrinsic) influences upon food reward represent a developing line of research, which is consistent with other ongoing research documenting age and gender influences on neuroendocrine and behavioral parameters (69–71). It has long been known that younger animals and humans have a greater preference for sweet taste relative to adults (72–74). My lab has recently confirmed the observation that peripubertal rats have a preference for sweeter taste compared with adults, and further, have shown that they have greater motivation for sucrose (26). This effect of age appears to interact significantly with dietary composition, being observed when the rats are eating a 31% fat diet.

Evidence from animal and human studies suggests that females are more vulnerable to drug abuse than males (75). Estrogen (facilitative) and progestins (opposing) may make unique contributions to different facets of drug abuse, such that gender effects may or may not be manifest in animal studies (76–79). There is evidence for gender-differential occurrences of and outcomes from, obesity in female vs. male rodents (80). Further, there are reports of altered stress responsivity in females vs. males (70,71). As discussed below, this could be expected to contribute to a 'gender effect' on reward vulnerability. How these phenomena fit (or do not fit) with any gender effects on food reward *per se* remains to be determined.

Environmental influences

It is becoming clear that environmental influences play a key role in the modulation of reward circuitry and behavioral responses. In fact, it seems likely that these influences—rather than primary changes or dysfunctions of reward circuitry components themselves—may account for the predilection of Westernized societies to consume and demand foods that are exceptionally palatable with the secondary consequences that they are high in sugars and fats. These choices, in turn, can lead to both immediate and long-term metabolic and cardiovascular pathology (4). As alluded to above, my lab has been focusing on the influence of high fat diet exposure to increase motivation for sucrose (57). This moderate high fat (31%), moderate exposure (3–4 wk), does not result in metabolic or body composition changes, or (as measured in peri-pubertal rats) changes of striatal amine levels,

but does result in increased hypothalamic AGRP mRNA and increased activation of AGRP neurons (26). I have interpreted this as, first, an effect of dietary fat independent of obesity; and, second, as an intermediate stage between lean phenotype and the onset of obesity. This is supported by additional animal-based (81), as well as recent human brain imaging research from Kessler and colleagues (82): Individuals with BMI in the 'overweight' but not 'obese' range appear to have increased DA responsivity to an amphetamine stimulus challenge. It is quite clear now that, in association with long-term very high fat diets (e.g., 40–60%) or development of frank obesity, components of reward circuitry are 'turned down'. This is manifest at the cellular and synaptic levels as decreased synthesis of dopamine, and decreased release and/or increased uptake of dopamine at the striatum; and it is manifested behaviorally as decreased reward behaviors not only to food but other rewarding stimuli (e.g., amphetamine) (83). The decreased 'rewarding' value of palatable or preferred foods has been documented in obese humans and is ascribed to decreased activation of D2 receptors (84–86). These collective findings emphasize the direct clinical relevance of dietary composition on reward and motivation behaviors in humans, and the biphasic pattern of CNS reward neurochemistry changes with the development of obesity. Current human brain imaging studies reveal distinctive changes of activation of brain regions associated with specific constructs (e.g., immediate hedonic valuation vs. response to a 'cue') with the obese or pre-obese condition. This literature, which has been growing over the past decade, has been somewhat confused owing to the lack of consistency of study populations (e.g., degree or duration of obesity), metabolic status, and type of psychological assessment carried out. However the current technical and theoretical knowledge base should allow for more informed interpretation of future studies and these will be of great value to the field.

The influence of stress and its related hormones—hypothalamic corticotropin releasing factor or hormone (CRF or CRH) and adrenal glucocorticoids (GCs)—on various aspects of reward circuitry and food reward has been known for almost twenty years. Pioneering studies from Stewart, Shaham, and colleagues in the 1990s documented the ability of stress to increase the motivating potency of many drugs of abuse (87). Piazza, LeMoal, and colleagues reported that GCs could increase striatal DA extracellular levels, and vulnerability to drug-taking and drug effects (88,89). Using a model of relapse, Shaham and colleagues demonstrated the capacity of acute stress to induce motivated behavior for an identified reward (90). Collectively, these findings fit with earlier, and extensive, observations from Carroll and colleagues, that food restriction could increase motivating aspects of many classes of abused drugs (91). Since food restriction is associated with increased activation of the hypothalamic-pituitary-adrenal (HPA) axis, it was logical to pursue studies evaluating the role of stress on reward circuitry function. Research from Dallman and colleagues has demonstrated the role of GCs, and of a chronic stress circumstance, to increase the choosing and taking of 'comfort foods' preferentially by rats (92). Although their studies did not focus on behavior paradigms of motivation and reward *per se*, their findings are directly of relevance to human eating behaviors (93,104). This work has been expanded and formalized by Ulrich-Lai, Herman, and colleagues who have been elucidating specific CNS circuitry components for these effects (94).

