Regulation of the Motivation to Eat

Stephen C. Woods and Denovan P. Begg

Abstract Although food intake is necessary to provide energy for all bodily activities, considering food intake as a motivated behavior is complex. Rather than being a simple unconditioned reflex to energy need, eating is mediated by diverse factors. These include homeostatic signals such as those related to body fat stores, to food available and being eaten, and to circulating energy-rich compounds like glucose and fatty acids. Eating is also greatly influenced by non-homeostatic signals that convey information related to learning and experience, hedonics, stress, the social situation, opportunity, and many other factors. Recent developments identifying the intricate nature of the relationships between homeostatic and non-homeostatic influences significantly add to the complexity underlying the neural basis of the motivation to eat. The future of research in the field of food intake would seem to lie in the identification of the neural circuitry and interactions between homeostatic and non-homeostatic influences.

Keywords Adipose tissue · Adiposity signal · Agouti-related protein · Allostasis · Amygdala · Anorexia nervosa

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Curr Topics Behav Neurosci (2016) 27: 15–34
DOI 10.1007/7854_2015_381
Published Online: 01 September 2015

> The concept of motivation has taken many forms. It appears in our folklore, in our traditions and customs, in our great philosophical systems, and in our more recent science of behavior. Sometimes it is made explicit so that it may be scrutinized, but more often it is implicit, unanalyzed, and unquestioned. The concept of motivation has been variously identified as an unquestionable fact of human experience, as an indisputable fact of behavior, and as a mere explanatory fiction. (Bolles 1967)

> Is the motivation to eat excess food, when living in an environment enriched with an overabundance of palatable and hedonically pleasing foods, so compelling that the so-called epidemic of obesity is inevitable? Stated another way, are homeostatic circuits simply overwhelmed by the reward value of overeating?

It is axiomatic that organisms must acquire energy in the form of nutrients to power growth and all other physiological functions including behavior. Most adult animals living in an environment with ample available food ingest nutrients at regular intervals, roughly matching energy intake to energy expenditure over an extended period of time and maintaining body weight/adiposity/energy stores within a narrow range. Individuals who have not ingested sufficient nutrients to maintain weight for some time will seek food and work harder to obtain it and, over time and with food available, will take in sufficient nutrients to reverse any energy deficits that have occurred. This is generally considered to be due to a need-based or homeostatic motivation intended to restore stored energy to optimal levels within the body. The strength of the motivation to obtain food by deprived animals underlies the foundations of many influential theories of learning and other behaviors of the last century (Hull 1931; Miller et al. 1950; Skinner 1930); i.e., organisms easily learn operant tasks that enable them to acquire needed food, and as they consume the food, the motivation apparently diminishes.

1 Motivation

In considering the motivation to eat, an important question is whether eating elicited by a critical deficit of energy is 'motivated?' And is such eating a common event in our everyday lives? The answer lies in the extent to which the act of eating is an unconditioned as opposed to an operant response. Simple reflexes such as the patellar response or salivation in response to food on the tongue have easily identifiable unconditioned stimuli and are consequently considered to be unconditioned responses. The concept of motivation does not enter into a description of the behavior; i.e., one is not considered to be motivated to knee-jerk, or to reflexively salivate. If eating that occurs in response to a deficit of stored or available energy is likewise a simple reflex, should it be considered motivated?

A perhaps more informative question to ask is whether any instances of food intake are truly unconditioned responses. The answer is that unconditioned eating is extremely rare and may never naturally occur in normal situations. It is undeniable that when the energy available to receptor cells in neural circuits linked to food intake is acutely lowered, eating is initiated. This occurs, for example, when blood glucose and consequently glucose entering the brain (where it is a necessary source

of energy) is precipitously lowered by systemic insulin administration (Lotter and Woods 1977; MacKay et al. 1940) or when the capability of brain cells to derive energy from available glucose is blocked by the administration of 2-deoxyglucose (Smith and Epstein 1969). In these instances, if food is available, the onset of eating is quick and robust across species including humans (Grossman 1986; Langhans 1996). Analogously, when an individual has become acclimated to deriving most of its energy from lipids as opposed to carbohydrates, compounds that block the conversion of fatty acids to cellular energy can also elicit acute eating (Langhans and Scharrer 1987). In all of these instances, the rapidly precipitated lack of utilizable energy is recognized by dedicated receptor cells and triggers a number of protective reflexes, including increasing glucose and fatty acid secretion into the circulation from storage organs and decreasing energy expenditure by non-critical tissues, and if food is at hand, it elicits eating behavior as well. Such behavior is innately predetermined and necessary for survival. It is not clear, however, whether such a rapid series of events ever happens other than in laboratories.

In contrast to what occurs when available energy is instantaneously lowered by pharmacological means, when an individual is chronically deprived of food, reductions of fuels (glucose or fatty acids) occur gradually as the body slowly consumes any available stores to keep vital tissues alive. When this occurs, the motivation to eat is strong and continuous, but the eating is not an acutely elicited unconditioned response. This can be readily demonstrated by requiring calorically deprived and underweight individuals to overcome hardships in order to obtain food. In such instances, they eat less if at all. As a common example, the availability of only unpalatable food to an animal results in reduced consumption over time (Sclafani et al. 1996) and maintenance of a body weight that is lower than that of control animals eating regular chow (Ferguson and Keesey 1975; Keesey and Boyle 1973; Naim et al. 1980); the individual is below optimal weight and in principle motivated to eat, but it constrains its behavior. The point is that eating is conditional as opposed to unconditional in physiologically relevant chronic food deprivation situations. We consequently contend that the concept of motivation to eat, rather than applying directly to energy-deficit or homeostatic-need-based behavior, applies principally (if not entirely) to situations that cannot be considered as unconditioned and rather are based on experience as discussed below. That said, there is no doubt that a food-deprived state amplifies the effect of other, non-homeostatic factors, on the motivation to eat.

Another potentially ambiguous situation with regard to motivation, homeostasis, and food taking concerns the concept of satiation. During a meal, ingested food interacts with receptors on the lining of the tongue and digestive tract to generate neural and hormonal signals that facilitate the digestive process, and some of the same signals also influence the brain to elicit a perception of satiation/fullness, and as these satiation signals accumulate, eating eventually ends (Moran 2004; Smith and Gibbs 1984; Woods 2009). Administration of the most-studied such satiation signal, cholecystokinin (CCK), to humans or animals, causes them to reduce meal size, and the administration of compounds that block the action of endogenous CCK results in an increase in meal size (Moran and Kinzig 2004; Smith and Gibbs 1985).

Analogous findings have been found with numerous putative endogenous satiation signals including glucagon-like peptide-1 (GLP-1), peptide YY (PYY), bombesin family peptides, amylin, and apolipoprotein A-IV (apoAIV) (see reviews in Begg and Woods 2013; Woods and D'Alessio 2008), and such phenomena are thought by some to reflect a natural, genetically determined or hardwired, braking system on the motivation to eat. It could be argued that this type of influence over meal size is unconditional, but as detailed below, there is considerable evidence that the ability of endogenous satiation signals, as well as of compounds that influence their availability or potency, is not only conditional but even conditionable.

