The obese brain: neuroendocrine modulations in the reward system

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Abstract

Obesity is a widely acknowledged problem, reaching even epidemic proportions. Despite awareness of the severe adverse consequences on health, food is excessively consumed. Why? Food intake is strongly influenced by the homeostatic balance, but this process can be overruled by hedonic systems that promote overconsumption. The reward system is thought to play a role in this hedonic regulation of food intake. This review will discuss neuroendocrine modulations found in reward pathways that may underlie obesity, with the focus on dopamine. Modulations in the corticomesolimbic system of obese individuals include reduced expression of dopamine 2 receptors, elevated dopamine levels, hyperactivity of sensory cortices, reduced prefrontal cortex activity and enhanced μ-opioid receptor binding. Many of these are associated with drug addiction as well. Yet these modulations are not well understood and may rather be consequences of an energy dense diet.

Contents

1 Introduction

Obesity is a widely acknowledged problem. The prevalence of overweight people not only already exceeds alarming numbers, but is still increasing further (Wang et al., 2011). Over 65 percent of the people in the USA are currently overweight (BMI $>$ 25), of which half is obese (BMI $>$ 30), and Europe is slightly behind (Flegal et al., 2010; WHO, 2012; WIN, 2012). Although obesity is mainly a problem of Western society, it really is a global epidemic. Approximately one in five people of the world population is overweight and the prevalence in developing countries is increasing as well (WHO, 2012). A link between obesity and severe secondary diseases, such as diabetes mellitus and cardiovascular diseases, has been clearly established (WHO, 2012). Cardiovascular disease is even the leading cause of death in the world (Roger et al., 2011). The global cost of the obesity epidemic due to the extra health care needed is ever rising, for example in the USA estimated to be as high as $150 billion per year (Finkelstein et al., 2009). Therefore, the risks and costs associated with obesity cannot be underestimated.

Despite being aware of the risks, people keep eating more and more unhealthy food. Lifestyle intervention and advice to exercise more are insufficient to bring back the number of obese people, even though many feel uncomfortable about it. Why are people eating more than necessary, why is it so difficult to simply limit food intake? To find an answer, the causes of overeating have to be elucidated. These causes are complex, since many different hormonal and neuronal pathways are involved in eating behaviour (Morton et al., 2006). Although satiety signals generally inhibit food intake, satiety can be overruled by the reward system (Zheng & Berthoud, 2007). The reward system, mainly consisting of midbrain dopamine and opioid pathways, may be modulated in obese individuals by neuroendocrine factors in such a manner that the motivation to eat is highly enhanced and predominates the homeostatic balance (Fulton, 2010). However, it is unclear whether obesity is a consequence or rather a cause itself of modulations in the reward system.

After a short overview of the regulation of food intake and motivation, I will therefore review neuroendocrine modulations found in reward pathways that may explain obesity, and discuss whether these modulations are cause or consequence of overconsumption. Because it goes beyond the scope of this thesis to include the entire reward system, the focus will be on dopamine pathways.

2 The regulation of food intake

2.1 Short-term and long-term signals

After a period of food deprivation, animals (including humans) become hungry due to various homeostatic signals that are released during fasting. There are short-term signals surrounding the meal and long-term signals relaying information about long-term availability of fuel. A low blood glucose level, detected directly in the brain, is a strong stimulus for food intake, which is necessary since neurons are highly dependent on glucose (Brown & Ransom, 2007). The 'hunger hormone' ghrelin is important for the initiation of a meal and is released when the stomach is empty, while its concentration in the blood sharply declines during food consumption (Klok et al., 2007). Other hormones are more chronically released. Leptin, for example, is secreted by adipose tissue, which is actually an endocrine organ and releases many other factors such as adiponectin, resistin and several cytokines (Kershaw & Flier, 2004). The concentration of leptin in the blood directly

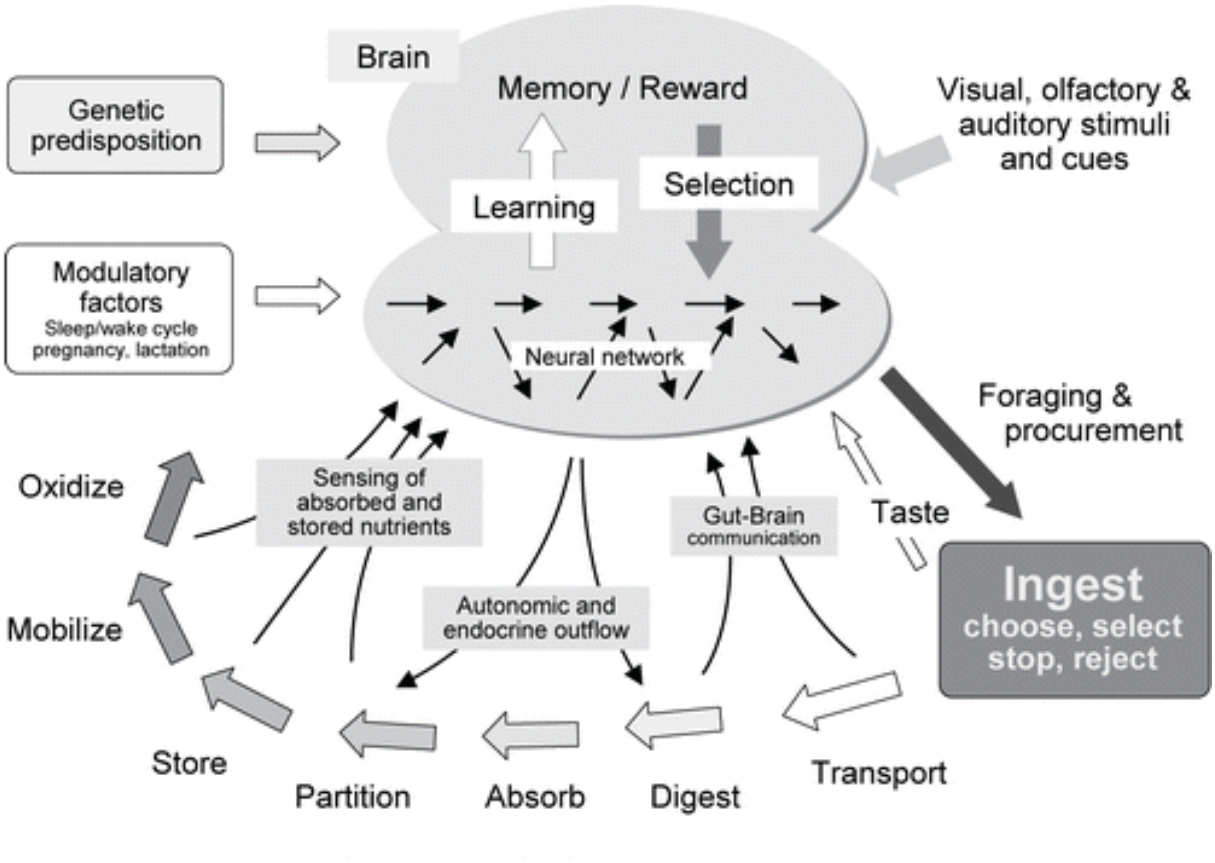

Figure 1: Signalling pathways from the gut to the brain. Taste, stimulation of the nervus vagus, and absorbed and stored nutrients influence brain areas that regulate ingestive behaviour. This process is also influenced by sensory food cues, memory, reward, and modulatory and genetic factors. Figure by Berthoud & Morrison, 2008.

reflects the amount of fat in storage proportionally (Considine et al., 1996): the more stored fat, the more leptin is secreted. That is the reason why leptin levels in obese people are generally elevated. The absence of leptin and glucose is a strong stimulator of food intake, while the hormones insulin and glucagon reflect blood glucose levels, but influence food intake quite weakly (Bruning et al., 2000). These hormones, among several others, travel via the bloodstream to the brain, where they bind to receptors in the hypothalamus.

During food consumption, information about smell and taste travels to the brainstem and the nucleus tractus solitarus (NTS) (Saper et al., 2002), eliciting a pleasurable or aversive feeling. Ingested nutrients like glucose and protein interact with receptors in the stomach that send signals to the brain, mainly via fibers of the nervus vagus that synapse in the NTS, and via the excretion of hormones (Morton et al., 2006; fig.1). Distension of the stomach stimulates these vagal afferents as well, simultaneously suppressing secretion of ghrelin (Cummings, 2006). Further in the gastrointestinal tract, most importantly cholecystokinin (CCK), Peptide YY3-36 (PYY3-36) and Glucagon Like Peptide-1 (GLP-1) are released in response to nutrients, signalling satiation (Morton et al., 2006).

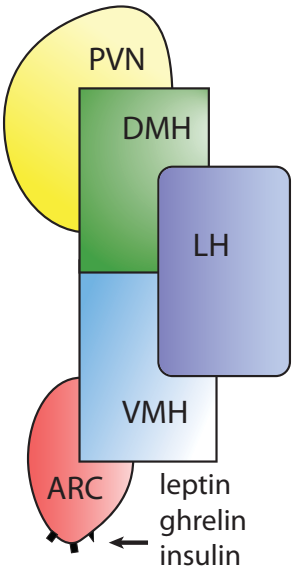

Figure 2: Regions in the hypothalamus involved in food intake. Paraventricular nucleus (PVN) and lateral hypothalamus (LH): integration centres of homeostatic signals; arcuate nucleus (ARC): detection of circulating hormones and nutrients; dorsomedial hypothalamus (DMH); ventromedial hypothalamus (VMH). Lateral view. Adapted from Kandel, Schwartz & Jessel, 2000.

2.2 The hypothalamus

The hypothalamus, the so-called 'satiety centre' of the brain (Wynne et al., 2005), subsequently integrates all homeostatic signals. The hypothalamus consists of several parts (fig.2) that are highly connected to each other and many other brain regions. Circulating glucose, fatty acids, amino acids and hormones are mainly detected by the arcuate nucleus (ARC), which is easily accessible as it is not protected by the blood-brain barrier (Wynne et al., 2005). Leptin, insulin, ghrelin and other hormones can directly bind to receptors expressed on neurons in the ARC. Neurons that detect glucose are present in the lateral (LH) and ventromedial hypothalamus (VMH) as well (Levin et al., 2011).

Two types of cells predominate in the ARC: neurons that express neuropeptide Y (NPY) and agouti-related peptide (AgRP), that stimulate eating, and neurons that express pro-opiomelanocortin (POMC), a precursor that is cleaved into α-melanocyte-stimulating hormone (α-MSH), which inhibits eating (Marks et al., 2001; Ollmann et al., 1997; fig. 3). NPY/AgRP neurons mainly project to the paraventricular nucleus (PVN) of the hypothalamus and the lateral hypothalamus (LH). NPY, binding to Y1-Y6 receptors (Lin et al., 2004), is one of the most potent stimulators of food intake that is known (Griffond & Risold, 2009) and can induce food intake when administered in the absence of hunger (Stanley et al., 1985). Both AgRP and α-MSH bind to melanocortin 3 (MC3R) and 4 (MC4R) receptors - as agonist and antagonist respectively (Adan & Kas, 2003; Lu et al., 1994; Tao, 2010) -, present in several different hypothalamic nuclei, most importantly the paraventricular nucleus (PVN), VMH and dorsomedial nucleus (DMH), and in other brain areas including some involved in reward (Berthoud, 2004; Lindblom et al., 2001). Melanocortin neurons are thought to tonically suppress food intake via inhibitory GABA-ergic signalling, which is enhanced by stimulation of the MC3R and MC4R (Fan et al., 1997). Activation of MC4 receptors decreases meal size and fat intake, but does not affect meal frequency, initiation and anticipation (Adan et al., 2006, Hillebrand et

al., 2006; Samama et al., 2003; Wallingford et al., 2009). Dysfunction of MC4 receptors, on the other hand, increases food intake and obesity (Chen et al., 2000a; Huszar et al., 1997; Mul et al., 2012), simultaneously reducing energy expenditure (Marsh et al., 1999; Marie et al., 2000). A high-fat diet can increase activation of the MC4 receptor (Adan et al, 2006), suggesting a negative feedback mechanism by which fat limits intake of itself. The MC3R is expressed on POMC neurons (Jegou et al., 2000) and inhibits their action, however, mice with a MC3R deficiency still become obese (Butler et al., 2000; Chen et al., 2000b), suggesting a minor role for MC3R in comparison with MC4R. Little is known yet about the downstream mediators of MC4R and MC3R signalling (Breit et al., 2011; Tao et al., 2010).

Leptin, insulin and PYY3-36 bind to receptors on ARC neurons and suppress NPY/AgRP neurons while stimulating POMC neurons, thereby decreasing food intake and obesity (fig. 3) (Cowley et al., 2001; Flier, 2004). Ghrelin also binds to ARC receptors, but functions in the opposite manner. The ARC projects to secondary neurons within the hypothalamus, such as the PVN, LH, VMH and DMH (Wynne et al., 2005). It is thought that information from the opposing NPY/AgRP and POMC neurons is integrated in these hypothalamic areas with information from other brain areas, whereupon it is further projected to third- and higher order neurons (Berthoud & Morrison, 2008). For example, in addition to the ARC, the LH receives information from brain areas associated with memory and learning (hippocampus), motivation (midbrain), and arousal and sensory input (brainstem, nucleus tractus solitarus) (Berthoud & Morrison, 2008). The LH then projects to areas throughout the entire brain, influencing almost all neural activity (Berthoud, 2002).

