Food intake and the reward system

The thin line between physiology and psychology

Bachelor thesis

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Abstract

Obesity is influenced by a complex interaction between genetic, environmental, behavioral and social factors and is a growing worldwide problem. Long and short-term signals contribute to the regulation of food intake, body weight and energy homeostasis, but all the complex regulation systems together do not prevent excessive energy intake. Food intake regulation could be overruled by psychology. In this review, we explore how the reward system interacts with the normal feedback mechanisms on food intake and focus on the role of melanin-concentrating hormone (MCH), leptin and ghrelin on reward. There is growing evidence for homeostatic energy balance regulators to be involved in the regulation of non-homeostatic behaviors and that they also modulate the rewarding nature of food. A deficit in the dopaminergic signalling pathway could provide a mechanism for food addiction and obesity, similar to the pathway of drug addiction. In obese individuals the dopamine receptor 2 expression in the dorsal striatum and VTA is reduced, which possibly increases food intake in order to compensate for the increased reward threshold. The hypothesis of food addiction is controversial. MCH is involved in regulating appetitive behavior and mediating rewarding aspects of food intake in the hypothalamic-limbic circuit. MCH increases dopamine levels and stimulates food intake. Leptin regulates motivational or hedonic elements of eating and interacts with hunger and satiety signals to induce satiety dependent suppression of liking and wanting of food. The leptin receptor (Lepr) in the ventral tegmental area (VTA) provides a direct function of a peripheral metabolic signal in the regulation of motivational or hedonic elements of eating. Ghrelin plays a role in hedonic and incentive responses to food-related cues. In the VTA, ghrelin stimulates food intake and reward-based feeding behavior via its receptor, which could contribute to development of obesity. Taken together, evidence is found that psychology, via the mesolimbic pathways, plays a major role in homeostatic food intake and adipose store regulation and seems to be able to overrule the physiological mechanisms of feeding behavior and could lead to obesity. Metabolic signals may favor food consumption by enhancing the hedonic and incentive responses to food-related cues and contribute thus to development of obesity.

Keywords: Obesity, food intake regulation, dopaminergic reward system, MCH, ghrelin, leptin, food addiction, VTA, nucleus accumbens, hypothalamus
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Introduction
Obesity is a growing worldwide problem and it is associated with many illnesses, for example hypertension, diabetes or dyslipidemia (Ryo, M. et al 2004). Obesity is defined as a Body Mass Index (BMI) of \( \geq 30 \text{ kg/m}^2 \) (Garrison, R.J. et al 1985). An individual with obesity has an excessive amount of body fat which affects physical and mental health (Adams, J.P. et al 2000) and increases morbidity and mortality rate (Garrison, R.J. et al 1985). The prevalence of obesity is associated with socioeconomic status. Poverty is associated with a higher risk of developing obesity (Sobal, J. et al 1989) because energy-dense foods are inexpensive (Drewnowski, A. 2004). An individual can develop obesity when energy intake exceeds energy output for a longer period of time, which increases adipose stores. Sedentary lifestyle, physical inactivity, hedonics, social factors, stress and a high fat diet are common external factors known to promote the development of obesity (Haslam, D.W. et al 2006). Internal, ‘genetic’ factors can also predispose to obesity. Together these factors influence body weight and fat mass by a complex interaction of genetic, environmental, behavioral and social factors (Considine, R.V. et al 1997).

Many systems in place to regulate food intake
One could wonder why obese individuals still eat such large amounts, as food intake, body weight, adipose stores and energy homeostasis are regulated by many systems. These mechanisms have evolved to provide an organism with a tool to keep track of its energy needs and accommodate a survival mechanism (Peters, A. et al 2007; Kennedy, G.C. 1966). The motivation to eat is used to keep energy reserves sufficient.

The hypothalamus is considered as a central regulator of feeding behavior. A physiological mechanism is provided by the short- and long-term food intake regulation, which consists of multiple interacting mechanisms. These physiological mechanisms are not the only way in which energy intake can be altered, as psychology plays a major role (for example reward and conditioning). The long-term signals control adipose stores, food intake and energy balance. Insulin and leptin are long-term regulation signals which both have widespread effects in the body and are secreted in proportion to recent energy intake and adipose tissue. The short-term signals primarily stem from the gastrointestinal (GI)-tract and are mainly involved in meal size and frequency regulation and inducing satiety. Short-term signals alone are not sufficient for regulating food intake, energy balance and adipose stores and are complemented in their actions or are overridden by long-term signals. Together, the short- and long-term mechanisms ensure energy balance by regulation of energy intake and expenditure (Havel, P.J. 2001).

There are many short-term peripheral signals contributing to the regulation of energy homeostasis and food intake. Important gut-released hormones known as incretins influencing energy metabolism, are glucagon-like peptide (GLP)-1, cholecystokinin (CCK) and ghrelin. CCK is secreted by endocrine cells in the mucosal layer of the proximal small intestine. This is stimulated by products of ingestion; dietary fat, amino acids and small peptides. CCK is also secreted from the hypothalamus during food intake and inhibits food intake via the CCKA receptor subtype and inhibits gastric emptying, which limit individual meal size and promotes satiety. Yet the feeding frequency increases, for example via leptin or insulin, to maintain energy balance (Havel, P.J. 2001). In contrast, ghrelin is a peptide secreted in the gut as a signal of hunger or just prior to the usual meal time to stimulate feeding (Sominsky, L. et al 2014; Cummings, D.E. et al 2002). Ghrelin concentrations decrease in the presence of nutrients in the stomach (Havel, P.J. 2001).
In the GI tract, the mechanoreceptors and chemoreceptors signal the presence and energy density of food and contribute to a feeling of satiety, via the vagal afferent nerves to the hindbrain, in the immediate postprandial period (the state in which the blood is filled with nutrients extracted from the ingested food). The chemoreceptors in the GI tract respond to nutrients. The mechanoreceptors and chemoreceptors have a major role in limiting the size of a single meal and can therefore influence the energy intake (Havel, P.J. 2001).