So, how is the issue of the motivation to eat to be conceptualized? We contend, like many before us (see comprehensive review in Bolles 1967), that the concept of motivation to eat implies some sort of incentive, whether homeostatically or non-homeostatically based. One is motivated to obtain what one knows is, or might be, available. This implies some sort of experience or learning with the situation. Caloric deprivation interacts with this in basic ways. A deprived individual works harder, or moves faster, or suffers more hardships, or more readily acquires new skills, in order to obtain food. Greater deprivation leads to increased activity and exploration, activities likely to bring one in contact with food. All of these fit well with the contemporary concept of motivation (Bouton 2011).

2 Eating

Eating is a complex behavior. In addition to providing both micro- (vitamins, minerals) and macronutrients (calories), ingesting food interacts with the reflexive control of many critical parameters including the circulating levels of plasma fuels (glucose, fatty acids, and others) and plasma osmolality (sodium, water, and other constituents), with blood pressure, with body temperature, with the maintenance of body fat, and others. Eating itself is not a regulated variable, but rather is a behavior that can be recruited in the maintenance of any of several key physiological parameters (Woods 2009). Given ample available food with no constraints, rats adopt a pattern of eating a large number of small meals each day [i.e., they become 'nibblers' (Collier et al. 1986, 1992)], and by so doing, they maintain a relatively consistent amount of body fat without having to deal with the metabolic consequences of large meals (Woods 1991, 2002). However, an individual will readily abandon this habitual and presumably preferred eating pattern when conditions are changed. These include situations such as having food available only at limited times each day, having to work hard to gain access to food, receiving treatments that limit the amount that can be consumed in one meal, having access to other activities (exercise; socializing), and the presence of nearby predators. When such constraints are imposed, animals eat at different times, or less often but with larger individual meals, or adopt any strategy that allows them to acquire sufficient calories to maintain body fat at its customary level and in the environment in which they find themselves (see reviews in Collier and Johnson 2004; Schneider et al. 2013;

Woods 2002). Likewise, eating can occur when unanticipated opportunities arise, or as the social situation dictates. All of these kinds of laboratory influences also impact human food taking. Babies, like most animals, prefer a large number of small meals each day, and as they age and social constraints are imposed (e.g., for the sanity of the parents), adapt to a schedule of less frequent and larger meals, and this persists throughout life as meals and snacking become integrated with life schedules and events.

The point is that eating itself (timing, meal size, etc.) is adaptable to a broad range of environmental conditions. As discussed above, living in a stable environment with ample and consistent food, such as occurs in most laboratory situations, provides the luxury of being able to establish regular eating patterns and optimally integrate caloric intake with other behaviors (Schneider et al. 2013; Strubbe and Woods 2004). The amount eaten in individual meals at specific and clearly predictable times of the day becomes habitual; i.e., because the food supply in most experiments is reliable, and the food itself is the same from meal to meal and day to day, the individual readily learns to make responses to take in and process energy most efficiently (Woods 1991). Highly predictable temporal cues (such as the timing of lights-on and lights-off) become optimal times to eat because the individual learns to make meal-anticipatory (also known as cephalic) responses at those times, responses that circumvent the negative impact of meals, such as extreme hyperglycemia, hyperthermia, and hyperlipidemia (Woods 2009). Stimuli reliably associated with consuming the customary food, such as odors, tastes, and mouth feel, therefore become bellwethers of food quality and quantity; such stimuli become distal controllers, and presumably motivators, of eating because when consistent associations with food and its caloric content occur, individuals can acquire the ability to use these distal cues to guide food-taking behavior. They are distal cues in the sense that while their presence has been reliably associated with energy content in the past, they do not inherently denote energy content themselves. In a less predictable environment, the association between distal cues and actual energy content can break down, requiring the individual to rely to a greater extent upon more proximal cues; i.e., cues more closely tied to actual caloric content. Satiation signals such as CCK are intermediate cues, being secreted in response to a physicochemical analysis of ingested food by intestinal cells. To summarize, when the food ingested is consistent for every bout of eating, diverse sensory signals become accurate indicators of the number of calories that can be anticipated to enter the blood from the intestines over the subsequent hours. These include sensations related to the amount of food passing through the mouth, or to the level of CCK once eating has begun, or to the degree of gastric distension as the meal progresses, or to any other stimuli that reliably correlate with ingested caloric content. Nonetheless, none of these surrogate 'satiation' signals is necessarily hardwired to a specific calorie content. The ultimate proximal cues that directly signal energy status to the neural circuits influencing eating are glucose, fatty acids, amino acids or other energy-rich molecules or their metabolites. The point is that there is an energy-reliability gradient that maps onto stimuli an individual can use to guide how much is eaten during a meal. In a *highly predictable* world, distal cues increase

the motivation to eat and a meal's initiation, and once the meal is underway, distal and perhaps intermediate cues signal how many calories are being eaten and consequently when the meal should end.

Therefore, in a consistent environment, distal cues such as the time of day collectively help prepare the body to anticipate and hence cope with the impending nutrients. An important principle is that it is advantageous to accurately gauge the best time to start eating as well as when to stop the meal so that the meal's adverse metabolic consequences are minimized (Woods 1991). Hence, signals that herald a meal is imminent, such as the timing of lights going off, elicit cephalic responses such as increased insulin and ghrelin prior to when the meal actually begins (Drazen et al. 2006; Teff 2000), and these cephalic responses render the digestive process more efficient. While time of day is a key determinant of mealtime in most laboratory settings, animals can also learn to make meal-anticipatory behaviors in response to arbitrary stimuli that reliably indicate food availability, and those same stimuli can elicit eating, even in sated animals (Sclafani 1997; Weingarten 1983). Therefore, the most reliable indicators of food availability acquire the ability to control meal onset, presumably by increasing the motivation for food. As an example, secretion of cephalic insulin renders the individual more glucose tolerant; in the absence of cephalic insulin individuals either must consume very small meals or else appear diabetic (Teff 2011).

The continuum of cues from distal to intermediate to proximal also correlates with time until ingested nutrients become available to the body via the blood. An individual using taste or other oral cues can stop eating long before most nutrients are digested and absorbed, with the assurance that sufficient but not excessive calories have been secured. As the individual shifts to using more proximal cues, the lag between ingestion and the physiological consequences lessens, increasing the probability of overconsuming and having to deal with too many calories entering the blood at once (leading to symptoms of diabetes). Controlling intake via distal cues additionally bestows the advantage of being able to eat relatively large meals because appropriate anticipatory responses can be made sufficiently far in advance to lessen the meal's metabolic impact. As discussed above, anticipatory responses made prior to the actual absorption and even ingestion of food, such as the secretion of cephalic insulin, reduce the prandial increase of glucose and other nutrients that would otherwise occur (Teff 2011; Woods 1991). An individual faced with a novel food (novel in the sense that its odor, taste, and other attributes have not been encountered previously, or else have not been associated with any particular food) eats very little when the food is first made available, even if it is food-deprived. Because the individual has no distal cues on which to rely, it appears neophobic (Armelagos 2014; Birch and Fisher 1998). Small meals continue to be consumed until the consequences of early ingestion prove to be safe, and reliable distal cues can be established (Rozin 1990). In such an instance, the absence of functional distal cues caused by the lack of experience with the food elicits little or no motivation to eat.