Indeed, the LH is an important centre for the integration of homeostatic signals: lesions in the LH in rats and cats resulted in decreased food intake (Anand & Brobeck, 1951), while electrical stimulation in rats had the opposite effect (Hoebel & Teitelbaum, 1962). The orexinergic peptides orexin A and B, and melanin concentrating hormone (MCH) are solely produced in the LH and are released under the influence of POMC and NPY neurons in the ARC (De Lecea et al., 1998; Sakurai et al., 1998; fig. 3). Orexin, or hypocretin, and MCH stimulate food intake via projections to various brain areas associated with arousal, reward and motivation (brainstem, nucleus accumbens, prefrontal cortex) (Cason et al., 2010; Griffond & Risold, 2009), binding to orexin-1, orexin-A and MCH receptors (Marsh et al., 2002; Rodgers et al., 2002). Injection of MCH in rats initiated eating behaviour (Qu et al., 1996), while mice and rats lacking MCH ate less and were lean (Marsh et al., 2002; Mul et al., 2010; Shimada et al., 1998). In addition to inducing food intake in response to food deprivation, orexins and MCH are involved in reward behaviour (Aston-Jones et al., 2009; Aston-Jones et al., 2010; Borgland et al., 2010; Harris et al., 2005; Mul et al., 2011) and other processes (Chung et al., 2011; Bradley et al., 2000; Hanriot et al., 2007). The main difference between these two peptides is that orexins are thought to affect food intake via inducing arousal and alertness, while MCH seems to be primarily involved in eating behaviour. This is illustrated by the fact that orexin deficient mice are narcoleptic (Chemelli et al., 1999; Willie et al., 2003).

Hypothalamic nuclei in turn project to third- and higher-order neurons in various other brain areas. Although the homeostatic balance strongly influences eating behaviour, it can be dominated by other systems. The process that controls eating without homeostatic need is often referred to as 'hedonic control of eating'. The reward system is thought to play a role in this by increasing the motivation to eat during a positive energy balance (Saper et al., 2002).

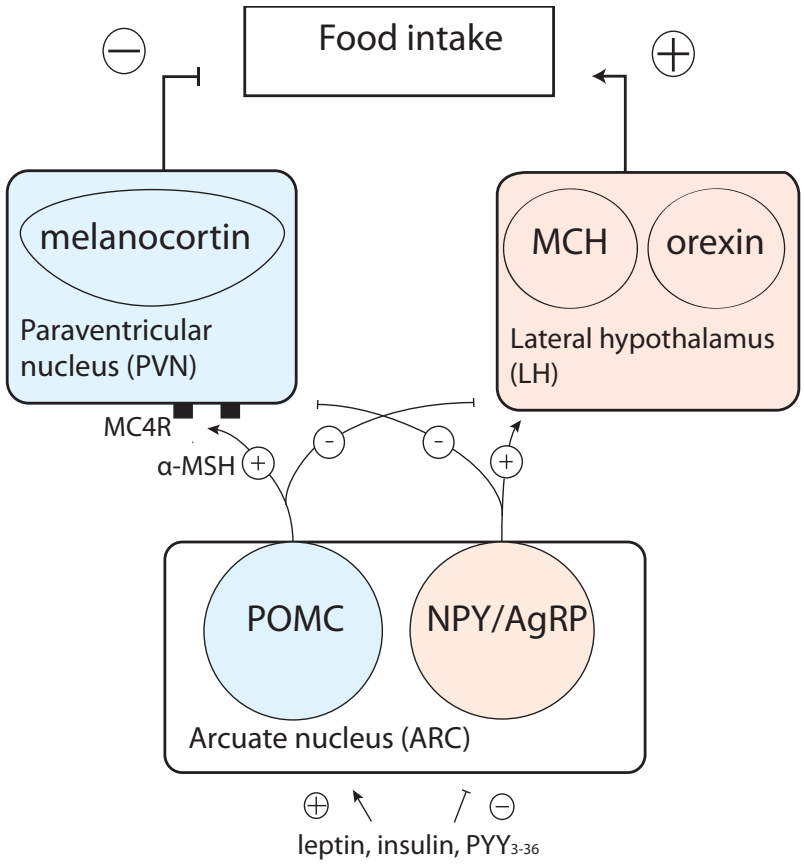

Figure 3: The main hypothalamic pathways involved in food intake. POMC neurons activate melanocortin neurons in the PVN through binding of α-MSH to MC4 receptors, and inhibit MCH and orexin neurons in the LH. NPY/AgRP neurons act in the opposite manner. Melanocortins inhibit food intake, while MCH and orexins stimulate food intake. Circulating hormones can bind to receptors expressed in the ARC, thereby influencing this pathway. α-MSH= α-melanocyte-stimulating hormone; AgRP= agouti-related peptide; MC4= melanocortin 4; MCH= melanin concentrating hormone; NPY= neuropeptide Y; POMC= pro-opiomelanocortin

3 The reward system

3.1 Motivation, liking and wanting

The motivation to eat is generally very high in animals (including humans), not surprisingly, because food intake is essential for survival. Nutrient-dense food is very cost-effective and extra pleasurable and therefore harder to resist than bland food. This is due to higher rewarding effects: a rewarding experience contributes to motivation to repeat the experience. The term motivation is used for a broad system of various neuronal and physiological factors that initiate, sustain and direct behaviour (Kandel, Schwartz & Jessell, 2000). Simple motivation arises from so-called drive states: states of discomfort that drive our attention and behaviour to remove the discomfort, like hunger or coldness. Reward, on the other hand, is involved in more complex motivation. The following formula illustrates how different factors can contribute to motivation (Hull, 1943):

$$M = E \cdot D \cdot V,$$

where M is motivation, E is the experience or habit strength, D is drive state or duration of deprivation and V is the rewarding value of the object. In the context of eating behaviour, D could be explained as the energy balance and V as the pleasure experienced during food consumption (Figlewicz & Benoit, 2009). This formula demonstrates that motivation to eat is usually small when the energy balance is positive, yet when the rewarding value or habit strength is sufficiently large, the motivation will be high after all, overruling the 'homeostatic control' of food intake (Saper et al., 2002).

The term reward is used for actions or objects that prioritize behaviour and cause the animal to put effort in procuring the reward, due to accompanying pleasurable feelings that cause positive reinforcement (Fulton, 2010). A distinction between 'wanting', more associated with dopamine, and 'liking', more associated with opioids, is often made (Berridge, 1996; Volkow et al., 2011): liking refers to the hedonic value, palatability or pleasurable feeling associated with food, while wanting, or incentive salience, is considered to be a desire that stimulates goal-directed behaviour to obtain the food and is therefore often regarded as motivation. Most often these terms overlap and depend on each other, since the more something is liked the more it is generally wanted. Yet wanting without liking can exist during an addiction, when a stimulus is intensely wanted despite that it is not liked, and people can like food without feeling the need to eat it. Wanting is generally measured by behaviour itself, while liking is not as easily measured because it depends on subjective feelings. Wanting is often measured with a 'progressive ratio schedule of reinforcement' (Richardson & Roberts, 1996) that demonstrates how much effort an animal is willing to spend for a food reward, often by progressively increasing the amount of levers that needs to be pressed for each subsequent reward. Liking in animals is often measured by orofacial reactions, although it is difficult to separate from wanting.

Food wanting arises from previous experiences with pleasurable food (liking). Subsequently, associated cues such as smell or sight can elicit or augment wanting, not necessarily consciously (Peciña & Smith, 2010). This mechanism of cue associated learning is widely used in experiments to teach laboratory animals tasks, by rewarding them with food (Figlewicz et al., 2007; Figlewicz et al., 2009). The fact that humans are confronted with many food cues in their daily life likely contributes to obesity (Jansen, 1998; Hill & Peters, 1998; Ulijaszek, 2002). This is illustrated by the fact that obese individuals are often more sensitive to food cues (Braet & Crombez, 2003; Castellanos et al., 2009) and

these cues can induce eating in the absence of hunger or overeating during ad libitum circumstances, if previously paired with food during a hungry state (Petrovich et al., 2002; Petrovich et al., 2007; Petrovich, 2011). Remarkably, food cues can even induce insulin release during anticipation (Woods, 1991). This 'cue induced feeding' or 'conditioned potentiation of feeding' can be mimicked with for example the 'Pavlovian-instrumental transfer test', in which rats receive a reward after pressing a lever, whereupon this reward is associated with a cue. The cue is then presented without the reward and the amount of lever pressing is an indication of the desire to receive the reward (Peciña & Berridge, 2008). Still, all humans are confronted with food cues like advertisement, while not everyone is obese: why do some people eat excessive amounts of food while others do not? Of interest is what exactly determines how rewarding food is, and how modulations in the reward system could contribute to obesity.

3.2 Structure and function of the dopamine system

Reward is thought to be mediated mainly by the dopaminergic mesolimbic or corticomesolimbic system and the opioid system. There are two distinct dopamine pathways. The pathway associated with reward consists of midbrain dopamine neurons that originate in the ventral techmental area (VTA) and project to the limbic system, including the nucleus accumbens (NAc) in the ventral striatum, the amygdala, hippocampus and ventral pallidium (VP), and to the prefrontal cortex (PFC) (Kandel, Schwartz & Jessell, 2000; fig. 4 and 5). Dopamine pathways originating in the substantia nigra are mainly involved in movement initiation, defects leading to Parkinson's disease (Dauer & Przedborski, 2003). Mice that completely lack dopamine, therefore, die of starvation (Zhou & Palmiter, 1995) likely due to movement disorders. There are three types of opioid receptors (μ, κ and δ) with their ligands (endorphin, enkephalins and dynorphins) and the opioid system co-localizes with dopamine neurons: binding to μ-opiod receptors in the VTA and κ-opioid receptors in the NAc influences dopamine release in the NAc (Herz, 1997; Spanagel et al., 1992). In addition, a population of opioid neurons is located in the NAc, projecting to the VP (Herz, 1997). Other neurotransmitters influence reward as well, most importantly cannabinoids, serotonin, GABA and glutamate (Fulton, 2010; Jamshidi & Taylor, 2000; Stanley et al., 2005; Zhang et al., 1998). Because describing the reward system in all its complexities is beyond the scope of this thesis, the focus here will be on the dopamine system.

The involvement of the NAc in rewarding sensations was first shown when electrical stimulation of the human NAc - mainly receiving input from VTA dopamine neurons - led to a strong feeling of pleasure (Bishop et al., 1963). Similar experiments in animals showed desire for electrical stimulation and self-administration of drugs of abuse directly in the NAc, sometimes even preferred to food intake (Corbett & Wise 1979; Olds & Milner, 1954; Olds, 1982). Additionally, dopamine release in the NAc correlated with a pleasurable feeling (Small et al., 2003; Wang et al., 2001), dopamine neurons showed phasic activity when animals encountered food rewards (Ljungberg et al., 1992), the midbrain and striatum were activated during intake of highly palatable food (Small et al., 2001), accompanied by increased dopamine levels in the NAc depending on sweetness (Hajnal et al., 2004; Hernandez & Hoebel, 1988) and the NAc showed increased activation during intake of drugs of abuse in rats (Di Chiara & Imperato, 1988; Imperato & Di Chiara, 1986) and humans (Drevets et al., 2001; Leyton et al., 2002). Particularly the NAc receives and integrates many projections from the limbic system (Kandel, Schwartz &

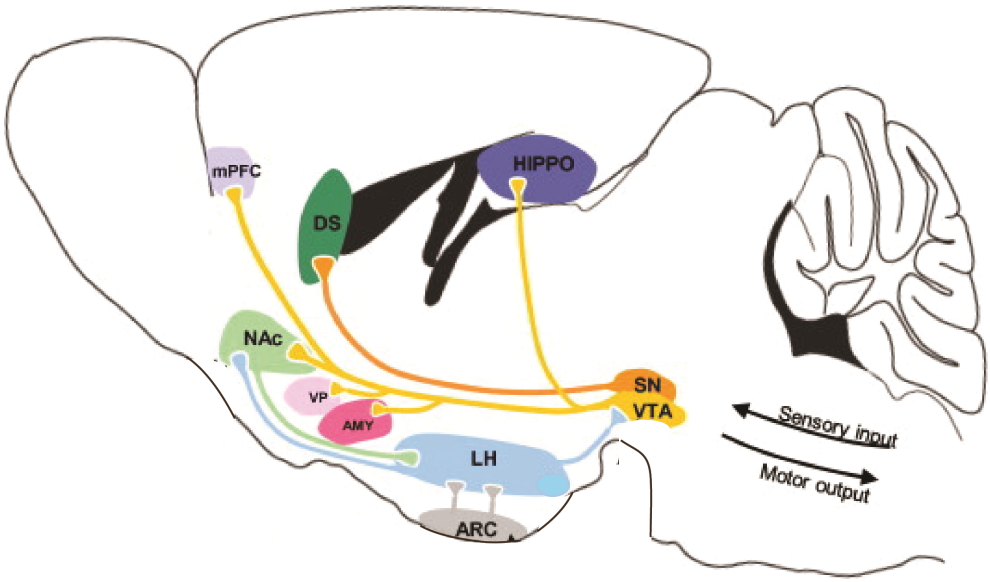

Figure 4: Structure of the mesocorticolimbic dopamine system. Midbrain dopamine neurons in the VTA project to several limbic and cortical sites. The NAc integrates information about emotion, cognition, metabolic state and sensory information arising from VTA, AMY, mPFC, HIPPO, ARC and LH, and projects to the VP. Descending projections to basal ganglia motor outputs convert motivation to action. AMY=amygdala, ARC=arcuate nucleus, DS=dorsal striatum, HIPPO=hippocampus, LH=lateral hypothalamus, mPFC=medial prefrontal cortex, NAc= nucleus accumbens, SN=substantia nigra, VP=ventral palladium, VTA=ventral techmental area. Adapted from Fulton, 2010.