On the other hand, long-term signals regulating food intake, such as leptin and insulin, have a broader role in energy homeostasis. Leptin is released by adipocytes and circulates in the blood, the amount is relative to body adiposity (Considine, R.V. et al 1997). Leptin is regarded as an important hormone in the regulation of food intake. Upon knockout of the leptin receptor, mice showed an increase in food intake, body mass and a decrease in basal energy expenditure (Scarpone, P.J. et al 1997; Rosenbaum, M. et al 2002). In addition, in a mouse model where leptin was overexpressed, food intake was diminished and animals were resistant to diet-induced obesity (Friedman, J.M. et al 1994). Taken together, these findings suggest that leptin is an efficient inhibitor of food intake and is important for control of basal energy expenditure. Likewise, insulin, secreted by β cells in the pancreas, is correlated with body adiposity. When insulin is administered to the brain, food intake and body weight are reduced and sympathetic neural activity and energy expenditure increase (Havel, P.J. 2001). Insulin interacts with other factors of the energy regulation and can for example reduce the dopaminergic neuron-mediated rewarding nature of food (Sominsky, L. et al 2014).

The hypothalamus contributes to body fat homeostasis and responds to leptin. Increased circulating leptin levels activate leptin receptors in the arcuate nucleus of the hypothalamus. The neurons in the arcuate nucleus possess alpha-melanocyte-stimulating hormone (αMSH) and cocaine- and amphetamine-regulated transcript (CART), and increase secretion of thyroid-stimulating hormone (TSH) and adrenocorticotropin hormone (ACTH) from the anterior pituitary. This inhibits food intake and increases the metabolic rate of cells throughout the body and increases the tone of the sympathetic. In addition, when leptin levels fall, the responses mediated by the αMSH and CART neurons diminish and in the arcuate nucleus neuropeptide Y (NPY) and agouti-related peptide (AgRP) neurons are stimulated, as melanin-concentrating hormone (MCH) is stimulated in the lateral hypothalamus. The NPY and AgRP neurons project to the paraventricular nucleus and the lateral hypothalamus and stimulate feeding behavior, activate the parasympathetic and inhibit the secretion of TSH and ACTH. AgRP and αMSH both mediate their effects through the melanocortin 4 (MC4) receptor in the lateral hypothalamus, αMSH as an agonist (inhibiting food intake) and AgRP as an antagonist (stimulating food intake) (Yang, Y. 2011). The lateral hypothalamus is not organized in well-defined nuclei and plays a role in food intake motivation. When the concentration of leptin in the blood falls, MCH and orexin levels rise in the brain. The MCH neurons contribute to food searching by informing the cortex about leptin blood concentrations. Orexin neurons in the lateral hypothalamus receive direct inputs from the arcuate nucleus and stimulate feeding behavior (Burdakov, D. et al 2013). Together, all these complex regulation systems do not prevent excessive energy intake in obesity. These regulation systems are considered to work on their maximum capacity which could lead to desensitization or resistance. Only a small portion of obesity can be ascribed to defects in the considered mechanism of homeostatic regulation, because a large portion of the obese population does not seem to carry faulty genes (Berthoud, H.R. 2012).
Environmental cues and availability of food

Eating can be triggered as a response to energy balance related signals, but also as a response to environmental signals or learned cues (Petrovich, G.D. et al 2002). In modern societies, the increasing availability and variety of (palatable) foods (Mela, D.J. 2006) elevates the chance of feeding behavior. Similarly, animals fed a high fat diet or a variety diet ad libitum can develop obesity and hyperphagia (Berthoud, H.R. 2012). Humans are often exposed to cues which stimulate memories of food (Pandit, R. et al 2011). The ability to resist this modulates an individual’s risks for overeating in the modern environment (Volkow, N.D. et al 2008).

Besides, a palatable diet is probably so pleasant because of its high energy content, thus high in sugar and/or fat content (Drewnowski, A. 1999). Palatability is defined as a positive, hedonic evaluation (liking) under a given set of conditions and is not a fixed property of food. Palatability is a driver of feeding behavior. It is obvious that other factors of food besides palatability, such as high energy density or deficiencies in minerals and vitamins, could contribute to chronic overconsumption. A distinction between variance in palatability of food (which is small in modern societies) and the variance in accessibility and composition of food should be made in an individual responsiveness to environmental cues that cause a desire to eat, which could include the availability and presence of foods (Berthoud, H.R. 2012).

Alongside of eating a palatable meal without metabolic needs, a phenomenon of sensory specific satiety can promote conditioned feeding behavior during periods of satiety (Rolls, B.K. et al 1981). In experiments with satiated rats and conditioned feeding behavior using learned cues paired with food delivery, imitating conditioned food intake through external cues in humans, certain brain regions were shown to control this phenomenon (Petrovich, G.D. et al 2002). These brain regions, lateral hypothalamus, amygdala and medial prefrontal cortex, link specific conditioned cues to appetitive actions. The (lateral) hypothalamus receives input from the medial prefrontal cortex and the basolateral amygdala and this could provide a mechanism for the overruling of normal homeostatic regulation of food intake by external signals. In this way satiety is overridden and food intake promoted in saturated rats. Another explanation for the hedonic hunger during periods of satiety could be that the cephalic phase responses of gastric secretion to sight, smell or thinking about food triggers appetitive behavior (Powley, T.L. 1977; Berthoud, H.R. 2012). These stimulation of appetitive behavior could be due to small increases in saliva, gastric acid, insulin and ghrelin secretion which have their effect on sensory nerves or directly on the brain by enhancing the effects of the conditioned stimuli. Under stress, humans could be even more sensitive to conditioned food cues. It has been shown that food intake relieves stress and can thus be regarded as a form of self-medication (Sominsky, L. et al 2014). Combining these observations leads to the conclusion that the increased response to food stimuli without direct metabolic needs in the postprandial period could be an adaptive behavior, especially in periods of uncertainty about food availability. At least it is clear that environmental stimuli have the possibility to overrule the hypothalamus and the homeostatic energy regulation and therefore could contribute to obesity development (Berthoud, H.R. 2012).

Another appealing explanation for overeating is that obese humans perhaps enjoy food more than lean people. Obese humans have shown to have normal chemosensory functions and likings for specific aromas and tastes, however react differently to high fat or energy dense food (de Graaf, C. et al 2005). Obese subjects and those at an increased risk for obesity, consume more high energy dense or high fat food items and report a higher preference for high fat food compared to lean subjects.
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(Mela, D.J. 2006; Rissanen, A. et al 2002). Similarly, it is commonly shown that obese humans have an increased appetitive reaction to food cues and palatability. This connects obesity to reinforcement sensitivity (Berthoud, H.R. 2012).