3 Homeostatic Versus Non-homeostatic Eating

Separation of influences over the motivation to eat into those that are need- or deprivation-based (homeostatic) and those that are not (hedonic, opportunistic, social, based on learning, stress or emotional-related, cognitive) has considerable face validity. Until the last ten or fifteen years, the brain was considered to have distinct and for the most part anatomically separated circuits collating these two types of influences, with integration occurring mainly very close to the behavioral act of eating itself in hindbrain motor control areas as depicted in Fig. 1. However, the ability to identify and molecularly and genetically map specific neuronal types, neurotransmitters and their receptors, as well as entire neural circuits has revealed that in fact, there is considerable cross talk and overlap at almost every circuit previously thought to be a distinct homeostatic or non-homeostatic pathway, as depicted in Fig. 2. There are many reviews of these phenomena and the change in thinking about the neurocircuitry of food intake (Berthoud 2004; Figlewicz and Sipols 2010; Petrovich 2013; Richard et al. 2013; Rinaman 2010; Zheng and Berthoud 2007) such that only a brief outline is presented here. An important principle is that homeostatic signals, in addition to triggering activity in the

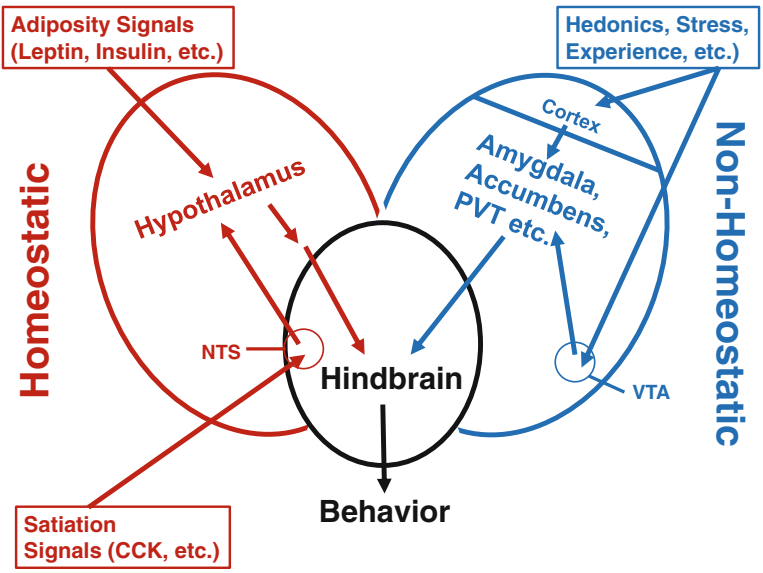

Fig. 1 Historic depiction of how homeostatic and non-homeostatic influences over the motivation to eat are considered. Large sections of the brain were considered distinct for the two types of influences and for the most part not in much contact with one another until the final decision to behave, i.e., to initiate or stop eating at the level of the hindbrain. NTS—nucleus of the solitary tract, which receives satiation signals during meals. VTA in the midbrain which is the source of the mesolimbic and mesocortical dopamine tracts. PVT—paraventricular nucleus of the thalamus is a region that can integrate information on cognitive, emotional, and anxious states with the reward value of food

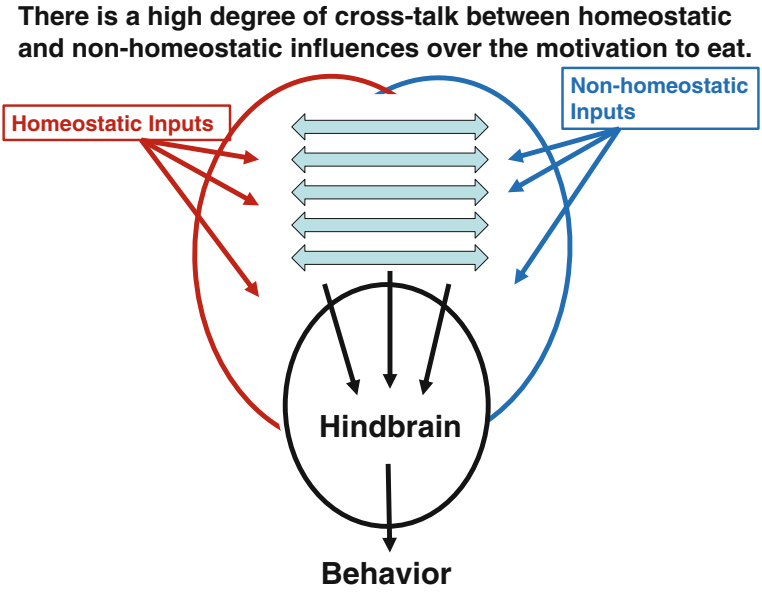

Fig. 2 More nuanced depiction of how homeostatic and non-homeostatic influences over the motivation to eat are considered. In this conception, integration of the diverse types of influence over the motivation to eat occurs throughout the brain. For example, traditional non-homeostatic factors such as stress and learned responses interact with adiposity signals to modify food intake

hypothalamus, also influence activity in essentially every non-homeostatic relay area. As an example, in addition to dense populations in the hypothalamus (see below), receptors for the adiposity-signaling molecules leptin and insulin are also located in neurons in the ventral tegmental area (VTA) of the midbrain (Figlewicz et al. 2003; Pardini et al. 2006), an area where the hedonic value of stimuli is determined and relayed to other areas via axons that release dopamine. Local administration of either insulin or leptin into the vicinity of the VTA dampens positive hedonic signals being relayed to other brain areas (Davis et al. 2010; Davis et al. 2011; Figlewicz and Benoit 2009; Konner et al. 2011). Insulin receptors are also expressed in areas of the neocortex (Corp et al. 1986; Zahniser et al. 1984) where experiential factors are integrated and in the hippocampus which is necessary for many forms of learning (Corp et al. 1986; Harvey et al. 2006; Zahniser et al. 1984).

Historically, subareas within the hypothalamus were considered to be the major controllers of specific behaviors (e.g., drinking, eating, satiety, sex). The roots of this thinking go back to the pioneering work of Hetherington and Ranson (1940, 1942), Hess (1956) and particularly to the influential treatise of Eliot Stellar (1954). For even though Stellar cautioned against considering behavior-controlling centers as being isolated and argued that each is under the influence of numerous types of inputs, he is generally regarded as popularizing the notion of eating and satiety

centers. One consequence was that a generation of scholars worked at identifying inputs, outputs, and integrative capacities of specific hypothalamic areas such as the ventromedial nuclei (VMN, considered a satiety center), the lateral hypothalamus (LH, considered a hunger and thirst center), the paraventricular nuclei (PVN, considered an integrative center that influences autonomic nervous system activity and the stress axis), and many more. Individual 'centers' such as these were considered the mediators of specific homeostatic behaviors.

More recently, scholars began dissecting what was considered the more primitive limbic brain and soon identified important pathways passing from the midbrain VTA to the nucleus accumbens and to areas of the cerebral cortex that signal reward and hedonics (Berridge 1996; Kelley 1999, 2004; Meredith et al. 2008). While different groups typically stuck with one or the other type of neural circuit (homeostatic vs. non-homeostatic), over the ensuing years, it has become obvious that a better conception considers the brain to have one complex circuit that integrates myriad and diverse signals that influence the initiation and consumption of meals (see Fig. 2). All that differs is the origin of specific information that influences the decision to eat or not, and where that information gets integrated in order to make the most informed decisions.