Activation of anxiety circuitry also facilitates aspects of reward behavior. Extra-hypothalamic CRF is implicated in anxiety, and Shaham and colleagues have carried out numerous studies documenting the effect of CRF or the anxiogenic drug yohimbine on motivation for many classes of stimuli, including sucrose. Using their relapse model, they have demonstrated that relapse to sucrose-taking is enhanced by yohimbine administration prior to a session (95), and CRF activity is implicated. This suggests that anxiety, in addition to stress, can modulate food reward. Thus, the peptide transmitter orexin—which is distributed substantially throughout the neuraxis (96) and has effects other than the stimulation of food intake (e.g., [97])—is implicated in some facets of anxiety (97), and may be a significant contributor to anxiety-related food reward perception and behaviors (98).

Identification of environmental factors which decrease food reward and food-seeking behaviors is an area of study that is ripe for investigation. The recent report from Grimm and colleagues (99), that an enriched living environment, with social interaction and novel objects to explore, decreases the strength of cues for sucrose-taking in rats is an important one as it provides two implications of relevance for both animal and human research. First, a deprived environment may contribute to food reward and the general relevance of food and food cues in humans. Second, studies in rodents housed individually in cages with no distractions or objects to interact with, may have limited relevance and applicability to the human environment. Viewed more positively, these findings identify an easy target for weakening the strength of food cues and vulnerability to seek food as a primary stimulus in our complex society: equivalent ‘enriched environments’ that are age- and socioculturally appropriate can and should be explored.

In conclusion, food reward behavior has both intrinsic biological regulators and modulators, and extrinsic modulators which can strongly influence food reward behaviors. Given the economic affordability and societal acceptability of food as the rewarding ‘stimulus of choice’, a strong and concerted effort to either change environmental factor availability, or change its physiological impact, appears warranted. Thus, many more people will become obese or diabetic in the next decade, relative to the number of individuals who will become addicted to drugs of abuse. I identify two key environmental factors—dietary fat and personal or interpersonal stress and anxiety—which lend themselves to change. Approaches that increase individuals’ sense of control and coping skills should improve their ability to deal with both of these environmental factors (dietary choice and stress reduction). I suggest that such approaches deserve attention by the biomedical community as an additional therapeutic alternative to the focus on medications as a solution for obesity and poor nutritional choices.

Acknowledgments

Source of Funding: Dianne Figlewicz Lattemann is a Senior Research Career Scientist, Biomedical Laboratory Research Program, Department of Veterans Affairs Puget Sound Health Care System, Seattle, Washington. The author’s research described in this article is the result of work supported by resources from the VA Puget Sound Health Care System, Seattle, Washington, and was supported by NIH grant DK40963 and by the American Recovery and Reinvestment Act (ARRA).

Abbreviations

AGRP	agouti-related peptide
ARC	arcuate nucleus of the hypothalamus
BMI	body mass index
CNS	central nervous system
CRF/CRH	corticotropin releasing factor/hormone
DA	dopamine
DAT	dopamine reuptake transporter
GABA	gamma aminobutyric acid
GLP-1	glucagon-like peptide 1
GCs	glucocorticoids
HPA	hypothalamic-pituitary-adrenal
MCH	melanin-concentrating hormone
mRNA	messenger ribonucleic acid
VMN	ventromedial nucleus of the hypothalamus