Jessell, 2000) that is involved in emotion, memory and the sensation of feelings (Cardinal et al., 2002; Mesulam, 1998; Olton et al., 1979), which emphasizes the importance of the NAc. Dopaminergic projections from the VTA likely influence this input and modulate the output of the NAc to structures like the VP and hypothalamus. In the VTA, dopaminergic neurons predominate, but GABAergic and glutaminergic neurons are also present (Nair-Roberts et al., 2008).

The NAc can be divided into core and shell, the latter more involved in motivation and hedonic aspects. In the shell, there are specific small regions that enhance the hedonic value of food ('hedonic hotspots'). Infusion of μ-opioid receptor agonists only in these sites strongly modulated the hedonic value of food (Peciña & Berridge 2005; Peciña & Smith, 2010), measured by taste-reactions in rats to sucrose (Grill & Norgren, 1978). As opposed to these hotspots, the entire NAc shell seems to be involved in 'wanting': after infusion with μ-opioid agonists in the shell, the willingness of rats to work for a sucrose reward during the progressive ratio test was increased (Zhang et al., 2003), as well as wanting measured by the Pavlovian instrumental transfer test (Peciña & Berridge 2008). Also, a specific neuron population within the NAc shell has been found to be inhibited immediately prior to food intake (Taha & Fields, 2005; Taha & Fields, 2006), possibly suggesting that inhibition of these neurons is important for initiating food intake.

The projection from the NAc to the ventral pallidium (VP), a limbic structure situated in the basal ganglia, may be a final common pathway for reward signals (Kalivas et al., 1999; Napier & Mitrovic, 1999). Rats with lesions in the caudal VP show aversive reactions to a normally pleasant taste like sucrose (Cromwell & Berridge, 1993). Also, neuronal firing in this brain site seems to correlate with hedonic value: these neurons fire with

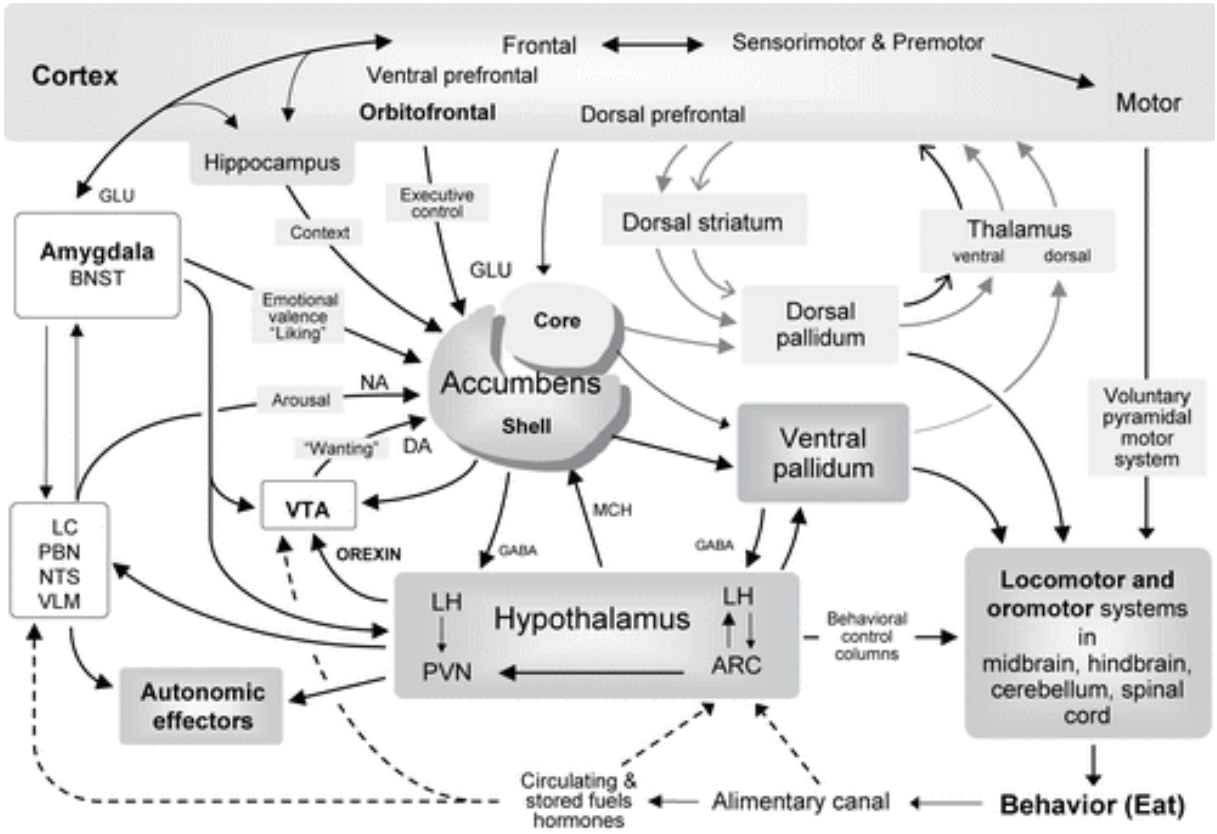

Figure 5: The nucleus accumbens is widely connected to for example cortical and limbic areas, the hypothalamus, VTA and ventral pallidium. These pathways are implicated in eating behaviour. DA=dopamine; NA=noradrenaline; GLU=glutamate. Figure by Berthoud & Morrison, 2008.

high frequency in response to palatable food (sucrose) and with low frequency in response to disliked food (salt), yet when the hedonic value of disliked food is enhanced (by salt depletion) frequency of firing increases (Aldridge & Berridge, 2010). In contrast, GABA release in the VP possibly corresponds with 'wanting' (Shimura et al., 2006; Smith & Berridge, 2005): neuron populations fire rapidly when cues are presented that predict a sucrose reward (Tindell et al., 2004). Of course, it is unknown if firing of these neurons is a cause or consequence of increases in hedonic value and wanting. Nonetheless, it might mean that specific sites both in the NAc shell and VP are involved in modulation of the hedonic and incentive value of food.

Besides the VP, the VTA and NAc are connected to many cortical and limbic areas, including the amygdala, hippocampus and prefrontal cortex (PFC) (Fulton, 2010; fig. 4 and 5). The amygdala and hippocampus can influence the value of an object or action with emotions and memories, while the PFC is involved in the control of impulses, in planning and attention (Spinella, 2004). In turn, the cortex and ventral pallidum project to the motor system, converting motivation to action (Fulton, 2010). Closely related to reward, the mesocortical dopamine system seems to be involved in learning, prediction and attention (Salamone & Correa, 2012; Schultz, 2002; see section 2).

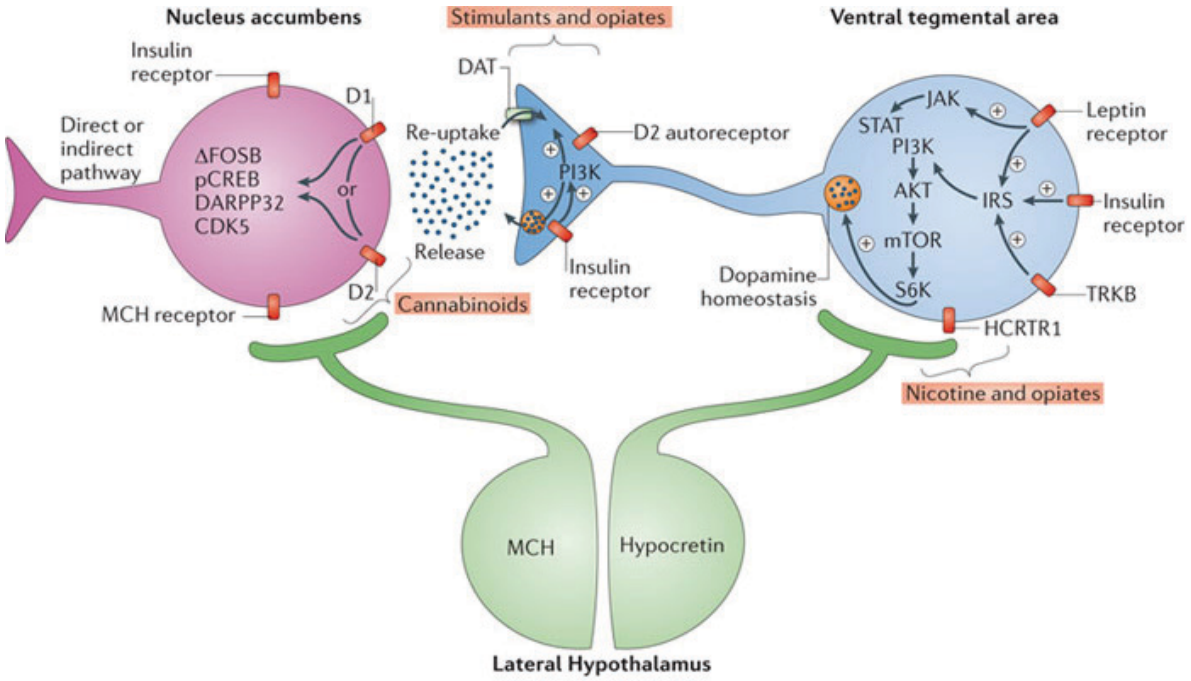

Figure 6: Projections from the LH to the VTA and NAc. Orexin, or hypocretin, is secreted in the VTA, while MCH binds to receptors in the NAc. Additionally, this figure shows how leptin, insulin, opiates and cannabinoids influence dopamine signalling. DAT= dopamine reuptake transporter; HCRTR1= hypocretin receptor 1. Figure by Kenny, 2011.

3.3 Interactions between the hypothalamus and corticolimbic system

The VTA and NAc receive input from the lateral hypothalamus (LH) via neurons expressing orexin and MCH (Chung et al., 2009; Fulton, 2010; fig. 5 and 6) and dopamine neurons express MC4 and NPY receptors (Saper et al., 2002). MCH+ and orexin+ neurons are very well-connected to the cerebral cortex as well, enabling them to influence many brain processes (Saper et al., 2002).

Evidence for a role of these neurons in reward behaviour has been found in several studies. An association between orexin activation in the LH and the reinforcing value of food was demonstrated by responsiveness to conditioned place preference (Davis et al., 2011a; Harris et al., 2005), a test in which a specific environment is associated with food rewards. In sated rats lacking orexin signalling in the VTA, opioid receptor activation in the NAc could no longer induce high-fat appetite (Zheng et al., 2007). This led researchers to hypothesize that the NAc, via opioid receptor stimulation, activates orexin neurons in the LH, which in turn project back to the VTA, eventually stimulating intake of high-fat food (Cason et al., 2010; Fadel & Deutch, 2002; Stratford & Kelley, 1999). Orexins not only induce food intake and arousal in response to food deprivation (De Lecea et al., 1998; Sarukai et al., 1998), but also independent of the homeostatic balance (Aston-Jones et al., 2009; Aston-Jones et al., 2010; Borgland et al., 2010), possibly mediated by the connection between the NAc, hypothalamic orexin neurons and the VTA. More specifically, orexins might be important for reward-seeking behaviour elicited by associative stimuli: orexin antagonists decreased intake of high-fat, high-sugar food and ethanol, but did not decrease intake of cocaine (Cason et al., 2010). Together these results show that orexin signalling may be involved in the hedonic regulation of food intake.

MCH signalling to dopamine neurons is important in the modulation of food intake as

well. MCH receptors are expressed throughout the entire dopamine system, most densely in the nucleus accumbens shell (Chung et al., 2009; Saito et al., 2001) and to a lesser extent in the VTA (Cason et al., 2010; Pandit et al., 2011). Injection of MCH directly into the NAc shell of rats stimulated food intake, while MCH receptor antagonist administration in the NAc had the opposite effect (Georgescu et al., 2005; Nair et al., 2009) and also led to diminished cocaine self-administration (Chung et al., 2009). Rats with MCH deficiency reduced meal size and responded less strongly to high-fat food reinforcement (Mul et al., 2011), which was reversed with injection of MCH into the NAc shell. Moreover, these rats had increased dopamine release and elevated levels of the DAT, indicating that MCH influences dopamine signalling.