4 Homeostatic Influences

As a short aside, we have argued elsewhere (Ramsay and Woods 2014) that terms such as homeostasis (and allostasis) that are often invoked to explain the apparent regulation of parameters such as core body temperature, plasma glucose, blood pressure, body fat, and others using terms such as set points, central controllers, error signals, and the like are misleading at best. Rather, there is sound evidence to suggest that there is in fact little actual basis for considering such terms and that the levels of body temperature or body fat represent a balance of all of the influences present (Ramsay and Woods 2014; Romanovsky 2007; Woods and Ramsay 2011). Nonetheless, we use the terms homeostasis/homeostatic throughout this article to denote influences on the motivation to eat based upon caloric deficits or surfeits as the terms are in common usage.

To review, the so-called homeostatic brain circuits that are thought to control eating that is based upon need or deprivation have been well described. Numerous signals related to all aspects of metabolism converge on circuits in the mediobasal hypothalamus and elsewhere in the brain. Included are signals whose levels in the circulation are directly proportional to the amount of fat stored in adipose tissue; i.e., the so-called adiposity signals such as insulin and leptin. Insulin, which is secreted by pancreatic B cells, and leptin, which is secreted mainly by adipocytes, are both able to penetrate the blood–brain barrier and gain access to brain cells expressing insulin and leptin receptors, respectively. Many such cells (neurons and glial cells) are found in the hypothalamic arcuate nuclei (ARC) and nearby areas. If body weight decreases due to dieting or being starved, circulating insulin and leptin

levels decline and a diminished 'adiposity' signal reaches these hypothalamic cells. One consequence is that circuits that enhance food taking are stimulated, whereas activity in those that enhance energy expenditure is reduced, and there is an increased probability of eating more food at mealtime until insulin and leptin levels return to baseline. Such a mechanism explains, at least in part, the tendency to regain weight after dieting. Conversely, if one overeats and gains weight, the increased insulin and leptin signals favor eating less and losing body fat. There are numerous reviews of these phenomena (Begg and Woods 2012; Belgardt and Bruning 2010; Guyenet and Schwartz 2012; Morton et al. 2014; Myers and Olson 2012; Schwartz et al. 2000; Sohn et al. 2013).

The ARC contains neurons that have a mainly catabolic action, favoring decreased food intake and increased energy expenditure and consequently loss of body fat (see Fig. 3). The best known of these are neurons expressing the large peptide proopiomelanocortin (POMC). POMC-synthesizing cells in the hypothalamus cleave the larger POMC molecule into smaller bioactive peptides, especially α-melanocyte concentrating hormone (αMSH) (Elmquist et al. 2005; Schwartz et al. 2000; Woods 2009). Administration of insulin or leptin into the vicinity of the ARC causes reduced food intake and loss of body weight/fat, a response that is mediated by, as well as mimicked by, the local administration of αMSH or related compounds (Benoit et al. 2002; Halaas et al. 1995; Niswender and Schwartz 2003; Seeley and Woods 2003; Seeley et al. 1997). People or animals with a genetic

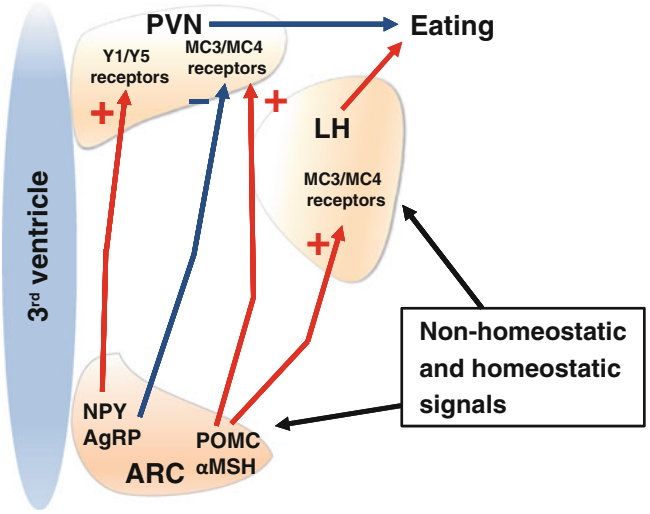

Fig. 3 Proopiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus (ARC) project to both the LH and the PVN (as well as many other areas). These neurons release α-melanocyte-stimulating hormone (αMSH) onto neurons expressing MC3/MC4 receptors, resulting in suppression of food intake. Also within the ARC, neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons also project to the PVN; NPY acts on Y1/Y5 receptors in the PVN to stimulate food intake, while AgRP acts to antagonize MC3/MC4 receptor signaling, further increasing food intake

disruption of this system (e.g., lacking leptin or its receptor, or lacking αMSH-3 or αMSH-4 receptors; or else are lacking insulin receptors uniquely in neurons) are hyperphagic and obese (Benoit et al. 2000; Farooqi and O'Rahilly 2006; Schwartz et al. 2000; Tao 2010). The ARC also has neurons opposing the action of αMSH. These neurons generate two anabolic peptides, neuropeptide Y (NPY) and agouti-related protein (AgRP). NPY acts on its receptors to activate eating, and with prolonged NPY signaling, body weight and adiposity are increased (Schwartz et al. 2000). AgRP functions as an endogenous antagonist of αMSH receptors and so blocks the action of leptin and insulin (Morton and Schwartz 2001; Schwartz et al. 2003). Both αMSH-secreting POMC neurons and NPY/AgRP neurons project from the ARC to several other hypothalamic areas and especially to the PVN where neurons express receptors for NPY and for αMSH/AgRP (Morton et al. 2006; Schwartz et al. 2000; Seeley and Woods 2003). The PVN in turn coordinates several activities related to metabolism. It projects to hindbrain areas that control the act of eating, it influences activity of the sympathetic and parasympathetic nervous systems, and it influences the secretions of the pituitary gland.

While this is a first-order and greatly simplified view of the role of homeostatic adiposity signals in influencing hypothalamic activity, it is nonetheless instructive. The importance of this adiposity-signaling circuit can be inferred from what happens when its activity is chronically altered. As discussed above, inhibiting the activity of insulin or leptin within the brain, and especially within the hypothalamus, results in individuals (including humans) with a greatly increased motivation to eat; when this condition occurs chronically, they maintain an elevated body weight (Begg and Woods 2013; Bruning et al. 2000; Farooqi and O'Rahilly 2006; Obici et al. 2002; Schwartz et al. 2000). Their exaggerated motivation to eat can be normalized by increasing the leptin or insulin signal locally within the brain, and if this occurs chronically, body weight returns to normal as well. If the insulin/leptin signal within the region of the ARC is experimentally or pathologically elevated above normal, individuals have reduced motivation to eat and they lose weight (Benoit et al. 2002; Schwartz et al. 2000; Woods et al. 1979, 1998). Thus, the determination by the brain as to how much body fat to carry is greatly influenced by this hypothalamic circuit that is sensitive to leptin and insulin. Motivation to eat or not to eat comes into play when an individual's body fat has been displaced from its customary level.