References

1. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. *J Am Med Assoc.* 2012; 307:491–7.
2. Stevens GA, Singh GM, Lu Y, Goodarz D, Lin JK, Finucane MM, Bahalim AN, McIntire RK, Gutierrez HR, Cowan M, Paciorek CJ, Farzadfar F, Riley L, Ezzati M. Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index). National, regional, and global trends in adult overweight and obesity prevalences. *Population Health Metrics.* 2012; 10:22–37. [PubMed: 23167948]
3. Danaei G, Singh GM, Paciorek CJ, Lin JK, Cowan MJ, Finucane MM, Farzadfar F, Stevens GA, Riley LM, Lu Y, Rao M, Ezzati M. Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group. The global cardiovascular risk transition: associations of four metabolic risk factors with national income, urbanization, and Western diet in 1980 and 2008. *Circulation.* 2013; 127:1493–502. [PubMed: 23481623]
4. Mendoza JA, Drewnowski A, Christakis DA. Dietary energy density is associated with obesity and the metabolic syndrome in U.S. adults. *Diabetes Care.* 2007; 30:974–9. [PubMed: 17229942]
5. Stanhope KL. Role of fructose-containing sugars in the epidemics of obesity and metabolic syndrome. *Ann Rev Med.* 2012; 63:329–43. [PubMed: 22034869]
6. Naleid AM, Grimm JW, Kessler DA, Sipols AJ, Aliakbari S, Bennett JL, Wells J, Figlewicz DP. Deconstructing the vanilla milkshake: the dominant effect of sucrose on self-administration of nutrient-flavor mixtures. *Appetite.* 2008; 50:128–38. [PubMed: 17707949]
7. Stice E, Burger KS, Yokum S. Relative ability of fat and sugar tastes to activate reward, gustatory, and somatosensory regions. *Am J Clin Nutr.* 2013; 98:1377–84. [PubMed: 24132980]
8. Davis JD, Smith GP. Analysis of the rhythmic tongue movements of rats ingesting maltose and sucrose solutions. *Behav Neurosci.* 1992; 106:217–28. [PubMed: 1554433]
9. Richardson NR, Roberts DC. Progressive ratio schedules in drug self-administration studies in rats: a method to evaluate reinforcing efficacy. *J Neurosci Methods.* 1996; 66:1–11. [PubMed: 8794935]