Food and reward and food addiction

Although, obese humans show a greater motivation for eating, this is not accompanied by subjective feelings of higher reward than in lean individuals (Mela, D.J. 2006). This could propose that obese individuals are addicted to eating. It has been suggested that low energy foods without a good nutritional balance and high energy dense foods are addictive as palatability could lead to overeating (Berthoud, H.R. 2012). Many times, food addiction is referred to as an analogy of drug or alcohol addiction, but the ability of food inducing compulsive behavior has only been considered in exceptional cases of extreme compulsive overeating (Pandit, R. et al 2011). In studies of food reward commonly a distinction is made between 'liking' and 'wanting' (Pandit, R. et al 2011; Berthoud, H.R. 2012; Berridge, K.C. et al 2009). The term 'liking' refers to the pleasurable feeling associated with the receipt and consumption of a reward. The term ‘wanting’ refers to a subjective desire that induces a goal-directed behavior to obtain such a reward (Pandit, R. et al 2011). In drug- and in food addiction it has been observed that the addict does not like the reward but wants it, when subjective responses, dependence and use rates are investigated (Pandit, R. et al 2011; Berthoud, HR 2012). This is consistent with the incentive sensitization theory that something is wanted that is not liked (Lambert, N.M. et al 2006; Berridge, K.C. et al 2009). There are multiple mechanisms involved in the appreciation of a food related reward and the simplest form of (dis)liking stems from to peripheral gustatory pathways in the brainstem (Berridge, K.C. et al 2009). The neural substrate of 'liking' stems from the deep brainstem structures which function as a pathway for sensory perception, and includes higher order centres as the nucleus accumbens (NAcc) and the ventral pallidum, involving GABA-ergic, opioid and endocannabinoid neurotransmission, as these were activated by palatable foods in neuroimaging studies of humans (Pandit, R. et al 2011; Berridge, K.C. et al 2009). The feeling of wanting is closely related to motivational influences on behavior and is associated with connections with the prefrontal cortex, amygdala, mesolimbic system and dopamine signalling (Pandit, R. et al 2011). Wanting can be triggered by reward-relating cues. The projections of the mesolimbic dopamine system from the ventral tegmental area (VTA) to the NAcc, prefrontal cortex, amygdala and hippocampus are considered key neural pathways of wanting (fig. 1). Dopamine signalling in the NAcc plays a role in the appetitive and consumatory phase of a meal. The dopamine neurons regulate the appetitive phase of food intake and the decision-making process by their phasic activity and project from the VTA to the NAcc. When palatable foods are eaten, this also influences the dopamine levels by constant increasing it in the NAcc. The neural mechanisms including the NAcc, lateral hypothalamus and VTA play are role in assigning salience to goal objects due to orexin neurons which transmit signals about the metabolic state from the lateral hypothalamus (Berthoud, H.R. 2012). It is not understood how sensory information elicits a subjective feeling of pleasure. The

Figure 1. Some brain structures involved in the mesolimbic pathway. The ventral tegmental area (VTA) of the midbrain projects to the nucleus accumbens (NAcc). The amygdala (A) and prefrontal cortex (PFC) send excitatory projections to the NAcc.
height of the reward is not determined by taste and flavour during consumption alone, the emotional state at that moment and various sensory stimuli are also involved in the appreciation of the reward (Mela, D.J. 2006).

Psychology overrules physiology?
It is clear that the hypothalamus is not the only regulator of feeding behavior, the cognitive and emotional brain should also be included in the energy regulation mechanism while trying to explain how obesity can develop in a rapidly changing environment (Berthoud, H.R. 2012). In other words, food intake physiology may be overruled by the psychology of food reward and addiction in obesity. In this review, we explore how the reward system interacts with the normal feedback mechanisms on food intake. We chose to focus on the role of MCH, leptin and ghrelin on the reward system because these peptides are involved in physiological as well as psychological processes. Besides their metabolic functions is MCH involved in regulating appetitive behavior and mediating rewarding aspects of food intake, does leptin regulate motivational or hedonic elements of eating and has ghrelin a role in hedonic and incentive responses to food-related cues.

Dopamine and reward
Food liking and wanting is related to overconsumption and obesity. Food is a common trigger for pleasure and smell and taste are the two most important senses involved in eating. These senses interact with the decision making and hedonic experience in humans (Berridge, K.C. et al 2008). Consumption of food is besides hunger, stimulated due to foods rewarding properties just as intake of some drugs is also initially driven by their rewarding properties. Both involve activation of the mesolimbic dopamine system (Volkow, N.D. et al 2008). The reward pathways could reinforce feeding behavior and the type of food ingested. It is shown in obese humans that they have an increased appetitive reaction to food cues and palatability, which connects obesity to reinforcement sensitivity (Berthoud, H.R. 2012). When obese subjects are shown images of their conditioned stimuli of high-caloric food, an increased neural activation response was found in the regions that mediated the reward and motivation pathways. In contrast, the lean control group responded with increased reward activation to low-caloric foods (Stoeckel, L.E. et al 2008). Perhaps food wanting could stem from behaviors performed in the past which can influence food perception and appetitive reactions. Models for non-homeostatic overeating don’t provide clear evidence if some reactions are in fact overconsumption or that it is an adaptive strategy as a response to contrived nutritional challenge (Berridge, K.C. et al 2008).

A ‘reward deficiency syndrome’, or deficit in the dopaminergic signalling pathway, has been proposed as a cause for obesity (Volkow, N.D. et al 2008). This hyposensitivity to reward could lead to obesity because overeating is used to compensate for the deficiency and to fulfill the desires. On the other hand, a reduced activity of the dopamine receptor could arise as a consequence of repeated stimulation of dopamine release due to chronic or compulsive overeating or even to other neuroendocrine changes caused by obesity (Volkow, N.D. et al 2008). It is hypothesized that the hypersensitivity to reward could be assigned to normal to overweight individuals (BMI 20-30 kg m\(^{-2}\)) and the hyposensitivity, the addiction to food, to obese subjects (BMI ≥ 30 kg m\(^{-2}\)). This process can be compared to drug dependence and addiction, there is a dose-response curve which starts with sensitization and liking and ends with tolerance and wanting. However, there are limitations in the analogies which can be made between obesity and drug addiction. The innate dependence on food
and the motivational aspects of energy deprivation provide a difference between food and abusive substances as alcohol, drugs and nicotine (Mela, D.J. 2006).