Melanocortins and NPY can bind to receptors on dopamine neurons, but it is unclear if this occurs via projections from POMC and NPY/AgRP neurons of the ARC since these neurotransmitters are also expressed in other brain sites. POMC overexpression in the ventral techmental area, processed to α-MSH, resulted in attenuated high-fat diet-induced obesity (Andino et al., 2011). MC4 receptors, binding α-MSH and AgRP, are expressed in the NAc (Kishi et al., 2003; Mountjoy et al., 1994) and injection of AgRP is accompanied by Fos expression in the NAc, an indication of activity (Hagan et al., 2001). NPY receptors and high levels of NPY were found in the NAc, VTA, hippocampus, amygdala and cerebral cortex (Liang et al., 2012; Widdowson, 1993), and NPY cell bodies were situated in the hippocampus and cerebral cortex (Adrian et al., 1983; Gray & Morley, 1986). Injection of NPY in the NAc induced conditioned place preference (Josselyn & Beninger, 1993) and NPY agonists stimulated dopamine release in the NAc (Quarta et al., 2011), while NPY knockout mice had increased DAT levels in the striatum (Gehlert et al., 2008). This demonstrates that NPY can influence dopamine signalling. Furthermore, NPY binding in the NAc may be involved in addiction, although results are contradictory: administration of NPY increased self-administration of cocaine (Maric et al., 2009), but NPY knockout mice were hypersensitive to cocaine as well (Sørensen & Woldbye, 2012).

Finally, top-down projections from the cortex, amygdala and hippocampus to the hypothalamus are involved in food intake (Petrovich et al., 2007). This demonstrates that the metabolic control of eating is part of a larger system, interacting with many other brain areas to allow complex behaviours associated with eating, such as locating, preparing or storing food. Moreover, almost all brain regions are influenced by the metabolic balance, even regions that regulate unrelated behaviours (Berthoud & Morrison, 2008), illustrating that food intake is highly important for survival.

3.4 Hormonal involvement in food reward

Various circulating hormones, most importantly leptin, insulin and ghrelin, can directly bind to receptors on VTA and NAc neurons, influencing dopamine signalling (Figlewicz et al., 2003; Naleid et al., 2005; Schoffelmeer et al., 2011). Leptin receptor activation in the VTA reduced dopamine release and food intake (Hommel et al., 2006) and leptin infusion reversed operant responding and conditioned place preference for palatable food (Figlewicz et al., 2001; Figlewicz et al., 2004; Figlewicz & Benoit, 2009). In contrast, absence of functional leptin receptors increased dopamine release and food intake (Hommel et al., 2006) and selective leptin receptor knockdown in the midbrain led to increased motivation for sucrose rewards in the progressive ratio test (Davis et al., 2011b). In congenital leptin deficient people, NAc activity corresponded with the hedonic value of food pictures during fasting and satiety: the better a picture was liked, the more NAc activity (Farooqi et al.,

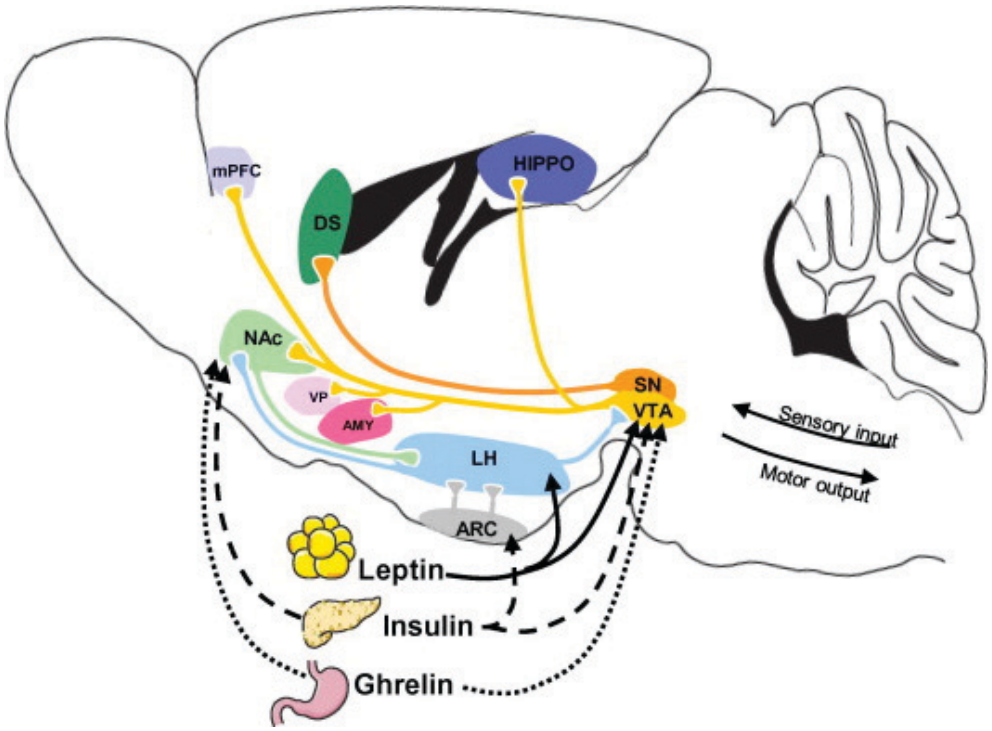

Figure 7: Leptin, insulin and ghrelin act on the mesolimbic dopamine system via receptors in the VTA and NAc, in addition to binding in the hypothalamic ARC and LH. Figure by Fulton et al., 2006.

2007; fig. 7). After leptin replacement therapy, food intake was reduced, feelings of satiety increased and the hedonic value of food pictures decreased.

Interestingly, the ratings of the pictures were not correlated any longer with NAc activity during satiety: NAc activity did not increase during presentation of highly liked food pictures. This suggests that leptin can influence NAc activity in response to visual food stimuli, reducing 'wanting' of food independent of 'liking' of food in a fasted state. Leptin also influences energy expenditure (Pelleymounter et al., 1995; Williams et al., 2001) and might be involved in addiction. Mice lacking leptin showed reduced amphetamine sensitization, which could be reversed by leptin administration (Fulton et al., 2006), and normalized sensitivity to heroin relapse caused by food restriction (Shalev et al., 2001).

It is suggested that only a small neuron population in the VTA contains leptin receptors, solely projecting to the amygdala (Leshan et al., 2010). This could indicate that leptin actually influences dopamine release via the amygdala. In contrast, leptin may primarily mediate energy expenditure via the LH, *increasing* dopamine release in a separate neuron population in the NAc (Leinninger et al., 2009; Ribeiro et al., 2011). However, Fulton et al. (2006) demonstrated that leptin responsive VTA dopamine neurons project to the NAc, which means that there might be different VTA neuron populations with leptin receptors projecting to different brain areas. They also showed that a subset of VTA GABA neurons expressed leptin receptors.

After binding to receptors in the VTA, leptin activates the Jak-STAT and IRS-PI3K pathway (Figlewicz et al., 2007; Fulton et al., 2006; Morton et al., 2009; fig. 6). This is comparable to its action in hypothalamic cells (Figlewicz et al., 2003; Saper et al., 2002). Insulin activates IRS-PI3K in the VTA as well, but also stimulates release of the dopamine reuptake transporter (DAT) in the NAc, which results in enhanced clearing of dopamine (Figlewicz et al., 1994; Figlewicz & Sipols, 2010; Speed et al., 2011; Williams

et al., 2007) and thus reduces dopamine signalling (Schoffelmeer et al., 2011).

As opposed to leptin and insulin, ghrelin administration in the VTA increased regular food intake and body weight (King et al., 2011; Naleid et al., 2005). Both central and peripheral administration of ghrelin resulted in increased operant responding to sucrose during the progressive ratio test, indicating an increased motivation for sucrose intake (Skibicka et al., 2012a). In contrast, administration of ghrelin antagonists into the VTA selectively reduced intake of high-fat food (King et al., 2011). Therefore, ghrelin in the VTA can increase food intake generally, but particularly increases intake of palatable food, suggesting a role in the hedonic value of food. This effect of ghrelin can be modulated by NPY and opioids, since NPY- and opioid-antagonists blocked the enhanced motivation to eat due to ghrelin infusion (Skibicka et al., 2012b).

Opioids particularly increase the hedonic value of energy dense food, as discussed briefly before. Infusion of μ-opioid receptor agonists in the NAc increased selective intake of high-fat food (Zhang et al., 1998; Zhang et al., 2003), while antagonists decreased intake of highly palatable food (Zhang et al., 2003). Opioids act in specific spots in the NAc shell (Peciña & Berridge, 2005) and they inhibit GABA-neurons that tonically suppress dopamine neurons in the VTA (Kandel, Schwartz & Jessell, 2000). Orexin neurons express μ-opioid receptors as well (Li & Van den Pol, 2008), suggesting another mechanism of action.

4 Neuroendocrine modulations in the obese brain

Because so many processes are involved in the regulation of food intake, it is difficult to disentangle all pathways and find the causes of overeating. What makes it even harder is that many disturbances in these pathways are compensated with modulations in other processes. For example, despite the fact that NPY and AgRP are very potent appetite stimulators, mice with NPY or AgRP deficiency during development can still become obese (Hollopeter et al., 1998; Oltmans, 1983; Qian et al., 2002). Early studies focussed on how satiety signalling influences eating behaviour and how disturbances in the hypothalamus can lead to overeating. The discovery of leptin and leptin resistance brought much progress to this field of study (Friedman, 2000). Today, more and more researchers expand their scope of research beyond the hypothalamus, with more interest in the role of other brain areas in excessive food intake, such as the reward system. By comparing the function of the reward system between obese and normal-weight people, several differences have been found that may explain overeating (Fulton, 2010). For example, in many obese people dopamine receptor expression in the striatum was reduced (Wang et al., 2009), while μ-opioid receptor binding was increased in others (Smith et al., 2002). Furthermore, increased activity of sensory areas and reduced inhibition by the PFC may contribute to obesity (Berthoud, 2011; Volkow et al., 2009). It is also hypothesized that leptin resistance occurs in dopamine neurons (Matheny et al., 2011). Finally, overeating has been compared to drug addiction (Kenny, 2011), which started the discussion about whether obesity could develop from a food addiction.

4.1 The hypothalamus and leptin resistance

A few genetic causes of obesity have been identified. For example, MC4 receptor deficiency is the most common monogenetic cause of human obesity (Farooqi & O'Rahilly, 2006; Tao, 2010; Xi et al., 2012) and Prader-Willi Syndrome patients suffer from insatiable hunger due to genetic hyperghrelinemia (Butler, 1990). Leptin or leptin receptor deficiencies also lead to pronounced obesity, which is illustrated by the *ob/ob* mouse, a widely used animal model for obesity (Tartaglia et al., 1995; Wilsey et al., 2003; Zhang et al., 1994). Prolonged levels of ghrelin after a meal were measured in non-Prader-Willi Syndrome patient as well (Cummings et al., 2002; English et al., 2002; Stanley et al., 2005), reversible by gastric by-pass surgery, while insufficient release of satiety signals like adiponectin and GLP-1 are also thought to contribute to overeating (Stanley et al., 2005).

When leptin was identified in 1994 as the important factor that was absent in spontaneously obese *ob/ob* mice (Zhang et al., 1994), it was thought that a cure for obesity had been discovered. Unfortunately, most obese people were found to have high concentrations of functional leptin (Considine et al., 1995; Hamilton et al., 1995; Linnqvist et al., 1995; Mapfei et al., 1995) that apparently were not able to prevent obesity. Likewise, high levels of insulin are not able to enhance the insulin receptor cascade further (DeFronzo & Ferrannini, 1991). This effect was called leptin resistance and actually might represent an evolutionary advantageous adaptation to a changing environment, ensuring that energy will be stored in times of food availability for periods when food is scarce. Nowadays, most people have unlimited access to food, but only since recently in human history and therefore we might still be adapted to a scarce environment where mechanisms to prevent obesity are unnecessary. Thus, leptin may simply be a hormone that effectively prevents starvation, but not obesity (Ahlma et al, 1996; Stanley et al., 2005).

The mechanisms of leptin resistance are not entirely clear yet. There are different theories that possibly overlap or may co-exist in different individuals. Impairment of leptin transport across the blood-brain barrier may contribute to resistance, since expression of the leptin receptor that mediates this transport - the short and soluble receptor isoform (Shimizu et al., 2007) - was decreased in obese humans (Ogier et al., 2002). Additionally, circulating triglycerides can hinder leptin transport across the blood-brain barrier (Banks et al., 2004). Both in obese and fasting individuals triglyceride levels are increased (Banks et al., 2004, Kastin & Akerstrom, 2000). Supporting this theory, leptin levels in the cerebrospinal fluid of obese individuals are decreased relative to blood levels (Caro et al., 1996; Schwartz et al., 1996). Contradictorily, leptin transport across the blood-brain barrier is enhanced by glucose and insulin (Kastin & Akerstrom, 2001), while obese individuals have increased leptin and insulin levels, but this effect may be minimal.