10. Carr, GD.; Fibiger, HC.; Phillips, AG. Conditioned place preference as a measure of drug reward. In: Lieberman, JM.; Cooper, SJ., editors. The neuropharmacological basis of reward. Oxford: Clarendon Press; 1989. p. 264-319.
11. Bardo MT, Bevins RA. Conditioned place preference: what does it add to our preclinical understanding of drug reward? *Psychopharmacology*. 2000; 153:31-43. [PubMed: 11255927]
12. Ikemoto S, Panksepp J. Dissociations between appetitive and consummatory responses by pharmacological manipulations of reward-relevant brain regions. *Behav Neurosci*. 1996; 100:331-45. [PubMed: 8731060]
13. McBride WJ, Murphy JM, Ikemoto S. Localization of brain reinforcement mechanisms: intracranial self-administration and intracranial place-conditioning studies. *Behav Brain Res*. 1999; 101:129-52. [PubMed: 10372570]
14. Wise RA. Forebrain substrates of reward and motivation. *J Comp Neurol*. 2005; 493:115-21. [PubMed: 16254990]
15. Margules DL, Olds J. "Feeding" and "rewarding" systems in the lateral hypothalamus of rats. *Science*. 1962; 135:374-75. [PubMed: 14469788]
16. Smith GP. Dopamine and food reward. *Prog Psychobiol Physiol Psychol*. 1995; 16:83-143.
17. Richardson NR, Gratton A. Behavior-relevant changes in nucleus accumbens dopamine transmission elicited by food reinforcement: an electrochemical study in rat. *J Neurosci*. 1996; 24:8160-69. [PubMed: 8987841]
18. Salamone JD, Correa M, Mingote S, Weber SM. Nucleus accumbens dopamine and the regulation of effort in food-seeking behavior: implications for studies of natural motivation, psychiatry, and drug abuse. *J Pharm Exp Ther*. 2003; 305:1-8.
19. Kirkham TC, Williams CM, Fezza F, DiMarzo V. Endocannabinoid levels in rat limbic forebrain and hypothalamus in relation to fasting, feeding and satiation: stimulation of eating by 2-arachidonoyl glycerol. *Brit J Pharmacol*. 2002; 136:550-7. [PubMed: 12055133]
20. Harrold JA, Williams G. The cannabinoid system: a role in both the homeostatic and hedonic control of eating? *Brit J Nutr*. 2003; 90:729-34. [PubMed: 13129440]
21. Choi DL, Davis JF, Fitzgerald ME, Benoit SC. The role of orexin-A in food motivation, reward-based feeding behavior and food-induced neuronal activation in rats. *Neuroscience*. 2010; 167:11-20. [PubMed: 20149847]
22. Mahler SV, Smith RJ, Moorman DE, Sartor GC, Aston-Jones G. Multiple roles for orexin/hypocretin in addiction. *Progress in Brain Research*. 2012; 198:79-121. [PubMed: 22813971]
23. Stice E, Figlewicz DP, Gosnell BA, Levine AS, Pratt WE. The contribution of reward circuits to the obesity epidemic. *Neuroscience and Biobehavioral Reviews*. 2013; 37:2047-58. [PubMed: 23237885]
24. Figlewicz DP, Bennett JL, Aliakbari S, Zavosh A, Sipols AJ. Insulin acts at different CNS sites to decrease acute sucrose feeding and sucrose self-administration in rats. *American Journal of Physiology*. 2008; 295:R388-94. [PubMed: 18525010]
25. Figlewicz DP, Bennett-Jay JL, Kittleson S, Sipols AJ, Zavosh A. Sucrose self-administration and CNS activation in the rat. *American Journal of Physiology*. 2011; 300:R876-84. [PubMed: 21307361]
26. Figlewicz DP, Jay JL, Acheson MA, Magrisso IJ, West CH, Zavosh A, Benoit SC, Davis JF. Moderate high fat diet increases sucrose self-administration in young rats. *Appetite*. 2013; 61:19-29. [PubMed: 23023044]
27. Hahn TM, Breininger JF, Baskin DG, Schwartz MW. Coexpression of Agrp and NPY in fasting-activated hypothalamic neurons. *Nature Neuroscience*. 1998; 1:271-72. [PubMed: 10195157]
28. Krashes MJ, Koda S, Ye CP, Rogan SC, Adams AC, Cusher DS, Maratos-Flier E, Roth BL, Lowell BB. Rapid reversible activation of AgRP neurons drives feeding behavior in mice. *Journal of Clinical Investigation*. 2011; 121:1424-28. [PubMed: 21364278]
29. Aponte Y, Atasoy D, Sternson SM. AGRP neurons are sufficient to orchestrate feeding behavior rapidly and without training. *Nature Neuroscience*. 2011; 14:351-55. [PubMed: 21209617]
30. Kelley AE, Bakshi VP, Haber SN, Steininger TL, Will MJ, Zhang M. Opioid modulation of taste hedonics within the ventral striatum. *Physiol Behav*. 2002; 76:365-77. [PubMed: 12117573]