A possible neural pathway involved in obesity

But, there is overlap found between food and drug addiction. In cocaine addicts as well as in obese individuals, the dopamine receptor 2 (D2R) expression in the dorsal striatum is reduced compared to lean non-addicts as shown in preclinical and clinical studies with PET-scans (fig.2) (Volkow, N.D. et al 2008; Wang, G.J. et al 2001; Martinez, D. et al 2005). This reduced availability of D2R in obese humans is in proportion to their BMI (Wang, G.J. et al 2001). The striatal regions, the NAcc and dorsal striatum, are involved in reward and habits and routine. Dopamine is a neurotransmitter in charge of pleasure and it is released on the experience of something pleasurable, into the NAcc. The dopaminergic pathway is part of the reward system (Volkow, N.D. et al 2008). From memory, the behavior will be induced to experience the pleasurable moment over again. The brain reward pathway is formed from well-repeated patterns of behavior. The more often the reward is given for a certain action, the stronger the pathway, which leads to a stronger reward. In a way, this causes the brain to become addicted to this specific reward pathway. When a response is triggered, the craving starts. For example, when food-related stimuli were given to obese individuals, the medial prefrontal cortex was activated and cravings were reported (Gautier, J.F. et al 2000). It is well established that repeated exposure to (abusive) drugs results in neuron-adaptive changes which increase reward threshold and increase the motivation to use drugs. The increased reward threshold is a consequence of tolerance resulting in decreased reward. Exposure to addictive foods has shown to elicit similar changes in the brain as seen in drug addicts. At first, the intake of palatable food increases dopamine release and constitutes the reward stage of food addiction. Following on this is conditioning and tolerance, while the received reward is reduced. The final stage of food addiction would be the reduced baseline of dopamine levels and less reward, similar to the stages involved in drug addiction. Addiction is generally regarded as arising from a combination of genetics, environment and stress (Kipper, D. et al 2010). These findings provide evidence for the hyposensitivity and hypersensitivity to reward, following a dose response curve to obesity.

There is preclinical evidence that decreased dopamine activity in the VTA is followed by a dramatic increase in consumption of high-fat foods (Volkow, N.D. et al 2008). In a rat model, hyperphagia is induced with an addictive and palatable cafeteria diet and sustained over 40 days of treatment (Berthoud, H.R. 2012). The rats had the possibility of electrical self-stimulation of the lateral hypothalamus. The results showed that the threshold for self-stimulation increased parallel to body weight gain, this threshold increased in a similar fashion as observed during treatment with cocaine or heroin. The D2R availability in the dorsal striatum decreased in accordance with the increase in reward threshold. Perhaps even more interesting is that when for 14 days the palatable cafeteria diet...
was not administered, the reward threshold did not return back to the baseline. This suggests that a high-fat diet has long term consequences in the brain. At this moment, there is little evidence found that humans can become dependent of a high-fat diet (Berthoud, H.R. 2012). Additionally, decreases in the D2R in the dorsal striatum are connected to compulsive feeding behavior in obese rodents and with decreased metabolic activity in orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC), which are involved in inhibitory control and emotional processing (Volkow, N.D. et al 2008) in obese humans. This decreased D2R signalling results in hyperphagia. Similarly, in obese subjects it has been shown that chronic overconsumption results in tolerance and lower D2R 2 binding in humans (Wang et al, 2001). This is expected to have an influence on the reward feeling, since dopamine is also involved in reward. Dopamine modulates reward and motivation pathways and dopaminergic deficiency in obese humans could result in lower sensitivity to natural rewards (Volkow, N.D. et al 2008) and persistent pathological eating to compensate for the diminished activation of these pathways (GJ Wang et al 2001). In normal weight subjects there is an interaction between the response of the reward regions to high-calorie foods (seen as activation of the OFC and ACC) and the amount of food intake. This connection seems to be lost in obesity (Volkow, N.D. et al 2008).

Dopamine regulates feeding behavior not only through modulation of its rewarding properties, but also by facilitating conditioning to food stimuli that then drive the motivation to eat. Voltammetry studies have shown that a neutral stimulus conditioned to food results in an increase in striatal dopamine and that the dopamine increases are linked to the motoric behavior required to procure the food (lever pressing). In humans, food stimulation significantly increased dopamine levels in the striatum and these increases correlated with the increases in self-reports of hunger and desire for food (Volkow, N.D. et al 2008). These results suggest that decreased dopamine signalling provides a pathway leading to overeating which could cause obesity. Additionally, N.D. Volkow and colleagues (2008) observed that obese individuals have increased activation of somatosensory cortical regions, involved in palatability and anticipation of food intake, but less actual activation of reward regions when food was eaten. In obese individuals the activity baseline of the somatosensory regions that process palatability was measured as increased glucose metabolic activity which provides an indication for higher activity. These changes in neural mechanisms could lead to the fact that obese humans favour food over other natural reinforcers and overeating to compensate for decreased D2R signals. These suggestions are in line with the increased sensitivity of the dopaminergic reward pathway to conditioned stimuli, for obese subjects the high-calorie foods, which predict reward and the decreased sensitivity to the rewarding effects of consumption. It could be that this so-called mismatch between expected and obtained reward and trying to get this expected reward stimulates hyperphagia (Volkow, N.D. et al 2008). Taken together the changes in D2R availability alter the dopaminergic reward pathway in a manner that obesity could be the outcome of food addiction. And thus it is suggested that overeating is a compensation mechanism for the altered reward sensation.

**Reward system and melanin concentrating hormone**

But dopamine is not the only substance which connects food and reward, melanin concentrating hormone (MCH) does for example also play a role and is a common feature of addiction. MCH is found in several places in the brain, including the lateral hypothalamus (Georgescu, D. et al 2005; DiLeone, R.J. et al 2003) and in the NAcc on neurons that also contain dopamine receptors (O’Donnell, P. et al 2001). MCH is known to play a role in energy balance and stimulating food intake (Georgescu, D. et al 2005). It is shown that elevations of MCH mRNA in the lateral hypothalamus are caused by overconsumption of a high-fat diet (Morens, C. et al 2005). And MCH mRNA levels also
increase in response to fasting and expression levels are elevated in obese rodents (Sánchez-Lasheras, C. et al 2010). Administering MCH to the brain activates the VTA and elevates dopamine levels and increases feeding behavior and hunger and reduces metabolic rate (O’Donnell, P. et al 2001). While injecting an MCH-1 receptor antagonist causes the food intake to stop (Bassareo, V. et al 1997) and also decreases the effectiveness of cocaine and alcohol intake (O’Donnell, P. et al 2001). Concluding from these findings, increases in MCH levels increases the amount of dopamine and can thus stimulate food intake and reward and reduce the metabolic rate. Therefore, this pathway could play a role in obesity as MCH is involved in regulating appetitive behavior. In the following sections MCH and its relation with obesity will be discussed in more detail.