Satiation signals such as CCK that are secreted during meals interact with the adiposity-signal system in that their potency is enhanced when leptin and/or insulin is higher than normal. When the insulin or leptin signal locally in the brain is increased, the ability of satiation signals to reduce meal size is enhanced, and a lower insulin or leptin signal reduces the efficacy of satiation signals (Emond et al. 1999, 2001; Matson et al. 1997, 2000; Riedy et al. 1995). Thus, an overweight individual, with an increased insulin and/or leptin signal in the brain, tends to eat smaller meals because the effects of meal-generated satiation signals acting in the hypothalamus, hindbrain, and other brain areas are potentiated. Conversely, a starved individual will have a tendency to eat larger-than-normal meals. This homeostatic explanation accounts for maintenance of body weight in most

individuals within relatively strict limits, but does not take into account motivation and consequent increased food intake due to non-homeostatic factors. Of note is that when living in an environment rich in palatable and hedonically pleasing foods, the motivation to eat is strong and can overpower the homeostatic influences, and this is abetted by the body's becoming relatively resistant to the actions of leptin and insulin as obesity progresses.

As noted above, CCK and other satiation signals are considered intermediate cues with regard to influencing meal size. When the macronutrient profile of available food is consistent, a certain amount of CCK secretion (as well, of course, of other satiation signals) indicates a certain number and type of calories entering the intestine from the stomach. Over hundreds of meals, the CCK–calorie content association becomes strong such that a certain level of CCK (and other satiation signals) triggering its receptors reliably causes a perception of fullness and the meal ends (Woods 2009). This association can be weakened, however, by frequently administering exogenous CCK during meals, thus weakening the CCK–calorie bond and rendering CCK a poor predictor of calories already consumed. When this is done, rats learn to ignore the CCK signal in the specific environment where the bond has been weakened (i.e., they no longer reduce their meal size when exogenous CCK is administered), but they do respond to the same CCK signal by reducing meal size normally in other environments (Duncan et al. 2005; Goodison and Siegel 1995). This suggests that the ability of so-called satiation signals to reduce eating is based on learned associations rather than being a hardwired reflex.

The motivation to eat based on the homeostatic maintenance of body weight was historically touted by ourselves and many others to be the primary determinant of eating (e.g., Elmquist 2001; Schwartz et al. 2000; Woods et al. 1998). However, research over the last decade or two has led to a major reconsideration of this model. Perhaps most importantly, the crisis of steadily increasing obesity rates around the world belies the importance of hardwired homeostatic controllers. Further, as detailed by (Woods and Langhans 2012), the ability of insulin, leptin, CCK, and other so-called homeostatic signals to influence food intake varies widely depending upon environmental, experiential, and other factors. Finally, the realization that circuits conveying learning, stress, hedonics, cognitive activity, etc., interact so extensively with the homeostatic circuits suggests that there is considerable adaptability and flexibility in the controls over the motivation to eat.

5 Non-homeostatic Influences over the Motivation to Eat

Detailed research on the non-homeostatic side of the brain circuits influencing eating has traditionally lagged that of the homeostatic circuits discussed above. Most researchers today base non-homeostatic eating upon the reward properties of specific foods or food-associated stimuli, and the so-called reward circuitry has been well established in the brain (see reviews in Berthoud 2004; Figlewicz and Sipols 2010; Petrovich 2013; Richard et al. 2013; Rinaman 2010; Zheng and

Berthoud 2007). A primary focus has been the neurons that synthesize dopamine in the midbrain and project anteriorly to several brain regions including the nucleus accumbens (Baik 2013). Stimulation of these dopaminergic fibers is highly rewarding as animals will learn responses that activate them. Likewise, neural circuits activated by palatable foods, by many drugs of abuse, by sex, and by other rewarding activities converge in the midbrain to activate those same dopaminergic neurons (Bjorklund and Dunnett 2007; see Salamone et al. in this volume). While there are several dopaminergic circuits emanating from the midbrain, some are concerned mainly with motor control and not discussed here. However, those originating in the VTA that project to cortical regions (mesocortical tract), and those that project to limbic areas such as the nucleus accumbens and parts of the amygdala (mesolimbic tract), convey aspects of reward and enhance motivation (Hegarty et al. 2013). Considerable research has identified specific properties of the circuits activated by the nucleus accumbens and other dopamine-sensitive regions, circuits that in turn project to the cortex, to the hypothalamus and elsewhere. Because the rewarding and consequently motivation-enhancing properties of these circuits relate to diverse behaviors in addition to eating, they are detailed in several other chapters in this volume and need not be reiterated here. The model that is generally accepted, and which is in common use today, was originated by Berridge and Robinson (1998). It posits that distinct components within the nucleus accumbens mediate what they term 'liking' and 'wanting,' with liking referring to the perception of pleasure that has become associated with stimuli typical of a particular food. It is based on experience, requires cortical inputs to the nucleus accumbens, and adds a positive hedonic aspect to consuming that food. Wanting, on the other hand, is considered as the motivational or driving component of eating. It is mediated by dopaminergic fibers from the VTA and is enhanced by food deprivation.

6 Integration of Homeostatic and Non-homeostatic Influences over Food Intake

An important example of how knowledge, and thinking, about the complexity of the interactions between homeostatic and non-homeostatic influences over food intake involves the LH. As discussed above, the LH was historically considered the quintessential 'hunger' or 'feeding center' of the brain because pharmacological or direct neural stimulation there elicits eating, even in sated individuals, and because lesions of the LH result in hypophagia and weight loss (Nicolaidis 1981; Teitelbaum and Epstein 1962). Further, because the LH receives diverse signals related to adipose stores, food available and being eaten, and current circulating levels of glucose and other energy-rich compounds, it is well positioned to integrate homeostatic factors and directly influence food intake (Bernardis and Bellinger 1996). The LH has also been historically recognized as an area where localized stimulation, in addition to eliciting eating, also elicits other motivated behaviors

including drinking and sex, and more recently, the LH has come to be viewed as an important site that integrates arousal with the reward value of specific stimuli related to food, water, sex, and drugs of abuse (Aston-Jones et al. 2009; Berridge 2009). A key neurotransmitter conveying this integrated information from the LH to other brain areas is the neuropeptide, orexin-A (Borgland et al. 2009; Cason et al. 2010). In particular, orexinergic neurons convey information from the LH to the midbrain VTA, and the message is then forwarded to the nucleus accumbens by dopaminergic neurons, and this hypothalamic–midbrain–accumbens system has come to be recognized as an important circuit indicating food reward since the accumbens in turn also innervates the LH (Aston-Jones et al. 2009). More recently, a second LH-originating circuit utilizing orexinergic fibers has been identified that innervates the paraventricular nucleus of the thalamus (PVT) (Kirouac et al. 2005). The PVT is an important site where information on cognition, emotion, and anxiety is integrated with the reward value of food and drugs (Li et al. 2010a, b), and fibers from the PVT have now been identified that proceed to the nucleus accumbens where they modulate dopaminergic activity (Choi et al. 2012). Thus, the LH, rather than being considered a 'hunger center,' might more appropriately be considered as one hub in a complex neural circuit that integrates homeostatic with diverse non-homeostatic information to inform all motivated behaviors. Consistent with this, a recent review concluded that LH orexinergic neurons function as integrators of information from the internal and external environments with the level of vigilance and arousal to inform decisions on multiple motivated behaviors (Sakurai 2014).