31. Smith SL, Harrold JA, Williams G. Diet-induced obesity increases mu opioid receptor binding in specific regions of the rat brain. *Brain Res.* 2002; 953:215–22. [PubMed: 12384255]
32. Yeomans MR, Gray RW. Opioid peptides and the control of human ingestive behavior. *Neurosci Biobehav Rev.* 2002; 26:713–28. [PubMed: 12479844]
33. Bodnar RJ. Endogenous opioids and feeding behavior: a 30-year historical perspective. *Peptides.* 2004; 25:697–725. [PubMed: 15165728]
34. Gosnell BA, Levine AS. Reward systems and food intake: role of opioids. *Int J Obes.* 2009; 33(Suppl 2):S54–8.
35. Mena JD, Sadeghian K, Baldo BA. Induction of hyperphagia and carbohydrate intake by mu-opioid receptor stimulation in circumscribed regions of frontal cortex. *J Neurosci.* 2011; 31:3249–60. [PubMed: 21368037]
36. Georgescu D, Sears RM, Hommel JD, Barrot M, Bolanos CA, Marsh DJ, Bednarek MA, Bibb JA, Maratos-Flier E, Nestler EJ, DiLeone RJ. The hypothalamic neuropeptide melanin-concentrating hormone acts in the nucleus accumbens to modulate feeding behavior and forced-swim performance. *J Neurosci.* 2005; 25:2933–40. [PubMed: 15772353]
37. Zhang M, Balmadrid C, Kelley AE. Nucleus accumbens opioid, GABAergic, and dopaminergic modulation of palatable food motivation: contrasting effects revealed by a progressive ratio study in the rat. *Behav Neurosci.* 2003; 117:202–11. [PubMed: 12708516]
38. Taylor SR, Badurek S, DiLeone RJ, Nashmi R, Minichiello L, Picciotto MR. GABAergic and glutamatergic efferents of the mouse ventral tegmental area. *J Comp Neurol.* 2014 Epub ahead of print. 10.1002/cne.23603
39. Uejima JL, Bossert JM, Poles GC, Lu L. Systemic and central amygdala injections of the mGluR_{2/3} agonist LY379268 attenuate the expression of incubation of sucrose craving in rats. *Behav Brain Res.* 2007; 181:292–96. [PubMed: 17537525]
40. Cunningham KA, Fox RG, Anastasio NC, Bubar MJ, Stutz SJ, Moeller FG, Gilbertson SR, Rosenzweig-Lipson S. Selective serotonin 5-HT(2C) receptor activation suppresses the reinforcing efficacy of cocaine and sucrose but differentially affects the incentive-salience value of cocaine- vs. sucrose-associated cues. *Neuropharmacology.* 2011; 61:513–523. [PubMed: 21575646]
41. Izquierdo A, Carlos K, Ostrander S, Rodriguez D, McCall-Craddolph A, Yagnik G, Zhou F. Impaired reward learning and intact motivation after serotonin depletion in rats. *Behav Brain Res.* 2012; 233:494–499. [PubMed: 22652392]
42. Fallon S, Shearman E, Serhsen H, Lajtha A. Food reward-induced neurotransmitter changes in cognitive brain regions. *Neurochem Res.* 2007; 32:1772–1782. [PubMed: 17721820]
43. Mahler SV, Smith RJ, Moorman DE, Sartor GC, Aston-Jones G. Multiple roles for orexin/hypocretin in addiction. *Progress in Brain Research.* 2012; 198:79–121. [PubMed: 22813971]
44. Guy EG, Choi E, Pratt WE. Nucleus accumbens dopamine and mu-opioid receptors modulate the reinstatement of food-seeking behavior by food-associated cues. *Behav Brain Res.* 2011; 219:265–72. [PubMed: 21262268]
45. El Khoury M-A, Gorgievski V, Moutsimilli L, Giros B, Tzavara ET. Interactions between the cannabinoid and dopaminergic systems: evidence from animal studies. *Prog Neuro-Psychopharm & Biol Psychiatr.* 2012; 38:36–50.
46. Smith DG, Tzavara ET, Shaw J, Luecke S, Wade M, Davis R, Salhoff C, Nomikos GG, Gehlert DR. Mesolimbic dopamine super-sensitivity in melanin-concentrating hormone-1 receptor-deficient mice. *J Neurosci.* 2005; 25:914–22. [PubMed: 15673672]
47. Marsteller DA, Gerald CPG, Kong R, Cajina M, Craig DA, Swanson CJ. The MCH1 receptor antagonist SNAP94847 induces sensitivity to dopamine D2/D3 receptor agonists in rats and mice. *Eur J Pharmacol.* 2009; 602:66–72. [PubMed: 19027732]
48. Baunez C, Amalric M, Robbins TW. Enhanced food-related motivation after bilateral lesions of the subthalamic nucleus. *J Neurosci.* 2002; 22:562–68. [PubMed: 11784803]
49. Pratt WE, Choi E, Guy EG. An examination of the effects of subthalamic nucleus inhibition or mu-opioid receptor stimulation on food-directed motivation in the non-deprived rat. *Behav Brain Res.* 2012; 230:365–73. [PubMed: 22391117]