The rodent MCH receptor (MCH1R) is found to be highly expressed in the NAcc shell which is important for regulating feeding behavior (Georgescu, D. et al 2005; DiLeone, R.J. et al 2003). Georgescu and colleagues found that direct administration of an MCH1R antagonist in the NAcc shell, inhibited food intake and induced an antidepressant-like effect in the forced swimming test. In contrast, when administration of MCH in the NAcc shell increased feeding behavior and depressive behavior in the forced swim test. These findings suggest that MCH regulates appetitive behavior via the NAcc. It was also shown that MCH signalling inhibited dopamine-induced phosphorylation of the AMPA glutamate receptor subunit GluR1 via biochemical analysis with phosphoisoform-specific antibodies in the NAcc shell obtained from rats (Georgescu, D. et al 2005). MCH-R is a G-protein coupled receptor and its activation decreases cellular cAMP levels (DiLeone, R.J. et al 2003). Taken together, MCH and its receptor seem to play a regulation role of food intake and related behaviors in the hypothalamic-limbic circuit in rodents (Georgescu, D. et al 2005).

Besides the NAcc, the lateral hypothalamus has been implicated in feeding behavior and reward and has neurons which express MCH. These neurons have extensive projections to brain regions implicated in behavioral responses to abusive drugs. These pathways could play a role in addiction. It is observed that MCH KO mice show a hypophagic response without MCH-R signalling in the NAcc and MCH seems to have an inhibitory effect on lateral hypothalamus neurons (DiLeone, R.J. et al 2003). Signalling of MCH between the lateral hypothalamus and the NAcc or mesolimbic pathways could play a general role in mediating responses to rewarding stimuli via communicating the rewarding or hedonic aspects of food intake. The MCH pathway therefore could have a role in addiction. It has been observed that MCH is capable of directly modulating food intake via the NAcc. MCH and melanocortins are antagonistic, suggesting that these peptides have interactions in the NAcc. It has been reported that opiate tolerance and dependence can be antagonized with melanocortin treatments and that melanocortin signalling can sensitizie an organism to rewarding effects of psychostimulants. The G-protein linked melanocortin receptor (MC4R) is also highly expressed in the NAcc. Combined, these findings suggest a role for MCH and melanocortins in food addiction (DiLeone, R.J. et al 2003). When MCH levels increase, this increases dopamine levels and thus stimulates food intake and reduces the metabolic rate which contributes to obesity development. As well as the ability of MCH to directly modulate food intake via the NAcc and mediating rewarding aspects of food intake.

**Reward system and leptin**

Nowadays, there is growing evidence for homeostatic energy balance regulators, such as insulin, ghrelin and leptin, and short-term fluctuations in available fuels (Mela, D.J. 2006; Naleid, A.M. et al 2005) to be involved in the regulation of non-homeostatic behaviors and that they also modulate the
rewarding nature of food. Leptin and ghrelin are homeostatic regulators which could be involved in the cognitive control over feeding behavior and conditioning to food stimuli because they interact with the midbrain VTA dopamine neurons which project to many different brain areas such as the NAcc and prefrontal and limbic regions (fig. 1). The VTA seems to be a detector of peripheral metabolic signals that responds with increasing or decreasing feeding behavior via modulation of mesolimbic and mesocortical mechanisms (Naleid, A.M. et al 2005).

Leptin is often associated wit

h regulation of feeding behavio

r and satiety, but recently leptin is also found to be involved in psychopathology. The high comorbidity of obesity with numerous mental illnesses has provided such evidence. Leptin acts on neurons in the arcuate nucleus, other hypothalamic nuclei and in the brainstem, including in the VTA where it may modulate mesolimbic dopamine circuits and food ‘wanting’ (Berridge, K.C. et al 2010). Leptin is considered to be able to induce negative alliesthesia during satiety. Alliesthesia is the affective component of sensation, pleasure or displeasure (Cabanac, M. 1988). Supposedly, leptin could also contribute to alliesthesia-induced ‘liking’ suppression by stimulating hypothalamic arcuate POMC/CART neurons to activate MCR4 receptors on paraventricular neurons, or by suppressing arcuate NPY-AGrP neurons to suppress orexin neurons in lateral hypothalamus, and thus finally reducing the opioid or orexin stimulation of hedonic hotspots in ventral pallidum or NAcc (Berridge, K.C. et al 2010).

It is observed in humans with a monogenic-based deficiency of leptin, which results in a genetic form of obesity, that leptin is not capable to inhibit liking or wanting. Normally, satiety should suppress the liking and wanting for foods, even if food reward cannot be entirely extinguished (Berridge, K.C. et al 2010). This leptin deficiency causes a constant demand for food which leads to obesity. Correlated with NAcc activation via food stimuli, exorbitant ratings of food liking were measured with functional magnetic resonance imaging (fMRI). The active NAcc was not inhibited by recent food intake. These results suggest an abnormal persistence of limbic activation of liking and wanting during satiety (Farooqi, I.S. et al. 2007; Farooqi, I.S. et al 2009). In addition, when exogenous leptin is administered to these humans the limbic activation can be inhibited by caloric satiety. In this case the ratings of food liking correlate with the NAcc activation, but only when hungry (Farooqi, I.S. et al. 2007; Billesa, S.K. et al 2012). Combined, these results suggest a role for leptin in the interaction of hunger and satiety signals to induce satiety dependent suppression of liking and wanting of food (Berridge, K.C. et al 2010).

Besides, in the VTA the leptin receptor (Lepr) has been found and Lepr comes also to expression in the hypothalamus, midbrain, cortex, brain stem and hippocampus. The VTA also contains dopamine neurons which express Lepr mRNA, as indicated by fluorescent immunohistochemistry (Hommel, J.D. et al 2006). The VTA is critical in the brain reward circuitry (Fulton, S. et al 2006). It is observed that direct administration of leptin in the VTA of rats, via surgically implanted bilateral cannulae, inhibits feeding behavior and there is primarily a dopamine neuron response (Hommel, J.D. et al 2006; Billesa, S.K. et al 2012). Dopamine neurons respond to leptin with a reduction in firing rate and activation of an intracellular JAK-STAT pathway, which is also observed in rat VTA brainslices, thus independent of the hypothalamus. Circulating leptin binds Lepr which results in phosphorylation of signal-transducer-and-activator-of-transcription 3 (STAT3) as seen in a phosphoprotein analysis (Hommel, J.D. et al 2006; Fulton, S. et al 2006). STAT3 was found to be increased and it is known that STAT activation has a role in food intake and long-term transcriptional changes (Hommel, J.D. et al 2006). Leptin-responsive VTA neurons project to the NAcc (Fulton, S. et al 2006). In addition, long-
term RNAi-mediated knockdown of Lepr in the VTA of rats increases feeding behavior, locomotor activity and sensitivity to high palatable foods (sucrose water and high fat rodent chow). Taken together, leptin decreases NAcc dopamine levels and inhibits firing of VTA dopamine neurons leading to a decrease in both dopamine release and food intake. Lepr regulates feeding behavior in the VTA and provides a direct function of a peripheral metabolic signal in the regulation of motivational or hedonic elements of eating (Hommel, J.D. et al 2006).