Another hypothesis by which leptin resistance is explained is negative regulation of the leptin receptor by leptin itself during prolonged receptor stimulation (review by Pandit et al., 2011). Upon activation of the leptin receptor-b - which is the most important receptor subtype for leptin signalling in the hypothalamus (Elmquist et al., 1998) - the Jak-STAT pathway is activated: signal transducer activator of transcription-3 (STAT-3) protein activates suppressor of cytokine signalling-3 (SOCS-3), which then suppresses Jak tyrosine kinase, eventually reducing expression of the leptin receptor (Mori et al., 2004). Overexpression of SOCS-3 therefore can lead to diminished leptin binding when leptin levels are elevated. SOCS-3 is indeed only significantly increased when leptin levels are high, thus leptin function is not hampered during small increases (Münzberg & Myers, 2005). Supporting this, SOCS-3 deficient mice reduced their food intake and were resistant to high-fat diet-induced weight gain, exhibiting normal leptin levels and no insulin resistance (Mori et al., 2004). Chronic leptin infusion itself leads to leptin resistance (Pal & Sahu, 2003), while a high-fat diet induces leptin resistance before changes in weight are seen, which can be reversed with a normal diet (Lin et al., 2001; Wilsey & Scarpace, 2004). These studies show that elevated leptin levels may solely, independent from diet side-effects, cause leptin resistance, while high leptin levels develop from an energy dense diet. Curiously, diet-induced STAT-3 activation - an indication of leptin resistance - only occurred in the ARC, not in other parts of the hypothalamus (LH, VMH, DMH), while leptin resistance induced by chronic leptin administration resulted in increased STAT-3 activation in all hypothalamic regions (Matheny et al., 2011). This suggests alternative mechanisms for leptin resistance, independent of the receptor binding pathway or transport into the brain. One downstream effect of leptin resistance may be sustained NPY levels: levels of NPY mRNA initially decreased after chronic central infusion of leptin, but normalized after a short period (Sahu, 2002), enhancing food intake. It has also been proposed that a shift in the leptin threshold occurs during chronically elevated leptin levels, meaning that smaller decreases in leptin will already activate anabolic processes, thereby reducing energy expenditure and increasing body weight (Leibel, 2008; Pandit et al., 2011).

It is unclear whether leptin resistance also develops in the dopamine system. Although leptin decreases food reward behaviour (Figlewicz & Sipols, 2010), high leptin levels are not effective in attenuating obesity (Mapfei et al., 1995). If impaired transport across the blood-brain barrier is the cause of leptin resistance in the hypothalamus, resistance in dopamine neurons is expected to develop as well. Supporting this, increased STAT-3 activation, thought to reflect leptin resistance, was found both in the ARC and VTA in animals fed a high-fat diet (Matheny et al., 2011). Unfortunately, further evidence for

leptin resistance in the dopamine system is lacking.

4.2 Dopamine pathways

4.2.1 The dopamine deficiency hypothesis

Reduced expression of dopamine 2 receptors (D2R) in the striatum has been found in obese animals and humans (Volkow et al., 2008a; Wang et al., 2001; Wang et al., 2009). There are five subtypes of dopamine receptors, named D1 to D5, that are categorized into D1-like (D1 and D5) and D2-like (D2, D3 and D4) receptors, the latter predominating in the striatum and limbic regions (Wang et al., 2009). D1 and D2 receptors are thought to be most important in the regulation of food intake (Kuo, 2002). In obese individuals, decreased dopamine release, presumably leading to reduced striatal activation by dopamine, was demonstrated as well (Geiger et al., 2008; Haltia et al., 2007). According to the dopamine deficiency hypothesis, or dopamine compensation theory, the consequence of a so-called dopamine deficiency is that, as compensation, dopamine release has to be stimulated excessively by seeking extra rewards (Blum et al., 1996; Blum et al., 2000). Since food intake induces dopamine release in the NAc (Bassareo & Di Chiara, 1999), eating could restore the dopamine levels. It also means that more food has to be eaten compared to normal individuals, because a similar amount of food leads to a diminished dopamine effect. By eating highly palatable food rich in fat and sugar extra dopamine is released (South et al., 2012), which may explain preference for this kind of food by many obese individuals. Interestingly, addiction has been linked to reduced D2R expression as well (Dalley et al., 2007; Hietala et al., 1994; Volkow et al., 1993), indicating a possibility of a common pathway for vulnerability to addiction-like behaviours.

The dopamine deficiency theory is supported by several studies that found an association between the TaqI A1 allele of the human D2 receptor gene - the phenotype being up to 30 percent reduced D2R expression (Noble et al., 1991; Pohjalainen et al., 1998) - and obesity, as well as other compulsive disorders such as drug abuse, alcoholism, smoking and gambling, and personality traits associated with impulsivity (Comings et al., 1993, Comings, 2000; Epstein et al., 2007b; Noble et al., 1994; Stice et al., 2008; Winkler et al., 2012). People with the A1 allele show decreased NAc activity, increased food craving and increased food consumption (Epstein et al., 2007a). Reduced D2R expression was also found in obese rats with a compulsive eating disorder (Johnson & Kenny, 2010). In addition, blocking of the D2 receptor resulted in increased food intake, appetite and weight gain (Allison et al., 1999; Lee & Clifton, 2002), which is also a well-known side effect of antipsychotic drugs that antagonize D2 receptors (Baptista, 1999). In contrast, administration of dopamine receptor agonists to *ob/ob* mice, that express few D2 receptors, normalized hyperphagia (Bina & Cincotta, 2000) and dopamine receptor agonists limited overeating in humans (Leddy et al., 2004). The dopamine deficiency theory is in line with the finding that exercise and certain drugs of abuse - being rewarding - stimulate dopamine release as well, simultaneously reducing food intake (Blum et al., 2000; Heyes et al., 1988). Finally, increased dopamine release was reported to be more pleasant in subjects with lower D2R levels than in subjects with higher D2R levels (Volkow et al., 1999; Volkow et al., 2002a), possibly indicating that dopamine release in people with lower D2R levels is more reinforcing. Other proteins that are involved in dopamine signalling, such as tyrosine hydroxylase - an enzyme necessary for dopamine synthesis - or the dopamine reuptake transporter (DAT), may contribute to overeating as well. However, this is not thoroughly investigated yet and one study found no association between

DAT concentration in the striatum and BMI (Van de Giessen et al., 2013).

4.2.2 Anticipation and prediction of reward

Dopamine is not only released during food consumption, but also involved in the anticipation and prediction of rewards. Dopamine neurons in the VTA fire in response to stimuli that predict rewards (Ljungberg et al., 1992; Schultz, 1998) and even shift from firing during unexpected rewards to firing during stimuli that predict a reward (Schultz, 2002), suggesting that they fire solely in response to *novel* rewards and in response to predictive cues. The strength of this dopamine response corresponds with the expected value of the reward, since single-cell activity was in proportion to the probability and magnitude of the expected reward (Fiorillo et al., 2003; Tobler et al., 2005). Thus, dopamine seems to be important for learning when to expect rewards of what magnitude, perhaps facilitating decisions to maximize efficient behaviour towards rewards or pleasurable experiences. In contrast, few to no dopamine neurons fired when confronted with aversive experiences (Schultz, 2010), indicating that dopamine does not play a role in directing behaviour away from negative experiences.

Dopamine signalling is also involved in prediction errors: in response to an unpredicted reward during a learning task dopamine neurons fired, while they were depressed when a reward was expected but did not come (Hollerman & Schultz, 1998; Schultz, 2002). Therefore, dopamine neurons seem to signal positive and negative prediction errors of the rewarding outcome. Supporting this, dopamine neurons fired as response to a reward during initial learning trials, but firing gradually decreased when prediction of the reward was learned. Schultz et al. (2002) proposed a model for dopamine neuron firing during reward prediction:

$$D_r = R_o - R_p,$$

where D_r is dopamine response, R_o is the occurred reward and R_p is the reward predicted. This model illustrates that the dopamine response is zero when the reward is correctly predicted.

4.2.3 The energy expenditure hypothesis

In addition to involvement in learning, it is hypothesized that the function of dopamine in the NAc might be primarily to regulate and prioritize energy expenditure, thereby also controlling the effort that will be spend on seeking and obtaining food (Beeler et al., 2012; Trinko et al., 2007). Energy expenditure has to be regulated tightly during food scarcity, while this is unnecessary when food is easily available. Beeler et al. (2012) suggest that dopamine is released when energy is abundant, stimulating energy expenditure and allowing unessential behaviours such as exploring, while low dopamine levels signal energy preservation and stimulate food intake, distributing energy and effort carefully, influenced greatly by the rewarding outcome of decisions. High levels of dopamine would allow decisions that are less biased by reward and would be protective against obesity, which corresponds with the association between overweight people and reduced D2R expression. People with reduced dopamine release would be in a sustained state of energy preservation, experiencing a constant urge to preserve energy and consume energy dense food. A diet would be very difficult to keep up and there would be little drive to exercise or spend effort in obtaining food, which may explain why obese people often eat energy dense fast-food instead of spending effort on elaborate home-cooked meals. Indeed, dopamine

depletion in both the NAc shell and core did not suppress food intake (Baldo et al., 2002) and dopamine stimulated general physical activity (Beninger, 1983; Kelly, 1975). Dopamine release also enhanced the willingness to work for sugar (Zhang et al., 2003) and the perseverance in a progressive ratio test with two levers that required different amounts of lever pressings, switching once in a while (Cagniard et al., 2006). In contrast, low dopamine levels reduced the effort an animal was willing to spend on food: low-cost chow food was preferred over more palatable food that was difficult to obtain (Randall et al., 2012; Salamone & Correa, 2009). The role of dopamine in anticipation and prediction error signalling supports the energy expenditure theory, since learning to predict rewards and adjusting expectations is essential for distributing the available energy efficiently.

4.3 Related corticolimbic modulations

Midbrain dopamine neurons are intertwined with other neurotransmitter systems and corticolimbic regions involved in reward, as mentioned before. Binding of opioids to receptors in the NAc influences dopamine signalling (Herz, 1997; Spanagel et al., 1992) and areas such as the sensory cortices or the prefrontal cortex (PFC) are closely connected to dopamine neurons. For example, the somatosensory cortex is believed to both influence and be influenced by dopamine neurons (Huttunen et al., 2003; Kuo et al., 2008) and activity of the orbitofrontal cortex is thought to be mediated by dopaminergic signalling (Wang et al., 2009). Interestingly, increased activity of the somatosensory cortex in obese people correlated with decreased D2R availability (Volkow et al., 2008b), indicating that dopamine might modulate the sensory perception of food stimuli, or vice versa. Reduced activity of the dorsolateral PFC was associated with genetically reduced D2R expression as well (Klein et al., 2007), both in obese (Volkow et al., 2008a) and addicted (Volkow et al., 2001) people. Also, depletion of dopamine in the PFC led to cognitive impairment in monkeys, which could be reversed by dopamine administration (Brozoski et al., 1979). Thus, altered dopamine signalling might correspond with modulations in other corticolimbic areas, whether one causes the other or not. These modulations possibly contribute to obesity or may cause obesity on their own.

4.3.1 Overexpression of the μ-opioid receptor

In obese rats on a high-fat diet, μ-opioid receptor binding in the dopamine system was increased (Smith et al., 2002). In contrast, suppression of opiod receptor binding in the NAc prevented obesity in rats (Lenard et al., 2010) and opioid receptor antagonists reduced taste preference for foods high in fat and sugar in people with binge eating disorders (Drewnowski et al., 1992). This suggests that μ-opioid receptor overexpression may contribute to obesity by increasing the hedonic value of food.

4.3.2 Hyperactivity of sensory and limbic areas

Increased sensitivity to sensory information may be involved in overeating as well. The experience of sensory information (e.g. taste and smell) occurs via the primary sensory cortices such as the insular cortex, somatosensory cortex, visual cortex and olfactory cortex, relaying information to the orbitofrontal cortex and amygdala (Hajnal & Norgren, 2005; Frank et al., 2008; Rolls, 2007). Increased baseline activity and increased activity in response to food cues and food consumption was measured in the sensory cortices in obese individuals compared to normal-weight controls, especially when the food was high

in sugar and fat, and sometimes accompanied by increased hunger (DelPariqi et al., 2005; Parigi et al., 2002; Seeger et al., 2002; Stice et al., 2008; Wang et al., 2002a; Wang et al., 2004). In contrast, dysfunction in these areas was associated with reduced pleasantness of taste (Naqvi et al., 2007; Wagner et al., 2008), overeating and other compulsive behaviours (King, 2006; Machado & Bachevalier, 2007) or anorexia (Giordano et al., 2001; Takano et al., 2001). Excessive activity in the sensory cortices in response to food stimuli may enhance the desire to eat when confronted with food associated cues (Berthoud, 2011; Wang et al., 2009), food appearing more attractive and pleasurable.