50. Kringelbach ML, O'Doherty J, Rolls ET, Andrews C. Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. *Cerebral Cortex*. 2003; 13:1064–71. [PubMed: 12967923]
51. Figlewicz DP. Adiposity signals and food reward: expanding the CNS roles of insulin and leptin. *Am J Physiol*. 2003; 284:R882–92.
52. Figlewicz DP, Sipols AJ. Energy regulatory signals and food reward. *Pharmacology, Biochemistry, and Behavior*. 2010; 97:15–24.
53. Carr KD, Kim GY, Cabeza de Vaca S. Hypoinsulinemia may mediate the lowering of self-stimulation thresholds by food restriction and streptozotocin-induced diabetes. *Brain Res*. 2000; 863:160–68. [PubMed: 10773204]
54. Fulton S, Woodside B, Shizgal P. Modulation of brain reward circuitry by leptin. *Science*. 2000; 287:125–28. [PubMed: 10615045]
55. Figlewicz DP, Higgins MS, Ng-Evans SB, Havel PJ. Leptin reverses sucrose-conditioned place preference in food-restricted rats. *Physiol Behav*. 2001; 73:229–34. [PubMed: 11399316]
56. Figlewicz DP, Bennett J, Evans SB, Kaiyala K, Sipols AJ, Benoit SC. Intraventricular insulin and leptin reverse place preference conditioned with high fat diet in rats. *Behavioral Neuroscience*. 2004; 118:479–87. [PubMed: 15174925]
57. Figlewicz DP, Bennett JL, Naleid AM, Davis C, Grimm JW. Intraventricular insulin and leptin decrease sucrose self-administration in rats. *Physiology and Behavior*. 2006; 89:611–16. [PubMed: 17045623]
58. Sipols AJ, Stuber GD, Klein SN, Higgins MS, Figlewicz DP. Insulin and raclopride combine to decrease short-term intake of sucrose solutions. *Peptides*. 2000; 21:1361–67. [PubMed: 11072123]
59. Garcia BG, Wei Y, Moron JA, Lin RZ, Javitch JA, Galli A. Akt is essential for insulin modulation of amphetamine-induced human dopamine transporter cell-surface redistribution. *Mol Pharmacol*. 2005; 68:102–9. [PubMed: 15795321]
60. Owens WA, Williams JM, Saunders C, Avison MJ, Galli A, Daws LC. Rescue of dopamine transporter function in hypoinsulinemic rats by a D2 receptor-ERK-dependent mechanism. *J Neurosci*. 2012; 32:2637–47. [PubMed: 22357848]
61. Mebel DM, Wong JCY, Dong YJ, Borgland SL. Insulin in the ventral tegmental area reduces hedonic feeding and suppresses dopamine concentration via increased uptake. *European Journal of Neuroscience*. 2012; 36:2236–46.
62. Krugel U, Schraft T, Kittner H, Kiess W, Illes P. Basal and feeding-evoked dopamine release in the rat nucleus accumbens is depressed by leptin. *Eur J Pharmacol*. 2003; 482:185–7. [PubMed: 14660021]
63. Hommel JD, Trinko R, Sears RM, Georgescu D, Liu ZW, Gao XB, Thurmon JJ, Marinelli M, DiLeone RJ. Leptin receptor signaling in midbrain dopamine neurons. *Neuron*. 2006; 51:801–10. [PubMed: 16982424]
64. Overduin J, Figlewicz DP, Bennett J, Kittleson S, Cummings DE. Ghrelin increases the motivation to eat but does not alter food palatability. *American Journal of Physiology*. 2012; 303:R259–69. [PubMed: 22673784]
65. Perelló M, Zigman JM. The role of ghrelin in reward-based eating. *Biological Psychiatry*. 2012; 72:347–53. [PubMed: 22458951]
66. Alhadeff AL, Grill HJ. Hindbrain nucleus tractus solitaries glucagon-like peptide-1 receptor signaling reduces appetitive and motivational aspects of feeding. *Am J Physiol*. 2014; 307:465–470.
67. Williams DL. Neural integration of satiation and food reward: Role of GLP-1 and orexin pathways. *Physiol Behav*. 2014 Epub ahead of print. 10.1016/j.physbeh.2014.03.013
68. van Bloemendaal L, IJzerman RG, Ten Kulve JS, Barkhof F, Konrad RJ, Drent ML, Veltman DJ, Diamant M. GLP-1 receptor activation modulates appetite- and reward-related brain areas in humans. *Diabetes*. 2014 pii: DB_140849 Epub ahead of print.
69. Sturman DA, Mandell DR, Moghaddam B. Adolescents exhibit behavioral differences from adults during instrumental learning and extinction. *Behavioral Neuroscience*. 2010; 124:16–25. [PubMed: 20141277]