Besides influencing hedonic elements of eating, leptin is able to modulate reward-seeking behavior and drug relapse (Figlewicz, D.P. et al 2004; Shalev, U. et al 2001), behaviors known to depend on the function of mesolimbic dopamine circuits. It is demonstrated that leptin can influence food intake and locomotor activity via direct actions on mesolimbic dopaminergic neurons. Leptin-deficient ob/ob mice appear to have impaired mesolimbic dopamine. It is suggested that the acute inhibitory effect of leptin on food intake is partially mediate via the D2R and dopamine signalling. This has been demonstrated with a selective D2R antagonist which had no effect on feeding behavior in fasted mice, but blocked the hypophagic action of leptin. Just as a D2R KO mouse did not significantly reduce food intake upon leptin administration. Additionally, leptin reduced body weight regain in fasted mice and significantly reduced food intake. But the D1R antagonist did not attenuate the acute hypophagic effect of systemic leptin treatment or significantly alter food intake or reduced weight gain in fasted mice. This suggests that leptin’s anorexic actions are mediated through the D2R, and not D1R. Leptin also directly stimulates POMC neurons, which project to mesolimbic dopaminergic structures like the VTA. Leptin possibly influences midbrain dopamine signalling indirectly via the melanocortin system, as shown by a melanocortin agonist. Food intake was significantly reduced after agonist administration and neither D1R nor D2R inhibition attenuated the acute anorectic effect (Billesa, S.K. et al 2012). These findings suggest that leptin seemingly uses D2R in mediating its acute inhibitory effect on food intake and that the DR blockade has no effect on the acute hypophagic effect of melanocortin stimulation. Perhaps does the dopaminergic pathway not constitute a normal part of melanocortin-dependent feeding regulation and that the dopaminergic neurocircuitry typically associated with regulation of hedonic feeding likely contributes to feeding regulation by leptin. Taken together, these studies underline that the melanocortin system is not the primary site of leptin action and that leptin can also regulate feeding behavior via extrahypothalamic sites (Billesa, S.K. et al 2012).

**Reward system and ghrelin**

Ghrelin is a homeostatic regulator involved in the cognitive control over feeding behavior. It is a gut-released peptide that promotes food intake. When administered centrally, food intake and body weight increase (Naleid, A.M. et al 2005; Abizaid, A. et al 2006), consistent with the idea that the effects of ghrelin are mediated through its effects on the arcuate nucleus of the hypothalamus. Ghrelin is also found in the VTA of rats (Naleid, A.M. et al 2005), suggesting this is the predominant effector site of ghrelin for cognitive involvement in food intake. Ghrelin is implicated in regulating short-term control of food intake since ghrelin has been shown to declines after a meal and rise before the next meal (Daniels, S.R. 2008). In addition, it has been shown that fasting plasma ghrelin stimulates food intake in rats using systemic or intracerebroventricular injections of doses of ghrelin (Wren, A.M. et al 2001). Ghrelin has also been implicated in the long-term regulation of food intake. Additionally, ghrelin was found to inversely correlate with body fat, BMI, leptin and insulin concentrations (Shiiya, T. et al 2002; Tschop, M. et al 2001) and positively with caloric intake and giving in to cravings for highly palatable food (Buss, J. et al 2014). Furthermore, the ghrelin
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Concentration is significantly decreased in obese humans compared to lean subjects (Tschop, M. et al 2001; English, P.J. et al 2013; Shiiya, T. et al 2002; Buss, J. et al 2014). Therefore, it can be surmised that in humans the nutritional state is determinative for circulating ghrelin levels with ghrelin release increasing in response to a negative energy balance and decreasing when the energy balance becomes positive.

Besides decreased ghrelin levels in obese, it is observed that after consuming a meal lean individuals return quickly to baseline levels of circulating ghrelin, but that there is no alteration in plasma ghrelin or leptin in obese individuals. It is suggested that the normal fall in leptin levels provides the orexigenic ghrelin with a food intake suppression mechanism following a meal. Otherwise without suppressing this, as seen in obese individuals, it could lead to increased food intake. These findings suggest a role for ghrelin in the pathophysiology of obesity (English, P.J. et al 2013). The total amount of ghrelin in the plasma and its associations with hedonic eating, food intake, and stress are decreased in obesity. This provides the suggestion that in obesity central resistance to ghrelin could develop and that ghrelin's function in appetite regulation may have evolved to prevent starvation in food scarcity rather than cope with modern food excess (Buss, J. et al 2014).

In the VTA, ghrelin stimulates food intake via its receptor, ghrelin receptor growth hormone secretagogue 1 receptor (GHSR) (Abizaid, A. et al 2006), and has a positive effect on reward responses. Especially on the short-term effect of reward-based feeding behavior. Normally it is thought that ghrelin increases feeding behavior via the activation of NPY and AgRP neurons in the arcuate nucleus (Wren, A.M. et al 2001), but ghrelin in the VTA is NPY independent. Ghrelin activates its own receptors and increases dopamine release at target sites. Binding of ghrelin to its receptor canonically activates a Gq protein signaling pathway increasing phospholipase C activity, inositol triphosphate, diacylglycerol and calcium influx. Also, the ghrelin receptor co-couples to Gs protein activating the cAMP/CREb pathway. In the VTA, since activation of Gq or Gs proteins activates neurons, ghrelin receptors would likely to be found on dopamine neurons, rather than on inhibitory neurons expressing gamma-aminobutyric acid (GABA). Stimulation of GABA neurons in the VTA leads to inhibition of dopamine realease in target sites thereby decreasing motivated behavior. Stimulation of dopamine neurons would enhance dopamine release in these sites resulting in an increase of food intake (Naleid, A.M. et al 2005). Earlier, it was stated that leptin requires the D2R to modulate some of its anorexigenic functions, but ghrelin seems to be independent of dopamine signalling for its hyperphagic effect. Accordingly, it was found in mice that administration of D1R or D2R antagonists followed by ghrelin, significantly increased food intake. This hyperphagic effect was not disturbed by the pretreatment with D1R or D2R antagonists. Additionally, ghrelin was administered systemic to D2R KO mice and a significant increase of feeding behavior was found. These findings suggest that ghrelin does not need dopamine signalling via the D1R or D2R for its hyperphagic effect (Billesa, S.K. et al 2012), but uses GHSR to stimulate food intake and reward-based feeding behavior which could contribute to development of obesity.