4.3.3 Reduced activity of the prefrontal cortex

The prefrontal cortex (PFC) is thought to control impulsive desires (Spinella, 2004). Since inhibition of the desire to eat is becoming more important to prevent weight gain in our current environment (Wardle, 2007), dysfunction of the PFC may contribute to obesity. Reduced function of the PFC indeed inversely corresponded with BMI (Batterink et al., 2010; Pannacciulli et al., 2006; Volkow et al., 2009) and was associated with craving for food (Holsen et al., 2012; Volkow et al., 2008b). In contrast, the PFC was more active in anorexia patients during presentation of food pictures than in controls (Uher et al., 2004), while transcranial magnetic stimulation of the PFC reduced food craving in people reporting frequent food craving (Uher et al., 2005). However, hyperactivation of the PFC was also seen in obese individuals during food image presentation (Bruce et al., 2010; Davids et al., 2010), also just after a meal (Gautier et al., 2000; Holsen et al., 2006).

4.4 Food addiction

Some investigators compare overeating with addictive disorders and suggest that obesity develops from a 'food addiction' because food and drug reward seem to be mediated in similar brain structures (Cason et al., 2010; Nestler, 2005). Psychoactive drugs like amphetamine or cocaine also increase dopamine levels in the NAc shell and food restriction leads to increased sensitivity to drug addiction (Carr, 2002), which implies that food and drug reward share similar mechanisms. Behavioural traits are in part comparable as well. Highly impulsive individuals have an increased risk of developing both drug addiction and obesity (Nederkoorn et al., 2006; Nigg et al., 2006; Perry & Carroll, 2008). Individuals displaying high impulsivity are possibly more sensitive to immediate rewards and less patient for long-term rewards, thereby being also less sensitive to the long-term adverse effects of their behaviour (De Jong et al., 2012). The term 'compulsive behaviour' is often used to describe addictive behaviour: continued behaviour that is no longer goal-directed or controlled by the outcome of the behaviour. The behaviour is dissociated from the consequences, so whether it will be liked or not, the reward is strongly wanted and the drug-seeking behaviour has become an automatic habit, not a voluntary act (Everitt & Robbins, 2005; Pandit et al., 2011). This is indeed sometimes seen in binge eating disorder (BED) patients who eat when they are not hungry and until they are uncomfortably full. According to the widely used medical DSM-IV criteria (American Psychiatric Association, 2000), BED patients resemble addicts in some other behavioural traits as well (Avena et al., 2008; De Jong et al., 2012), although dependence and tolerance are no symptoms of BED. However, these criteria are quite vague and arbitrary.

Both in drug addicts and obese individuals, the NAc, amygdala, orbitofrontal cortex, PFC and insula seem to be involved (De Jong et al., 2012; Kober et al., 2010). Changes observed in the reward system of addicts include hyperactivity of the dorsal striatum and

decreased activity of the PFC (Everitt & Robbins, 2005), similar to what is found in some obese people. Interestingly, D2R availability in the striatum was decreased in drug addicts as well (Martinez et al., 2005; Morgan et al., 2002; Nader et al., 2002; Porrino et al., 2004; Volkow et al., 2002b; Volkow & Wise, 2005; Volkow et al., 2007) and healthy individuals with lower D2R expression reported amphetamine administration to be more pleasant than controls with higher D2R expression (Volkow et al., 1999; Volkow et al., 2002a). In contrast, upregulation of D2 receptors in the NAc decreased alcohol intake in animals during self-administration (Thanos et al., 2001). Opioid neurotransmission (Kelley et al., 2002a; Peciña & Smith, 2010; Trigo et al., 2010), orexin release (Trinko et al., 2007) and stress pathways (Robinson & Berridge, 1993) also seem to be involved in both overeating and drug addiction. There is evidence for a few similar molecular mechanisms downstream of dopamine receptor binding as well (Kenny., 2011).

However, the above findings are not very specific and there are also differences (Avena et al., 2009). For example, there is evidence that different dopamine neuron populations are involved in drug reward and natural rewards like food and water (Carelli et al., 2000; Carelli, 2002). Of course, natural reinforcers are necessary for survival, while drugs of abuse are not.

5 Discussion

Different theories exist about dopamine function and various associations were found between modulations in the reward system and obesity. This led to several hypotheses that may explain excessive food intake. But are these hypotheses valid, and could these modulations really cause obesity, or are they rather consequences, secondary to changes induced by overeating itself? This is essential to know for the understanding of the processes underlying obesity and for the development of novel treatments.

5.1 The dopamine deficiency hypothesis

On the one hand, the dopamine deficiency hypothesis sounds promising. Indeed, reduced D2R expression was found in many obese individuals (Volkow et al., 2008a; Stice et al., 2008;Wang et al., 2001), NAc activity was experienced as pleasurable (Olds, 1982) and dopamine release in the NAc correlated with desire (Bishop et al., 1963; Wang et al., 2001). This supports the view that people with intrinsically less dopamine binding would compensate with excessive food consumption.

Of the alterations in dopamine signalling associated with obesity, reduced D2R expression as a cause of obesity is best supported. Although most studies simply compared brains in obese state with a lean control cross-sectional, making distinction between cause and consequence impossible, reduced D2R expression is a hereditary trait of people with the TaqI A1 allele and thus precedes onset of obesity in those cases. Although *increased* striatal activity was weakly associated with future weight gain in people without this allele, reduced striatal activity in people with the A1 allele in response to food intake was more strongly associated with future weight gain (during a 1-year follow-up period) (Stice et al., 2008). This apparent discrepancy might just represent two different mechanisms that lead to obesity, depending on the A1 allele, and explains why both elevated and reduced dopamine levels were measured in obese people. Furthermore, studies comparing dopamine signalling before and after obesity onset show that reduced dopamine binding was already present before obesity onset, for example in obesity-prone rats (Levin et al., 1997). Yet these rats only became obese when fed a palatable caloric dense diet, which suggests that both altered dopamine release and diet are needed to cause obesity. In addition, experimentally blocking of the D2 receptors increased appetite and food intake (Allison et al., 1999; Baptista, 1999; Lee & Clifton 2002) and only led to overeating in obese rats compared to lean rats in another study (Fetissov et al., 2002), possibly implying that lean rats possess more than sufficient D2 receptors to have no effect, while receptors in obese rats are already underexpressed. Although these results support the hypothesis that reduced D2R expression can cause overeating, they still do not provide conclusive proof. It may therefore be fruitful to investigate whether excessive food intake can be reversibly induced in lean people or animals by reducing D2R expression to the levels seen in obese people.

Interestingly, other modulations in the reward circuit of obese individuals occur simultaneously with reduced D2R expression and the presence of the TaqI A1 allele, which indicates that these modulations may be secondary to congenital altered D2R expression. For example, reduced D2R expression correlated with reduced PFC activity in obese subjects (Volkow et al., 2008a; Volkow et al., 2009), high impulsivity (Eisenberg et al., 2007), increased activity of the sensory cortices (Wang et al., 2009) and high leptin levels (Dunn et al., 2012). Metabolic activity in the NAc, insula and PFC in people with the TaqI A1

allele was reduced (Noble, 2003). Although these associations are not conclusive (Ariza et al., 2012), many of these alterations increase the risk for obesity on their own, as discussed before. Additionally, treatment of *ob/ob* mice with dopamine agonists normalized elevated NPY levels, suggesting that NPY action is (partly) downstream of dopamine control (Bina & Cincotta, 2000). To clarify these associations and to dissociate cause from consequence, all different parameters should be measured simultaneously, preferably before and after obesity onset in large cohort studies with lean people. Measuring these outcomes before and after weight reduction will be helpful as well.

On the other hand, there are several drawbacks with the dopamine deficiency theory. First, evidence for reduced expression of D2 receptors in obese people is not always convincing. For example, the much-cited article of Wang et al. (2001) showed an inverse correlation between D2R availability and BMI, but the linear regression lines do not show a strong association: sample sizes were small and there is much overlap (fig. 8).

Second, there is insufficient support for the assumption that humans and animals need to strive for a certain dopamine level. Even if this proves to be so, obesity might simply arise from higher maximum plateau levels of dopamine above which stimulation of dopamine neurons has no longer effect, or leads to adverse effects. If the plateau levels vary in different individuals, the higher the plateau level, the more food might be consumed before eating stops to stimulate dopamine release, enhancing the motivation to eat and possibly the associated pleasure as well. Prolonged stimulation of D2 receptors may consequently result in downregulation of these receptors.

Third, there is a flaw in the argument that the rewarding effects of dopamine release would drive the need for compensation of low D2R levels: if dopamine release corresponds with a pleasurable feeling, why would people eat more if the pleasurable feeling elicited by food intake is weaker? Logically, food consumption would be disappointing, reducing the motivation to eat. The assumption that blunted dopamine signalling would lead to attenuated rewarding feelings that need to be compensated is also difficult to reconcile with the fact that individuals with reduced D2R expression reported to experience more pleasure from drugs that stimulate dopamine release (Volkow et al., 1999). Similarly, if dopamine is rewarding, why does blocking of D2 receptors lead to increased food intake? The question therefore is whether dopamine release is rewarding, especially since opioids are associated with liking, while dopamine is more associated with wanting. Dopamine release solely in the NAc at least did not maintain sufficient food intake (Cannon & Palmiter, 2003; Hnasko et al., 2005; Szczypka et al., 2001), suggesting that dopamine release only in the NAc does not strongly motivate to eat. However, this effect may be attributable to disruption of the dopamine signal or to other functions of dopamine, such as initiating movement, and should be clarified, for instance by depletion of dopamine only in the NAc. Still, food restriction increases dopamine release in the NAc as well (Wang et al., 2009). If dopamine release is rewarding, this means that starvation is rewarding, which cannot be from an evolutionary point of view. Therefore, it is not convincing that dopamine release is simply rewarding: the function of dopamine has to be more complex. Indeed, many functions are described (Salamone et al., 2005; Salamone & Correa, 2012) that are not explained by such a simple model as the deficiency hypothesis. Of course, different functions could be mediated by various pathways, release patterns, receptor expression and dopamine concentrations (Kelley, 2004; Richfield et al., 1989; Schultz, 2002; Smith-Roe & Kelley, 2000). Yet dopamine is not *always* released during food consumption, for example when food is expected. Dopamine may contribute to pleasure,

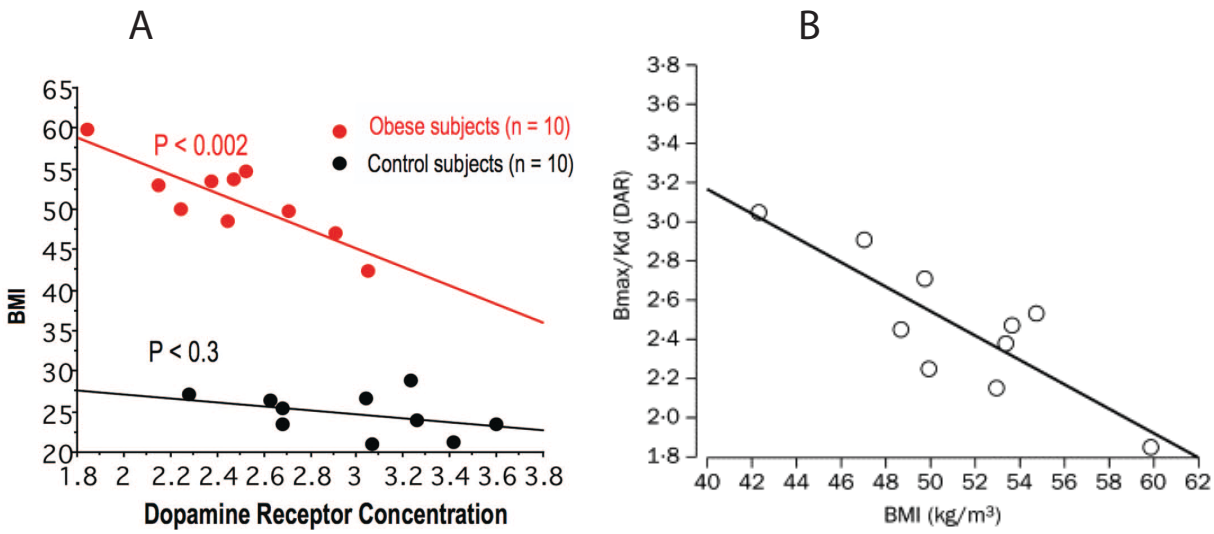

Figure 8: Inverse correlation between dopamine receptor availability and BMI in obese individuals compared to control subjects (A) and in obese individuals (B). Figure by Wang et al., 2001 and Wang et al., 2009.

but does not seem solely responsible for pleasure. For example, it may only reflect peaks in excitement or craving for food and interactions with other processes are likely crucial. Perhaps the association between dopamine release and pleasure is even mediated by opioid and serotonin pathways that activate the NAc, in turn activating dopamine neurons in the VTA – for example to store the memory.