70. Carvalho-Netto EF, Myers B, Jones K, Solomon MB, Herman JP. Sex differences in synaptic plasticity in stress-responsive brain regions following chronic variable stress. *Physiol Behav.* 2011; 104:242–47. [PubMed: 21315096]
71. Trainor BC. Stress responses and the mesolimbic dopamine system: social contexts and sex differences. *Horm Behav.* 2011; 60:457–69. [PubMed: 21907202]
72. Desor JA, Beauchamp GK. Longitudinal changes in sweet preferences in humans. *Physiology & Behavior.* 1987; 39:639–41. [PubMed: 3588712]
73. Mennella JA, Pepino MY, Reed DR. Genetic and environmental determinants of bitter perception and sweet preferences. *Pediatrics.* 2005; 115:216–22.
74. Coldwell SE, Oswald TK, Reed DR. A marker of growth differs between adolescents with high vs. low sugar preference. *Physiology & Behavior.* 2009; 96:574–80. [PubMed: 19150454]
75. Anker JJ, Carroll ME. Females are more vulnerable to drug abuse than males: evidence from preclinical studies and the role of ovarian hormones. *Curr Topics Behav Neurosci.* 2010; 8:73–96.
76. Anker JJ, Carroll ME. The role of progestins in the behavioral effects of cocaine and other drugs of abuse: human and animal research. *Neurosci Biobehav Rev.* 2010; 35:315–33. [PubMed: 20398693]
77. Cifani C, Koya E, Navarre BM, Calu DJ, Baumann MH, Marchant NJ, Liu QR, Khuc T, Pickel J, Lupica CR, Shaham Y, Hope BT. Medial prefrontal cortex neuronal activation and synaptic alterations after stress-induced reinstatement of palatable food seeking: a study using c-fos-GRP transgenic female rats. *J Neurosci.* 2012; 32:8480–90. [PubMed: 22723688]
78. Pickens CL, Cifani C, Navarre BM, Eichenbaum H, Theberge FR, Baumann MH, Calu DJ, Shaham Y. Effect of fenfluramine on reinstatement of food seeking in female and male rats: implications for the predictive validity of the reinstatement model. *Psychopharmacol.* 2012; 221:341–53.
79. Mauvais-Jarvis F, Clegg DJ, Hevener AL. The role of estrogens in control of energy balance and glucose homeostasis. *Endo Rev.* 2013; 34:309–38.
80. Baladi MG, Daws LC, France CP. You are what you eat: Influence of type and amount of food consumed on central dopamine systems and the behavioral effects of direct- and indirect-acting dopamine receptor agonists. *Neuropharmacology.* 2012; 63:76–86. [PubMed: 22710441]
81. Kessler RM, Zald DH, Ansari MS, Li R, Cowan RL. Changes in dopamine release and dopamine D2/3 receptor levels with the development of mild obesity. *Synapse.* 2014; 1002/syn.21738
82. Davis JF, Tracy AL, Schurdak JD, Tschop MH, Clegg DJ, Benoit SC, Lipton JW. Exposure to elevated levels of dietary fat attenuates psychostimulant reward and mesolimbic dopamine turnover in the rat. *Behavioral Neuroscience.* 2008; 122:1257–63. [PubMed: 19045945]
83. Stice E, Spoor S, Bohon C, Veldhuizen MG, Small DM. Relation of reward from food intake and anticipated food intake to obesity: a functional magnetic resonance imaging study. *Journal of Abnormal Psychology.* 2008; 117:924–935. [PubMed: 19025237]
84. Martin LE, Holsen LM, Chambers RJ, Bruce AS, Brooks WM, Zarccone JR, Butler MG, Savage CR. Neural mechanisms associated with food motivation in obese and healthy weight adults. *Obesity.* 2010; 18:254–60. [PubMed: 19629052]
85. de Weijer B, van de Giessen E, van Amelsvoort T, Boot E, Braak B, Janssen I, van de Laar A, Fliers E, Serlie MJ, Booij J. Lower striatal dopamine D2/3 receptor availability in obese compared with non-obese subjects. *EJNMMI Res.* 2011; 1:37.10.1186/2191-219X-1-37 [PubMed: 22214469]
86. Shaham Y, Stewart J. Exposure to mild stress enhances the reinforcing efficacy of intravenous heroin self-administration in rats. *Psychopharmacol.* 1994; 114:523–7.
87. Piazza PV, Maccari S, Deminiere JM, LeMoal M, Mormede P, Simon H. Corticosterone levels determine individual vulnerability to amphetamine self administration. *Proc Natl Acad Sci USA.* 1991; 88:288–92.
88. Piazza PV, Rouge-Pont F, Deroche V, Maccari S, Simon H, LeMoal M. Glucocorticoids have state-dependent stimulant effects on the mesencephalic dopaminergic transmission. *PNAS.* 1996; 93:8716–20. [PubMed: 8710937]
89. Shalev U, Erb S, Shaham Y. Role of CRF and other neuropeptides in stress-induced reinstatement of drug seeking. *Brain Res.* 2010; 1314:15–28. [PubMed: 19631614]