Besides the effect of ghrelin on reward responses and its anorexigenic effect, ghrelin is also involved in responses to food related stimulation. Ghrelin injected intravenously in human subjects during fMRI increased the neural response to food pictures in different regions of the brain, including amygdala, orbitofrontal cortex, anterior insula and striatum. These regions are implicated in encoding the incentive value of food cues. These effects of ghrelin on the amygdala and OFC were correlated with self-rated hunger ratings. Metabolic signals such as ghrelin may favor food
consumption by enhancing the hedonic and incentive responses to food-related cues (Malik, S. et al 2008) and contribute thus to development of obesity.

**Discussion**

Obesity is a growing worldwide problem, while energy homeostasis is regulated by multiple systems. Short- and long-term food intake regulation and the hypothalamus provide a physiological mechanism for energy homeostasis (Havel, P.J. 2001). Feeding behavior can be triggered by depletion signals or by environmental or learned cues or it is triggered by the reward related to foods (Petrovich, G.D. et al 2002). The reward system interacts with normal feedback processes on food intake and metabolic factors and provides humans with a mechanism which stimulates non-homeostatic feeding. Thus hedonic responses can be modulated by homeostatic factors (Naleid, A.M. et al 2005). The mesolimbic mechanism does not only regulate locomotion and reward, but also energy balance. The dopamine neurons in the VTA express receptors for leptin and ghrelin and the mesolimbic dopamine neurons also respond to MCH and caloric availability. Ghrelin and leptin can influence short-term feeding in mice and in humans it is shown that they can influence striatal activity in response to food pictures (Naleid, A.M. et al 2005; Berridge, K.C. et al 2010). The hypothalamus is no longer considered as a single regulator of energy homeostasis. It is a complex process and many mechanisms are involved directly or indirectly.

Most research focusses on hormonal and neuronal mechanisms regarding to feeding behavior. There is actually sporadic evidence for failures of homeostatic systems and a large portion of the obese population does not seem to carry faulty genes (Berthoud, H.R. 2012). Research seems to conclude that the hormonal systems that inhibit eating are insensitive, but evidence points at intact and functioning systems working at the limits of their biological potency which are overruled by other factors which enhance food intake (Mela, D.J. 2006). Furthermore, there is little literature found which integrates multiple aspects of (non)homeostatic and hedonic components in the research on obesity, though it is known that it is a complex and integrated process which leads to obesity.

Here, homeostatic and hedonic components in relation to obesity were reviewed together. The reward pathways can reinforce feeding behavior and the type of food ingested. Obese individuals have an increased appetitive reaction to food cues and palatability, and high-caloric food activates the dopaminergic reward system (Berthoud, H.R. 2012). Overeating could be stimulated as a compensation for a ‘deficit dopaminergic signalling pathway’ leading to a hyposensitivity for reward. A decrease of dopaminergic activity in the VTA leads to an increase of high fat consumptions. A decrease in D2R expression in the dorsal striatum is seen in both obese subjects and cocaine addicts (Volkow, N.D. et al 2008). In obese individuals this change in D2R availability is considered a consequence rather than the cause of overeating (Berridge, K.C. et al 2010). On the other hand, a hypersensitivity to reward, could lead to reduced activity of the dopamine receptor due to repeated dopamine release from chronic overeating. This dose response curve is similar to those of drug addiction (Mela, D.J. 2006). It is questioned if obesity could be a form of food addiction. Under certain conditions there is supportive evidence for rats that become sugar dependent (Avena, N.M. et al 2007), but there is little evidence found which confirms that humans can be dependent of a high fat diet (Volkow, N.D. et al 2008). The hypothesis of food addiction is controversial but evidence has been found in some cases of compulsive overeating. The debate about food addiction is hindered with two different views on the definition of food addiction, since it is not clearly defined. The first view focusses on the artificially intense fatty, salty or sweet sensory stimulation and the
technologically-enhanced nature of modern processed foods, which supposes to become superincentive stimuli which possess drug-like motivating potency. The second view keeps the term food addiction limited to exceptions, in special for cases of extreme (compulsive) overeating. The debate continues about whether wanting for food can reach quite the same high levels of intensity that are thought to characterize drug addiction (Berridge, K.C. et al 2010). The biggest problem is that other forms of addiction are treated with changing the environment and completely stop the intake of the drug, this is not possible for food addiction. Food and drugs are thought to activate the dopamine pathway in a different manner. Food is considered to activate it via palatability which involves opioids and cannabinoids and elevation of insulin and glucose concentrations, which involves a dopamine increase, while drugs activate the dopamine pathway via their pharmacological effects. The drug abuse regulation is considered simpler than that of food intake, because feeding behavior is regulated by central, endocrinological and peripheral factors besides reward systems. In obesity and food addiction there are multiple brain pathways considered to be involved: reward/saliency, motivation/drive, learning/conditioning, inhibitory control/emotional regulation/executive function, emotion/mood regulation and interception. All together they modulate the propensity to eat or take drugs. A failure in one of these pathways is considered to enhance the value of one type of reinforcer (food or drugs). This could be a consequence of conditioned learning and resetting reward thresholds after repeated stimulation by for example high-density food or large quantities of food (Volkow, N.D. et al 2008).

And even dopamine’s function in the reward system is not firmly proven. K.C. Berridge and colleagues state that there is no direct evidence pointing out dopamine as a pleasure neurotransmitter in the mesolimbic system. The mesolimbic dopamine neurons are possibly not reliably activated by pleasure, but by predictive, motivational and attentional properties rather than hedonic properties of reward stimuli (Berridge, K.C. et al 2008). Currently there is a hypothesis that dopamine systems are only involved in ‘wanting’ and not in ‘liking’. ‘Wanting’ is thought to have directional aspects, such as appetite to consume food, and activational aspects, such as tendency to work for food (Salamone, J.D. et al 2002).