To provide a more specific example of how homeostatic and non-homeostatic influences interact in the motivation to eat, consider the phenomenon of stress-induced eating. There is compelling evidence that some stressors, and especially those eliciting psychological stress, increase the motivation to consume so-called comfort foods (Adam and Epel 2007; Dallman 2010). The reason seems to be that consuming these foods dampens the response to stressors and is consequently, by definition, rewarding. Recent research using a rat model has identified circuits in the amygdala and cortex that are stimulated when sweet and otherwise hedonically pleasing foods are consumed (Ulrich-Lai et al. 2010; Ulrich-Lai and Ryan 2014). Further, there is evidence that consuming such comfort foods on a regular basis strengthens synaptic connections in the amygdala, connections that tie consumption of the food to the stress axis dampening phenomenon (Christiansen et al. 2011). Note that this is tied to overeating certain foods as opposed to being based on a change of body weight, although it may be that if the behavior becomes habitual, body weight will follow.

7 Summary

Examining food intake as a motivated behavior is complex, given that eating is regulated by diverse factors including 'homeostatic' brain circuits influenced by adiposity and satiation signals, as well as by 'non-homeostatic' circuits that convey

information related to learning and experience, hedonics, stress, and many other factors. Recent developments identifying the intricate nature of the relationships between homeostatic and non-homeostatic influences significantly add to the complexity underlying the neural basis of the motivation to eat. The future of research in the field of food intake would seem to lie in the examination of the interactions between homeostatic and non-homeostatic influences.

Living in a world with a seemingly endless supply of highly palatable food makes it appear as though the homeostatic circuits that have evolved to regulate eating in historic environments are overwhelmed by the motivation to eat excess food for its rewarding value. This situation is exacerbated by a novel type of distal cue in the form of omnipresent advertisements that appeal to hedonic and other non-homeostatic motivations to eat. At the same time, the reliability of customary distal cues of caloric content, such as taste, smell, and mouthfeel, is often degraded by the use of artificial sweeteners and fats, and this in turn dictates that more proximal cues be used to help determine meal size and runs the risk of overeating (Woods 1991, 2009). The reliability of distal cues is also compromised by the use of super-sweet compounds such as those containing added high-fructose corn syrup or artificial sweeteners, a practice that has been associated with the development of metabolic disorders and obesity (DiNicolantonio et al. 2015; Swithers 2013). Finally, since taking in food is itself a biological stressor (Woods 1991), the complexity and interactions of so many homeostatic, hedonic, cognitive, and emotional factors that can become associated with meals and which may also therefore become associated with stress responses may predispose some individuals to eating disorders such as anorexia nervosa. Therapies that treat both the biological/homeostatic (i.e., starvation-based) and the learned and other non-homeostatic factors associated with food are likely to be most efficacious.

References

Adam TC, Epel ES (2007) Stress, eating and the reward system. Physiol Behav 91(4):449–458

Armelagos GJ (2014) Brain evolution, the determinates of food choice, and the omnivore's dilemma. Crit Rev Food Sci Nutr 54(10):1330–1341

Aston-Jones G, Smith RJ, Moorman DE, Richardson KA (2009) Role of lateral hypothalamic orexin neurons in reward processing and addiction. Neuropharmacology 56(Suppl 1):112–121

Baik JH (2013) Dopamine signaling in reward-related behaviors. Front Neural Circ 7:152

Begg DP, Woods SC (2012) The central insulin system and energy balance. Handb Exp Pharmacol 209:111–129

Begg DP, Woods SC (2013) The endocrinology of food intake. Nat Rev Endocrinol 9(10):584–597

Belgardt BF, Bruning JC (2010) CNS leptin and insulin action in the control of energy homeostasis. Ann N Y Acad Sci 1212:97–113

Benoit S, Schwartz M, Baskin D, Woods SC, Seeley RJ (2000) CNS melanocortin system involvement in the regulation of food intake. Horm Behav 37(4):299–305

Benoit SC, Air EL, Coolen LM, Strauss R, Jackman A, Clegg DJ, Woods SC (2002) The catabolic action of insulin in the brain is mediated by melanocortins. J Neurosci 22(20):9048–9052

Bernardis LL, Bellinger LL (1996) The lateral hypothalamic area revisited: ingestive behavior. Neurosci Biobehav Rev 20(2):189–287

Berridge K (1996) Food reward: brain substrates of wanting and liking. Neurosci Biobehav Rev 20:1–25
Berridge KC (2009) 'Liking' and 'wanting' food rewards: brain substrates and roles in eating disorders. Physiol Behav 97(5):537–550
Berridge KC, Robinson TE (1998) What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev 28(3):309–369
Berthoud HR (2004) Mind versus metabolism in the control of food intake and energy balance. Physiol Behav 81(5):781–793
Birch LL, Fisher JO (1998) Development of eating behaviors among children and adolescents. Pediatrics 101:539–549
Bjorklund A, Dunnett SB (2007) Dopamine neuron systems in the brain: an update. Trends Neurosci 30(5):194–202
Bolles RC (1967) Theory of motivation. Harper & Row, New York
Borgland SL, Chang SJ, Bowers MS, Thompson JL, Vittoz N, Floresco SB, Bonci A (2009) Orexin A/hypocretin-1 selectively promotes motivation for positive reinforcers. J Neurosci 29(36):11215–11225
Bouton ME (2011) Learning and the persistence of appetite: extinction and the motivation to eat and overeat. Physiol Behav 103(1):51–58
Bruning JC, Gautam D, Burks DJ, Gillette J, Schubert M, Orban PC, Kahn CR (2000) Role of brain insulin receptor in control of body weight and reproduction. Science 289(5487):2122–2125
Cason AM, Smith RJ, Tahsili-Fahadan P, Moorman DE, Sartor GC, Aston-Jones G (2010) Role of orexin/hypocretin in reward-seeking and addiction: implications for obesity. Physiol Behav 100(5):419–428
Choi DL, Davis JF, Magrisso IJ, Fitzgerald ME, Lipton JW, Benoit SC (2012) Orexin signaling in the paraventricular thalamic nucleus modulates mesolimbic dopamine and hedonic feeding in the rat. Neuroscience 210:243–248
Christiansen AM, Dekloet AD, Ulrich-Lai YM, Herman JP (2011) "Snacking" causes long term attenuation of HPA axis stress responses and enhancement of brain FosB/deltaFosB expression in rats. Physiol Behav 103(1):111–116
Collier G, Johnson DF (2004) The paradox of satiation. Physiol Behav 82(1):149–153
Collier GH, Johnson DF, Hill WL, Kaufman LW (1986) The economics of the law of effect. J Exp Anal Behav 48:113–136
Collier GH, Johnson DF, Morgan C (1992) The magnitude-of-reinforcement function in closed and open economies. J Exp Anal Behav 57:81–89
Corp ES, Woods SC, Porte D Jr, Dorsa DM, Figlewicz DP, Baskin DG (1986) Localization of ^{125}I-insulin binding sites in the rat hypothalamus by quantitative autoradiography. Neurosci Lett 70:17–22
Dallman MF (2010) Stress-induced obesity and the emotional nervous system. Trends Endocrinol Metab 21(3):159–165
Davis JF, Choi DL, Benoit SC (2010) Insulin, leptin and reward. Trends Endocrinol Metab 21(2):68–74
Davis JF, Choi DL, Schurdak JD, Fitzgerald MF, Clegg DJ, Lipton JW, Benoit SC (2011) Leptin regulates energy balance and motivation through action at distinct neural circuits. Biol Psychiatry 69(7):668
DiNicolantonio JJ, O'Keefe JH, Lucan SC (2015) Added fructose: a principal driver of type 2 diabetes mellitus and its consequences. Mayo Clin Proc 90(3):372–381
Drazen DL, Vahl TP, D'Alessio DA, Seeley RJ, Woods SC (2006) Effects of a fixed meal pattern on ghrelin secretion: evidence for a learned response independent of nutrient status. Endocrinology 147(1):23–30
Duncan EA, Davita G, Woods SC (2005) Changes in the satiating effect of cholecystokinin over repeated trials. Physiol Behav 85:387–393
Elmquist JK (2001) Hypothalamic pathways underlying the endocrine, autonomic, and behavioral effects of leptin. Physiol Behav 74(4–5):703–708