90. Carroll ME, Meisch RA. Increased drug-reinforced behavior due to food deprivation. *Advances in Behavioral Pharmacology*. 1984; 4:47–88.
91. Dallman MF, Pecoraro NC, laFleur SE. Chronic stress and comfort foods: self-medication and abdominal obesity. *Brain Behav Immun*. 2005; 19:275–80. [PubMed: 15944067]
92. Conner MFM, Fletcher W. Stress and snacking: A diary study of daily hassles and between meal snacking. *Psychology and Health*. 1999; 14:51–63.
93. Ulrich-Lai YM, Christiansen AM, Ostrander MM, Jones AA, Joes KR, Choi DC, Krause EG, Evanson NK, Furay AR, Davis JF, Solomon MB, de Kloet AD, Tamashiro KL, Sakai RR, Seeley RJ, Woods SC, Herman JP. Pleasurable behaviors reduce stress via brain reward pathways. *PNAS*. 2010; 107:20529–34. [PubMed: 21059919]
94. Ghitza UE, Gray SM, Epstein DH, Rice KC, Shaham Y. The anxiogenic drug yohimbine reinstates palatable food seeking in a rat relapse model: a role of CRF₁ receptors. *Neuropsychopharm*. 2006; 31:2188–96.
95. Peyron C, Tighe DK, van den Pol AN, de Lecea L, Heller HC, Sutcliffe JG, Kilduff TS. Neurons containing hypocretin (orexin) project to multiple neuronal systems. *J Neurosci*. 1998; 18:9996–10015. [PubMed: 9822755]
96. Kotz C, Nixon J, Butterick T, Perez-Leighton C, Teske J, Billington C. Brain orexin promotes obesity resistance. *Ann New York Acad Sci*. 2012; 1264:72–86. [PubMed: 22803681]
97. Johnson PL, Molosh A, Fitz SD, Truitt WA, Shekhar A. Orexin, stress, and anxiety/panic states. *Prog Brain Res*. 2012; 198:133–61. [PubMed: 22813973]
98. Richards JK, Simms JA, Steensland P, Taha SA, Borgland SL, Bonci A, Bartlett SE. Inhibition of orexin-1/hypocretin-1 receptors inhibits yohimbine-induced reinstatement of ethanol and sucrose seeking in Long-Evans rats. *Psychopharmacol*. 2008; 199:109–17.
99. Grimm JW, Osincup D, Wells B, Manaois M, Fyall A, Buse C, Harkness JH. Environmental enrichment attenuates cue-induced reinstatement of sucrose seeking in rats. *Behav Pharmacol*. 2008; 19:777–85. [PubMed: 19020412]