The brain reward circuits can be altered by homeostatic balance regulators such as dopamine, leptin, ghrelin or MCH signalling in a way that functions toward foods in much the same way if they were drug-sensitized. Thus the rewarding nature of food is modulated (Mela, D.J. 2006). This could lead to extreme cue-triggered wanting for foods, without being very hungry. The MCH mRNA levels increase in response to a high fat diet (Morens, C. et al 2005) which causes dopamine levels to rise and ultimately stimulates feeding behavior and reducing metabolic rate. And MCH mRNA levels also increase in response to fasting and expression levels are increased in obese (Sánchez-Lasheras, C. et al 2010). The MCH receptor is found in the NAcc were it regulates appetitive behavior. It is suggested that MCH has a general role in mediating responses to rewarding stimuli via communicating rewarding or hedonic aspects of food intake via the mesolimbic pathway (Salamone, J.D. et al 2002). The MCH neurons also express the leptin receptor, this suggest that these neurons can also respond to peripheral leptin signals in a direct manner (Hakansson, M.L. et al 1998; Coll, A.P. et al 2007). MCH research in rodents could provide functional differences in the expected and actual mechanisms in humans, because rodents have one MCH receptor while humans have a two (Georgescu, D. et al 2005).
The dopamine mesolimbic pathway could also serve as a potential mediator of the effects of leptin on energy homeostasis. Leptin is often associated with regulation of feeding behavior and satiety, but recently leptin is also found to be involved in reward pathways (Mela, D.J. 2006; Naleid, A.M. et al 2005). Lepr regulates feeding behavior in the VTA and provides a direct function of a peripheral metabolic signal in the regulation of motivational or hedonic elements of eating (Hommel, J.D. et al 2006). The decrease in dopamine and the regulation via the D2R contribute to the inhibition of feeding behavior. The effects of leptin on the D2R receptor could be exaggerated. It is shown that overnight fasting could influence studies of D2R, because D2R expression increases in food restricted states as well as that chronic obesity is associated with altered D2R availability. Additionally, it is also shown that centrally administered leptin has increased sensitivity in D2R KO mice. The contradictory outcomes could originate from differences of methodology, as a difference of injecting leptin systemically or centrally (Billesa, S.K. et al 2012). Leptin itself does not seem to be capable to inhibit liking and wanting, it is more likely that it supresses it. In contradiction with this view, in lepin deficient mice (ob/ob) leptin actually seemed to stimulate innate low levels of dopamine in the NAcc. The mesolimbic dopamine circuits and food wanting can be modulated by leptin via the arcuate nucleus and the ventral tegmental area (Berridge, K.C. et al 2010). Taken together, it is suggested that leptin in the hypothalamus inhibits overeating and in the midbrain it regulates the food reward response. This could be explained by the idea that mesolimbic dopamine signalling regulates hedonic food intake while the melanocortin system regulates homeostatic food intake. This idea stems from the role of mesolimbic signalling in drug addiction and reward and the role of the hypothalamus in energy homeostasis. According to this theory, mesolimbic systems are separate and ancillary to the primary role of the mediodsal hypothalamus in regulation of energy intake and expenditure. The melanocortin system does not work alone in the regulation of homeostatic feeding behavior and the mesolimbic dopamine signalling does not only regulate behavior motivation (Billesa, S.K. et al 2012).

Hedonic and incentive responses to food-related cues could also be enhanced by ghrelin and thus favors food consumption (Malik, S. et al 2008) and is involved in the pathophysiology of obesity (English, P.J. et al 2013). Fasting plasma ghrelin stimulates food intake (Wren, A.M. et al 2001) and is negatively correlated with body fat, BMI, leptin and insulin concentrations (Shiiya, T. et al 2002; Tschop, M. et al 2001) and positively with caloric intake and giving in to cravings for highly palatable foods (Buss, J. et al 2014). The effects of ghrelin are mostly the opposite of that of leptin, but not always. This is confirmed by the fact that leptin requires D2R, but D2R antagonists or KO did not reduce the increase in feeding behavior caused by ghrelin. Ghrelin does not require dopamine signalling, but intact hypothalamic pathways for this function (Billesa, S.K. et al 2012). This is interesting, as ghrelin can elicit a positive effect on reward responses via the GHSR in the VTA. It is speculated that ghrelin can modulate reward pathways without interacting with dopamine.

**Concluding remarks**

It is clear that eating and energy regulation are not simple regulated mechanisms and that there is a complex interaction of genetic, environmental, behavioral and social factors (Considine, R.V. et al 1997). Here, evidence is found that psychology plays a major role in homeostatic food intake and adipose store regulation. The mesolimbic dopaminergic signalling pathway and several factors contribute to this (Billesa, S.K. et al 2012). The psychology seems to be able to overrule the physiological mechanisms of feeding behavior. This leads to adaptive behavior, changes in survival strategies (Naleid, A.M. et al 2005) and in the case of obesity to (psycho)pathologies. Physiology and psychology and thus metabolism and reward are extremely connected regarding to feeding behavior.
Often the physiological mechanisms of the hypothalamus are investigated in relation to food intake and energy homeostasis. This review provides evidence for a much more complex system, where the reward pathways are involved. Understanding these intertwined mechanisms, could provide an impulse in obesity prevention and treatment since cause and effect of obesity and changes in the reward system are not yet fully understood.

Although dopaminergic systems are known to influence reward-based feeding, this review underlined the importance of the mesolimbic dopamine systems for homeostatic regulation of feeding (Billesa, S.K. et al 2012). Dopamine is involved in food motivation and reward. A lot of research focusses on the role of dopamine in mediating reward-based food intake. This review also focussed on other, peripheral signals which affect this reward system and feeding behavior as dopamine’s function is influenced by many factors (Berridge, K.C. et al 2010). Keep in mind that there are many other metabolic signals proposed to have influence on reward related to food, such as insulin and glucose, which are not discussed here. Most of the research used here interpreted the data to describe mesolimbic dopamine actions, but possibly some of the effects of dopamine signalling may occur in the hypothalamus or other brain regions. Further research is needed to determine which brain regions provide the location for the interactions between metabolic signals and the reward pathway. And research should investigate what the mesolimbic systems contribute to physiologic feeding regulation and how this may contribute to obesity (Billesa, S.K. et al 2012). As well as it would contribute to better and personalized prevention strategies and therapeutic treatments for obesity, if the liking and wanting mechanisms would be unravelled. Improving these treatments with environmental control while structuring and limiting food stimulation and providing a balanced diet could provide better outcomes than of those contemporary treatments (Mela, D.J. 2006).

It is tempting to suggest that obesity is the consequence of humans failing to resist their own highly palatable foods and that even metabolic mechanisms function to stimulate and motivate to eat beyond satiation. One could speculate that modern humans have to cope with an energy homeostasis programmed for survival and food scarcity in ancient times.
References


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**Figures**