Elmquist JK, Coppari R, Balthasar N, Ichinose M, Lowell BB (2005) Identifying hypothalamic pathways controlling food intake, body weight, and glucose homeostasis. J Comp Neurol 493 (1):63–71

Emond M, Ladenheim EE, Schwartz GJ, Moran TH (2001) Leptin amplifies the feeding inhibition and neural activation arising from a gastric nutrient preload. Physiol Behav 72(1–2):123–128

Emond M, Schwartz GJ, Ladenheim EE, Moran TH (1999) Central leptin modulates behavioral and neural responsivity to CCK. Am J Physiol 276:R1545–R1549

Farooqi S, O'Rahilly S (2006) Genetics of obesity in humans. Endocr Rev 27(7):710–718

Ferguson NB, Keesey RE (1975) Effect of a quinine-adulterated diet upon body weight maintenance in male rats with ventromedial hypothalamic lesions. J Comp Physiol Psychol 89(5):478–488

Figlewicz DP, Benoit SC (2009) Insulin, leptin, and food reward: update 2008. Am J Physiol Regul Integ Comp Physiol 296(1):R9–R19

Figlewicz DP, Evans SB, Murphy J, Hoen M, Baskin DG (2003) Expression of receptors for insulin and leptin in the ventral tegmental area/substantia nigra (VTA/SN) of the rat. Brain Res 964(1):107–115

Figlewicz DP, Sipols AJ (2010) Energy regulatory signals and food reward. Pharmacol Biochem Behav 97(1):15–24

Goodison T, Siegel S (1995) Learning and tolerance to the intake suppressive effect of cholecystokinin in rats. Behav Neurosci 109:62–70

Grossman SP (1986) The role of glucose, insulin and glucagon in the regulation of food intake and body weight. Neurosci Biobehav Rev 10:295–315

Guyenet SJ, Schwartz MW (2012) Clinical review: Regulation of food intake, energy balance, and body fat mass: implications for the pathogenesis and treatment of obesity. J Clin Endocrinol Metab 97(3):745–755

Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Friedman JM (1995) Weight-reducing effects of the plasma protein encoded by the obese gene. Science 269(5223):543–546

Harvey J, Solovyova N, Irving A (2006) Leptin and its role in hippocampal synaptic plasticity. Prog Lipid Res 45(5):369–378

Hegarty SV, Sullivan AM, O'Keeffe GW (2013) Midbrain dopaminergic neurons: a review of the molecular circuitry that regulates their development. Dev Biol 379(2):123–138

Hess WR (1956) Hypothalamus und thalamus: experimental-dokumente. Thieme, Stuttgart, Germany

Hetherington AW, Ranson SW (1940) Hypothalamic lesions and adiposity in the rat. Anat Rec 78(2):149–172

Hetherington AW, Ranson SW (1942) The spontaneous activity and food intake of rats with hypothalmic lesions. Am J Physiol 136:609–617

Hull CL (1931) Goal attraction and directing ideas conceived as habit phenomena. Psychol Rev 38(6):487–506

Keesey RE, Boyle PC (1973) Effects of quinine adulteration upon body weight of LH-lesioned and intact male rats. J Comp Physiol Psychol 84(1):38–46

Kelley AE (1999) Functional specificity of ventral striatal compartments in appetitive behaviors. Ann N Y Acad Sci 877:71–90

Kelley AE (2004) Ventral striatal control of appetitive motivation: role in ingestive behavior and reward-related learning. Neurosci Biobehav Rev 27(8):765–776

Kirouac GJ, Parsons MP, Li S (2005) Orexin (hypocretin) innervation of the paraventricular nucleus of the thalamus. Brain Res 1059(2):179–188

Konner AC, Hess S, Tovar S, Mesaros A, Sanchez-Lasheras C, Evers N, Bruning JC (2011) Role for insulin signaling in catecholaminergic neurons in control of energy homeostasis. Cell Metab 13(6):720–728

Langhans W (1996) Metabolic and glucostatic control of feeding. Proc Nutr Soc 55:497–515

Langhans W, Scharrer E (1987) Role of fatty acid oxidation in control of meal pattern. Behav Neural Biol 47:7–16