Elevated levels of dopamine have been found in several obese rats instead of lower levels (Gainetdinov, 2007), which led to the contradictory hypothesis that *increased* dopamine release may enhance the motivation to eat (Davis et al., 2004), consistent with the finding that stimulation of dopamine neurons results in overeating (Kenny, 2011) and increased willingness to work for sugar (Zhang et al., 2003). According to the dopamine deficiency theory, stimulation of dopamine neurons would result in decreased instead of increased food intake, since dopamine binding would already be partly restored. In addition, this theory explains some of the findings mentioned above that are difficult to reconcile with the dopamine deficiency theory, such as increased dopamine release during food restriction (Wang et al., 2009) and the association of dopamine with craving. Yet, the elevated levels of leptin and insulin - that inhibit dopaminergic transmission (Hommel et al., 2006) - in obese people contradict this hypothesis.

Furthermore, reduced D2R expression does not automatically mean that dopamine binding and activation of the post-synapse is attenuated, altering dopamine signalling. There may be an excess of D2 receptors or only a minor or subthreshold influence, not affecting neuronal activity. Additionally, reduced receptor expression may be compensated with for example increased dopamine release, increased expression of and binding to other dopamine receptor subtypes, or delayed DAT action - although one study did not find altered DAT concentration in the striatum of obese people (Van de Giessen et al., 2013). Despite the finding that activation or blocking of the D2R results in altered eating behaviour (Allison et al., 1999; Baptista, 1999; Bina & Cincotta, 2000; Leddy et al., 2004; Lee & Clifton, 2002), it does not mean that the effects of reduced D2R expression are similar. Inhibition of these receptors might have a more pronounced effect on dopamine action, perhaps by prolonged depression of receptor function. Thus, these kind

of experimental results have to be properly compared with the natural occurring D2R depression in obese people. In addition, D2 receptors in the entire brain were blocked, without taking into account that separate brain sites may execute specific dopamine functions. An experiment aimed at improving D2R availability could investigate the function of D2 receptors further.

Last, reduced D2R expression may be a consequence of overeating itself, which will be discussed later.

5.2 Anticipation and prediction of reward

The dopamine release patterns strongly correspond with a role for dopamine in the anticipation and prediction of rewards. Involvement in anticipation in addition to involvement in food reward could be an alternative explanation as to why both decreased and elevated dopamine levels are found in obese individuals: dopamine release may reflect two different processes, dependent on the timing of release. If anticipation is increased (Pelchat et al., 2004; Roefs et al., 2005; Wyvell & Berridge, 2000) - possibly reflected by elevated dopamine levels -, food consumption may increase as well. Although very high anticipation could lead to disappointment during food intake, it may induce overeating in itself, or, consistent with the dopamine deficiency theory, it may require more food intake as compensation. Supporting this, increased anticipation of food was related to BMI (Franken & Muris, 2005), just as it increases during food restriction. Moreover, the temporal difference in dopamine levels before and during food consumption might be involved in perceived reward values, if dopamine reflects reward. For example, enhanced dopamine levels during food consumption following normal or reduced dopamine release during anticipation might lead to increases in meal size, because food will be more pleasurable than expected. However, the mechanism that consequently adjusts this expectation has to be impaired then, while we should question to what extent humans will forget their food experiences. Many more brain pathways are presumably involved in this process. As mentioned earlier, it is also unlikely that dopamine mediates pleasure, at least in such a simple manner. In addition, this does not explain the association between decreased D2R expression and obesity, nor are all of the above hypotheses supported by the finding that a shift occurs in dopamine neurons from firing during novel rewards to firing during anticipation, which implies that dopamine is either released during anticipation or during food consumption, not both. Possibly dopamine signals the importance of rewards encountered unexpectedly, which is then stored as memory in order to predict the reward value during repeated encounters with predictive cues. It would therefore be interesting to find out if the magnitude of the dopamine response on encountering novel food rewards is subsequently reflected by that in response to associated food cues.

Although involvement of dopamine in prediction error signalling is very plausible and not contradicted by most experimental findings discussed earlier, it is unclear how it could contribute to overeating. Overeating could intuitively arise from wrong prediction error information, because if dopamine fails to signal prediction errors correctly, there could be bias towards obtaining the reward. Yet it is not convincing. One could argue that reduced firing of dopamine neurons may impair learning to predict positive rewards, perhaps reducing responding to food cues, while increased firing could improve prediction of positive rewards. However, slight deviations in the ability to predict rewards seem irrelevant in humans: we can all predict, upon seeing for example a chocolate bar in a vending machine, that buying and eating the chocolate bar will be pleasurable. Only

subconscious enhancement of the motivation to eat upon seeing predictive cues would logically have an effect, but this is likely mediated by other processes, such as craving or pathways in the sensory cortices. It is also important to mention that most experiments with prediction errors were done with laboratory animals that possess very different - less sophisticated - cognitive abilities than humans have. Experiments in humans would therefore be more conclusive. Furthermore, it may be that dopamine release per se signals a right or wrong prediction of 'a' reward, regardless of the reward value, that would not be affected by enhanced or attenuated dopamine binding.

5.3 The energy expenditure hypothesis

The energy expenditure theory is an alternative explanation for the association between reduced D2R expression and obesity and explains the fact that dopamine influences physical activity as well. It seems better supported than the dopamine deficiency hypothesis, while showing some overlap. Yet, there are a few objections and ambiguities. Beeler et al. (2012) suggest that dopamine diminishes biasing of behavioural choice by reward value, which could explain why obese people often prefer energy dense food if they have attenuated dopamine binding, since palatable, energy dense food generally has a higher reward value. However, how does reduction of reward value influence relate to the fact that dopamine is released in response to rewards and reward predictive cues? According to the energy expenditure theory, the reward value of food will thus have little influence on behavioural choice during reward anticipation or consumption, but food cues often elicit or enhance a desire to eat. It is therefore unlikely that phasic firing of dopamine neurons - the high frequency pattern resulting in high extracellular dopamine levels that activate postsynaptic neurons (Fulton, 2010) - in response to predictive cues or food reward is involved in reward bias. Of course, tonic dopamine release - slow and single spikes resulting in low and diffuse extracellular dopamine levels (Fulton, 2010) - following food consumption could signal that energy expenditure is permitted, but this needs to be investigated yet. An indication is that high-frequency activity in the NAc was measured during presentation of rewards or reward predictive cues (Schultz, 1998), followed by tonic activity during reward delivery (Mirenowicz & Schultz, 1996; Tobler et al., 2005).

The role of dopamine in the effort an animal is willing to spend on food procurement is also unclear. The theory that dopamine would both increase this effort and signal energy abundance to allow unessential behaviours, seems conflicting. Yes, in both cases the consequence is that more energy will be spent, but this includes spending more energy on obtaining *food*, which is no unessential exploratory behaviour, but necessary to ensure that food will be obtained even under difficult circumstances – the opposite of energy abundance. It also means that people with increased dopamine signalling will be willing to spend more effort in obtaining food, potentially increasing food intake, which does not correspond with the fact that obesity is often associated with reduced D2R expression. Yet, there may be one explanation. Dopamine release would be very important during food scarcity and unnecessary to ensure energy intake when food is available *at libitum*. Since food is currently easily available in Western society, reduced D2R expression may simply reflect superfluous dopamine, not reducing food intake, but reducing the *effort* spent in obtaining food, unnecessary anyway. This is supported by the finding that rats that were administered a D2R antagonist reallocated their behaviour from obtaining high-effort palatable food towards low-cost chow food (Randall et al., 2012). In addition, obese people generally have a sedentary lifestyle. Then, overeating could be mediated by other

pathways, such as opioid receptor activation, but reduced dopamine could also bias food choice towards the most easily obtainable food, which is often fast food rich in sugar and fat, as opposed to elaborately home cooked meals. Alternatively, spending more energy on food procurement as effect of high dopamine levels may be a by-product of spending more energy in general, or, both seemingly contradictory dopamine functions may be executed by different firing patterns or different signalling pathways. The effort spent on food procurement may also passively result from the reinforcing effects of food and the motivation to eat.

Finally, according to the energy expenditure theory, dopamine stimulates exercise. However, exercise itself elicits dopamine release, yet we are not constantly active - how is this possible? The environment and other brain activity could attenuate this effect of dopamine. Moreover, if dopamine stimulates energy expenditure, but the environment encourages a sedentary lifestyle, the balance between energy intake and expenditure may be disturbed, leading to obesity.

Worth to mention, there seems to be a discrepancy of wanting in obese humans and animals: implicit wanting increased in obese humans (Finlayson et al., 2011), while wanting in obese animals decreased (Davis et al., 2008). Yet, wanting in animals is measured by different behavioural tests such as the progressive ratio test, that all include effort-related wanting. Thus it is possible that in obese humans and animals wanting of easily available food is increased, but not wanting of effort-requiring food. This is supported by the finding that obese mice lacking MC4 receptors took more sucrose pellets when only two lever presses were required, but took fewer when fifty lever presses were required, compared to normal mice (Atalayer et al., 2010). Increased liking of palatable food while the willingness to work for food is decreased may therefore only lead to obesity when food is abundant. Impatience to wait for a delayed reward may also contribute to effort-related decreased wanting in obese individuals, which is supported by studies in humans (Epstein et al., 2010; Weller et al., 2008). Or this apparent discrepancy may simply develop from the use of different kinds of diets.

5.4 The influence of diet on dopamine signalling

Contradictorily, there is evidence that food components affect the physiology of the dopamine system. Therefore, modulations in the reward system of obese individuals may be consequences of overeating itself. Not only can increased availability of food, energy density and portion sizes of food stimulate overeating and weight gain (Hill & Peters, 1998; Ulijaszek, 2002), but specific nutrients can influence the dopamine system. The effects of sugar tasting and consumption - inducing dopamine and opioid release in the NAc (Hajnal et al., 2004; Wang et al., 2009) - can just reflect a pleasurable experience or a learning process, but some diets induce chronic changes in basal dopamine signalling. A 12-week restricted high-fat (HF) diet reduced dopamine turnover in the NAc in rats, for example, without inducing significant weight gain (Davis et al., 2008). These effects may be mediated by leptin, but the absence of weight gain suggests other mechanisms. Since after 12 weeks on a HF diet self-administration of sucrose decreased, while after 5 weeks sucrose self-administration increased (Figlewicz et al., 2006), duration of the diet seems to be important for its precise effect. Still, only basal dopamine turnover was measured and adaptations in the dopamine system in response to such a diet not necessarily lead to overeating and may even prevent obesity. It would therefore be interesting to compare dopamine release during food intake in lean animals fed a HF with dopamine release in

those fed a chow diet, both with and without inducing weight gain.

A diet is also capable of altering dopamine receptor expression: excessive intake of sugar and fat resulted in downregulation of D2 receptors and decreased D2R sensitivity in the striatum of rats, while sugar increased D1 expression in the NAc (Bello et al., 2002; Colantuoni et al., 2001; Johnson & Kenny, 2010) – comparable to some drugs of abuse (Volkow et al., 2008b). Reduced D2R expression is mainly caused by fats, instead of calories and sugar (Van de Giessen et al., 2012b). Rats fed a restricted high-fat and high-sugar (HFHS) diet had decreased D1 receptor levels in the NAc (Alsiö et al., 2010), supporting the theory that nutrients themselves, rather than physiological consequences of obesity, are sufficient to modulate dopamine signalling.

Studies in rodent models using calorie restriction and gastric bypass surgery found that some modulations are reversible by weight loss and are therefore secondary to excessive food intake. For example, HF diet- induced obese rats responded differently to sugar than lean control rats: they liked higher concentrations more and lower concentrations less, and weight loss due to food restriction resulted in a similar response as lean rats, which was reversible again by unlimited access to food (Berthoud et al., 2012; Shin et al., 2011a; Shin et al., 2011b). In addition, obese humans and rats that underwent bariatric surgery showed decreased preference for HF and HS food (Burge et al., 1995; Zheng et al, 2009), although this might be due to changes in stomach physiology. Further studies could therefore investigate whether changes in dopamine receptor expression in obese animals are reversible by a chow diet, without causing weight loss, to really find out if nutrients can modulate dopamine signalling independently. To exclude the possibility that the intention to eat can alter dopamine signalling, for which there are indications (Van de Giessen et al., 2012a), lean animals or humans could be force-fed a HF, HS or HFHS diet, although this of course involves ethical difficulties.