Li Y, Li S, Wei C, Wang H, Sui N, Kirouac GJ (2010a) Changes in emotional behavior produced by orexin microinjections in the paraventricular nucleus of the thalamus. Pharmacol Biochem Behav 95(1):121–128
Li Y, Li S, Wei C, Wang H, Sui N, Kirouac GJ (2010b) Orexins in the paraventricular nucleus of the thalamus mediate anxiety-like responses in rats. Psychopharmacology 212(2):251–265
Lotter EC, Woods SC (1977) Injections of insulin and changes of body weight. Physiol Behav 18(2):293–297
MacKay EM, Calloway JW, Barnes RH (1940) Hyperalimentation in normal animals produced by protamine insulin. J Nutr 20:59–66
Matson CA, Reid DF, Cannon TA, Ritter RC (2000) Cholecystokinin and leptin act synergistically to reduce body weight. Am J Physiol Regul Integr Comp Physiol 278(4):R882–890
Matson CA, Wiater MF, Kuijper JL, Weigle DS (1997) Synergy between leptin and cholecystokinin (CCK) to control daily caloric intake. Peptides 18:1275–1278
Meredith GE, Baldo BA, Andrezjewski ME, Kelley AE (2008) The structural basis for mapping behavior onto the ventral striatum and its subdivisions. Brain Struct Funct 213(1–2):17–27
Miller NE, Bailey CJ, Stevenson JA (1950) Decreased "hunger" but increased food intake resulting from hypothalamic lesions. Science 112(2905):256–259
Moran TH (2004) Gut peptides in the control of food intake: 30 years of ideas. Physiol Behav 82(1):175–180
Moran TH, Kinzig KP (2004) Gastrointestinal satiety signals II, Cholecystokinin. Am J Physiol 286:G183–G188
Morton GJ, Cummings DE, Baskin DG, Barsh GS, Schwartz MW (2006) Central nervous system control of food intake and body weight. Nature 443(7109):289–295
Morton GJ, Meek TH, Schwartz MW (2014) Neurobiology of food intake in health and disease. Nat Rev Neurosci 15(6):367–378
Morton GJ, Schwartz MW (2001) The NPY/AgRP neuron and energy homeostasis. Int J Obes Relat Metab Disord 25:S56–62
Myers MG Jr, Olson DP (2012) Central nervous system control of metabolism. Nature 491 (7424):357–363
Naim M, Brand JG, Kare MR, Kaufmann NA, Kratz CM (1980) Effects of unpalatable diets and food restriction on feed efficiency in growing rats. Physiol Behav 25(5):609–614
Nicolaidis S (1981) Lateral hypothalamic control of metabolic factors related to feeding. Diabetologia 20(Suppl):426–434
Niswender KD, Schwartz MW (2003) Insulin and leptin revisited: adiposity signals with overlapping physiological and intracellular signaling capabilities. Front Neuroendocrinol 24:1–10
Obici S, Feng Z, Karkanias G, Baskin DG, Rossetti L (2002) Decreasing hypothalamic insulin receptors causes hyperphagia and insulin resistance in rats. Nat Neurosci 5(6):566–572
Pardini AW, Nguyen HT, Figlewicz DP, Baskin DG, Williams DL, Kim F, Schwartz MW (2006) Distribution of insulin receptor substrate-2 in brain areas involved in energy homeostasis. Brain Res 1112(1):169–178
Petrovich GD (2013) Forebrain networks and the control of feeding by environmental learned cues. Physiol Behav 121:10–18
Ramsay DS, Woods SC (2014) Clarifying the roles of homeostasis and allostasis in physiological regulation. Psychol Rev 121(2):225–247
Richard JM, Castro DC, Difeliceantonio AG, Robinson MJ, Berridge KC (2013) Mapping brain circuits of reward and motivation: in the footsteps of Ann Kelley. Neurosci Biobehav Rev 37(9 Pt A):1919–1931
Riedy CA, Chavez M, Figlewicz DP, Woods SC (1995) Central insulin enhances sensitivity to cholecystokinin. Physiol Behav 58:755–760
Rinaman L (2010) Ascending projections from the caudal visceral nucleus of the solitary tract to brain regions involved in food intake and energy expenditure. Brain Res 1350:18–34
Romanovsky AA (2007) Thermoregulation: some concepts have changed. Functional architecture of the thermoregulatory system. Am J Physiol Regul Integr Comp Physiol 292(1):R37–46
Rozin P (1990) Acquisition of stable food preferences. Nutr Rev 48(2):106–113 (discussion 114–131)

Sakurai T (2014) The role of orexin in motivated behaviours. Nat Rev Neurosci 15(11):719–731
Schneider JE, Wise JD, Benton NA, Brozek JM, Keen-Rhinehart E (2013) When do we eat? Ingestive behavior, survival, and reproductive success. Horm Behav 64(4):702–728
Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG (2000) Central nervous system control of food intake. Nature 404(6778):661–671
Schwartz MW, Woods SC, Seeley RJ, Barsh GS, Baskin DG, Leibel RL (2003) Is the energy homeostasis system inherently biased toward weight gain? Diabetes 52:232–238
Sclafani A (1997) Learned controls of ingestive behavior. APPETITE 29:153–158
Sclafani A, Lucas F, Ackroff K (1996) The importance of taste and palatability in carbohydrate-induced overeating in rats. Am J Physiol 270:R1197–R1202
Seeley RJ, Woods SC (2003) Monitoring of stored and available fuel by the CNS: implications for obesity. Nat Rev Neurosci 4(11):901–909
Seeley RJ, Yagaloff KA, Fisher SL, Burn P, Thiele TE, van Dijk G, Schwartz MW (1997) Melanocortin receptors in leptin effects. NATURE 390(6658):349
Skinner BF (1930) On the conditions of elicitation of certain eating reflexes. Proc Natl Acad Sci U S A 16(6):433–438
Smith GP, Epstein AN (1969) Increased feeding in response to decreased glucose utilization in rat and monkey. Am J Physiol 217:1083–1087
Smith GP, Gibbs J (1984) Gut peptides and postprandial satiety. Fed Proc 43(14):2889–2892
Smith GP, Gibbs J (1985) The satiety effect of cholecystokinin. Recent progress and current problems. Ann N Y Acad Sci 448:417–423
Sohn JW, Elmquist JK, Williams KW (2013) Neuronal circuits that regulate feeding behavior and metabolism. Trends Neurosci 36(9):504–512
Stellar E (1954) The physiology of motivation. Psychol Rev 61:5–22
Strubbe JH, Woods SC (2004) The timing of meals. Psychol Rev 111:128–141
Swithers SE (2013) Artificial sweeteners produce the counterintuitive effect of inducing metabolic derangements. Trends Endocrinol Metab 24(9):431–441
Tao YX (2010) The melanocortin-4 receptor: physiology, pharmacology, and pathophysiology. Endocr Rev 31(4):506–543
Teff K (2000) Nutritional implications of the cephalic-phase reflexes: endocrine responses. APPETITE 34(2):206–213
Teff KL (2011) How neural mediation of anticipatory and compensatory insulin release helps us tolerate food. Physiol Behav 103(1):44–50
Teitelbaum P, Epstein AN (1962) The lateral hypothalamic syndrome: recovery of feeding and drinking after lateral hypothalamic lesions. Psychol Rev 69:74–90
Ulrich-Lai YM, Christiansen AM, Ostrander MM, Jones AA, Jones KR, Choi DC, Herman JP (2010) Pleasurable behaviors reduce stress via brain reward pathways. Proc Natl Acad Sci 107 (47):20529–20534
Ulrich-Lai YM, Ryan KK (2014) Neuroendocrine circuits governing energy balance and stress regulation: functional overlap and therapeutic implications. Cell Metab 19(6):910–925
Weingarten HP (1983) Conditioned cues elicit feeding in sated rats: a role for learning in meal initiation. Science 220:431–433
Woods SC (1991) The eating paradox: how we tolerate food. Psychol Rev 98(4):488–505
Woods SC (2002) The house economist and the eating paradox. APPETITE 38:161–165
Woods SC (2009) The control of food intake: behavioral versus molecular perspectives. Cell Metab 9(6):489–498
Woods SC, D'Alessio DA (2008) Central control of body weight and appetite. J Clin Endocrinol Metab 93(11 Suppl 1):S37–50
Woods SC, Langhans W (2012) Inconsistencies in the assessment of food intake. Am J Physiol Endocrinol Metab 303(12):E1408–E1418
Woods SC, Lotter EC, McKay LD, Porte D Jr (1979) Chronic intracerebroventricular infusion of insulin reduces food intake and body weight of baboons. Nature 282:503–505
Woods SC, Ramsay DS (2011) Food intake, metabolism and homeostasis. Physiol Behav 104 (1):4–7

Woods SC, Seeley RJ, Porte D Jr, Schwartz MW (1998) Signals that regulate food intake and energy homeostasis. Science 280(5368):1378–1383

Zahniser NR, Goens MB, Hanaway PJ, Vinych JV (1984) Characterization and regulation of insulin receptors in rat brain. J Neurochem 42(5):1354–1362

Zheng H, Berthoud HR (2007) Eating for pleasure or calories. Curr Opin Pharmacol 7(6):607–612