Food can induce preference for its own food type, which could enhance weight gain especially after exposure to HF and HS foods: rats fed a chronic HF diet preferred HF foods over HS foods, compared to rats fed a normal-fat or HS diet (Reed & Friedman, 1990; Warwick & Synowski, 1999). Unfortunately, in both studies the age of the rats was not mentioned, while it would be interesting to find out if preference for a certain food type is mainly established during young age, or could still be altered easily during adulthood. In another study, a 1-week HF diet fed to mice two weeks old induced preference for fat in adulthood, accompanied by changes in the dopamine receptor signalling pathway: ΔFosB levels were increased in the NAc (Teegarden et al., 2009). ΔFosB (fig. 6) is a transcription factor thought to enhance the motivational properties of food (Olausson et al., 2006) and is upregulated during food restriction as well (Stamp et al., 2008). Interestingly, dopamine signalling from VTA to NAc was decreased in ΔFosB-overexpressing mice (Teegarden et al., 2008), which was reversed with a HF diet. Although these results will have to be quantitatively compared to dopamine signalling in obese animals to demonstrate the functional consequences, they suggest that a HF diet early in life is capable of inducing long-lasting changes in dopamine release, enhancing the motivation for fat intake. The finding that foods actually enhance preference for similar foods seems a normal process because it means learning to appreciate what is available. Similarly, the increase in dopamine binding directly after fat intake might just reflect a fulfilment of the desire for fat, or a learning signal. Exaggeration of these processes, however, for example due to excessive availability of HF food, leads to a vicious circle: motivation to eat increases the motivation to eat and so on, resulting in obesity (La Fleur et al., 2007). Yet, there was no weight gain in ΔFosB-overexpressing mice compared to wild-type mice, not even with

access to a HF diet (Teegarden et al., 2008), indicating that ΔFosB-overexpression cannot solely cause obesity. Importantly, if dopamine binding in these animals resembles that in obese animals, these results oppose the hypothesis that reduced dopamine binding will cause overeating. In addition, contradictory results were found: animals that could choose between regular chow, HF and HS food overate and gained weight, but animals that could choose between chow and either HF or HS food did not increase food intake after an initial period of hyperphagia (La Fleur et al., 2010; La Fleur et al., 2011), suggesting that only a diet high in both sugar and fat normally increases the motivation to eat similar food, while a diet of only HF or only HS food normalizes its own intake. Yet, these experiments were done with normal animals, while obesity-prone animals might behave differently.

Hormonal imbalances accompanying obesity can induce changes in the dopamine system as well. Leptin and insulin, for example, influence dopamine signalling (Hommel et al., 2006). It would therefore be interesting to establish whether changes in dopamine binding in response to a HF diet are mediated by leptin or leptin resistance.

Alternatively, reduced D2R expression could be a compensation for *increased* dopamine release in obese people, actually being a - failing - mechanism to limit overeating. This would explain again why both increased and decreased dopamine signalling are found in obese individuals. Remarkably, bariatric surgery in humans, normalizing body weight, food intake, insulin and leptin levels, emphdecreased D2R expression (Dunn et al., 2010). Another study reported increased dopamine levels, increased D2R expression and decreased DAT concentration after 20 days on a HF and high-calorie diet (South & Huang, 2008), opposing many results of experiments with obese individuals. Thus, the authors hypothesized that the initial response to an energy dense diet is elevated dopamine binding, followed by a chronic decrease in dopamine binding (South et al., 2012). However, the question remains why blocking of D2 receptors increases food intake, while activation of dopamine receptors inhibits overeating, if reduced dopamine binding is a compensatory mechanism to prevent excessive energy intake.

5.5 Leptin resistance in the dopamine system

It is unclear whether leptin resistance occurs in the dopamine system. Although a HF diet induces increased STAT-3 activation in the VTA, it cannot be stated with certainty. Surprisingly, leptin administration in the VTA decreased dopamine release and food intake (Hommel et al., 2006), while leptin receptor knockdown in the midbrain increased motivation for sucrose (Davis et al., 2011a), but *ob/ob* mice that lack leptin show decreased dopamine turnover in the NAc and a decreased response to D2 agonists as well (Cincotta et al., 1997; Fulton et al., 2006). Because of these contradictory results it is difficult to draw conclusions. It is possible that leptin indeed both increases and decreases dopamine release in different neuron populations in the VTA, as is proposed by Leshan et al. (2010).

Alternatively, leptin resistance in the dopamine system may occur via leptin resistance in the hypothalamus, or not at all. The finding that STAT-3 expression varies according to area and circumstances (Matheny et al., 2011; Münzberg et al., 2004) supports the possibility that the effect of leptin may differ in separate neuron populations.

The reduction of dopamine release by leptin is not in line with the dopamine deficiency hypothesis and the energy expenditure hypothesis, since leptin is more or less protective against obesity. Then again, this may be a sign of leptin resistance, although it remains elusive why the effect of leptin resistance would be completely the opposite of the effect of

leptin itself. It is possible, of course, that reduced dopamine signalling induced by leptin - whether there is resistance or not - may still inhibit food intake, only ineffectively due to influences from other brain processes.

Generally, leptin resistance is a reversible consequence of a HF diet (Lin et al., 2001) and therefore the effects of leptin resistance are consequences of obesity. However, leptin can rearrange neuronal circuits during early development and during adulthood (Bouret et al., 2004; Pinto et al., 2004) and thus prenatal altered leptin function - for example during maternal obesity - might influence leptin function and dopamine signalling later in life.

5.6 Overexpression of μ-opioid receptors

Obesity may develop from overexpression of μ-opioid receptors (Bartoshuk et al., 2006; Drewnowski et al., 1992; Kelley et al., 2002a; Lenard et al., 2010; Smith et al., 2002), whether this is related to altered dopamine signalling or not (Kelley et al., 2003). Yet, there is evidence that a diet itself enhances opioid receptor signalling. For instance, a highly palatable diet resulted in increased release of μ-opioid receptor ligands and increased opioid receptor expression in the NAc (Adam & Epel, 2007; Colantuoni et al., 2001; Kelley et al., 2000), while μ-opioid receptor binding was reduced during food restriction (Wolinsky et al., 1994). A HF and calorie dense diet could even reduce gene expression of enkephalin in the striatum (Kelley et al., 2000; Kelley et al., 2003) and induce epigenetic changes in the opioid receptor gene (Vucetic et al., 2011). It is likely that HF and HS diets enhance opioid release, whereafter opioid receptors are downregulated in lean people. Attenuated downregulation may then result in overconsumption. Another possible mechanism may be via stress pathways: stress can induce opioid release (Adam & Epel, 2007).

5.7 Related corticolimbic modulations

Experimental findings suggest that, on the one hand, hyperactive sensory regions, and on the other hand, attenuated inhibition by the prefrontal cortex (PFC) may contribute to obesity. Both are very plausible, considered that food cues are everywhere and that we can eat what we fancy. Although increased activity not necessarily reflects enhanced sensitivity to food cues, most sensory cortices seem to be overactive in obese people and activity correlates with desire for food.

In Prader-Willi Syndrome patients, hyperactivity was both seen in limbic regions and in the PFC in response to pictures of food, just after a meal (Holsen et al., 2006). This does not exclude the possibility that dysfunction of the PFC leads to overeating. First, hyperactivity of the PFC in obese people could represent increased top-down inhibitory control on food intake, compensating for hyperactivity in other brain regions such as the limbic system. Of course, this implicates that the PFC functions correctly in these individuals, but a dysfunctional PFC may still contribute to obesity in other people. Second, it is thought that specific regions in the PFC have different functions: the medial PFC seems to signal goal-directed decisions (Hare et al., 2009) and was hyperactive in obese people just before and after eating (Martin et al., 2010), while hyperactivity of the dorsolateral PFC correlates with a higher self-control during food-related decision making in people with normal weight (Alonso-Alonso & Pascual-Leone, 2007; Hare et al., 2009), especially when watching images of high-calorie food (Killgore et al., 2003).

Thus, both increased activity in the medial PFC and decreased activity in the dorsolateral PFC could contribute to obesity. In line with this, transcranial magnetic stimulation of the dorsolateral PFC in people with bulimic-type eating disorders resulted in diminished craving for food and fewer binge eating episodes (Van den Eynde et al., 2010).

Altered function of the somatosensory cortex and the dorsolateral PFC were both associated with decreased D2R expression, but it is unclear what developed first. In addition, HF and HS diets can cause cognitive impairments (Petrovich, 2011) and stress may contribute to eating of palatable 'comfort foods', engaging the corticolimbic system (Dallman et al., 2003; Dallman et al., 2005). Still, it is plausible that modulations in the sensory cortices and corticolimbic system initiate overconsumption. Nummenmaa et al. (2012) propose that implicit reward processing of visual food stimuli is modulated in obese people, possibly by decreased activity of the PFC and/or increased activity of the amygdala and insular cortex, all projecting to the striatum. Lenoir et al. (2007) speculate that an inborn hypersensitivity to sweetness - adapted to environments poor in sugar - results in supranormal reward signals in response to modern HS diets, contributing to addictive-like consumption of HS foods when self-control mechanisms are not strong enough.

5.8 Food addiction

It remains controversial whether obesity can be explained as some sort of 'food addiction'. One interesting possibility is that a 'food addiction' arises from a deviation from the well evolved food reward mechanism - due to maladaptation to the rapidly increased food availability -, and that a drug addiction is a further deviation. Another theory is that two types of motivation to eat exist: 'rational motivation', which is mainly regulated by homeostatic signals and involves increased wanting and liking simultaneously, and 'irrational motivation', which involves increased wanting dissociated from liking (Peciña & Smith, 2010). The first mechanism is a normal process, since the desire to eat is expected to increase when food is highly palatable, but the latter mechanism is a pathological process that is comparable to drug addiction, leading to intense desire for something that is not even highly liked (Robinson & Berridge, 1993). Both mechanisms may lead to overconsumption, but only one comes close to a food addiction, although the term 'food addiction' is of course a question of definition. For further reviews on this topic, see (Avena et al., 2009; De Jong et al., 2012; Dileone et al., 2012; Kelley & Berridge, 2002b; Kenny, 2011; Volkow & Wise, 2005; Volkow et al., 2008b).

5.9 Obesity versus food deprivation

Counter-intuitively, obesity shares aspects of food deprivation, such as increased motivation to obtain food, especially energy dense food (Hodos, 1961; Jewett et al., 1995; La Fleur et al., 2007; Temple et al., 2008), enhanced response of dopamine neurons to food (Wilson et al., 1995), increased circulating triglycerides (Banks et al., 2004, Kastin & Akerstrom, 2000), little effect of leptin on the motivation to eat. Although it seems contradictory, it is logical that a wrong representation of the energy balance or modulations in the reward system that resemble fasting, will lead to increased food consumption. Another common mechanism may be stress-induced eating, which is both associated with food restriction and obesity (Bina & Cincotta, 2000; Cottone et al., 2009; Macht, 1996; Teegarden & Bale, 2007).

5.10 Cause and consequence

Taking all together, there is evidence for both possibilities: modulations in the reward system as cause and consequence of obesity, which is difficult to unite. However, the finding that nutrients like fat and sugar can elicit a vicious circle of eating may be a pathological process, or may even be a normal process to ensure sufficient food intake in a scarce environment. The fact that this does not lead to a world of only obese humans might be due to inhibitory processes that compensate for this effect in lean people.

Epigenetic modulations of gene expression may facilitate this vicious circle and underlie hereditary adaptations to diet, since methylation of genes involved in the motivation to eat were transmitted to the next generation (Dunn & Bale, 2011; Vucetic et al., 2010). Indeed, a chronic HF diet increased methylation of dopamine gene promoters in the VTA, accompanied by decreased gene expression (Vucetic et al., 2012), and changed methylation of the MC4R gene and the μ-opioid receptor promoter (Vucetic et al., 2012; Widiker et al., 2010). In addition, a maternal diet could induce changes in the dopamine system during the prenatal and breast-feeding period (Marichich et al., 1979; Teegarden et al., 2009), and children of obese parents were more at risk of becoming overweight (Fisher & Birch, 1995).

Diet-induced alterations in these genes may explain how modulations in the reward system can simultaneously be cause and consequence of obesity, leading to a vicious circle. This is a remarkable and horrific possibility, but explains the epidemic proportions of obesity. All areas associated with reward are closely connected and slight modulations in one of them may lead to changes in the other areas as well. Yet, it does not seem likely that small alterations in any of the discussed areas can initiate overconsumption, inducing a vicious circle that is even further aggravated by the effect of the diet itself. This model is too complex to be very likely (Myung & Pitt, 1997). Therefore, modulations in dopamine and opioid signalling are more likely consequences of diet, rather than both initial cause and consequence. Once on a HFHS diet, however, these modulations may aggravate obesity.

6 Conclusion

The association between reduced D2R expression and obesity is best supported. However, the dopamine deficiency hypothesis is unconvincing and it is unclear how reduced D2R expression may initiate excessive food intake. Importantly, modulations in dopamine and opioid pathways are more likely secondary to a diet of energy dense food, although they could contribute to further obesity. What then initiates excessive food intake? It is likely that a disturbance in the balance between sensitivity to food cues and self-control, in an environment with much exposure to food cues, initiates overconsumption of energy dense food. From evolutionary perspectives this is not surprising and inhibitory systems might even be hyperactive in lean people. Still, large prospective cohort studies with lean people are necessary to provide the conclusive evidence. We should also keep in mind that the regulation of food intake is influenced by many other processes not described here.

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8 List of abbreviations

α-MSH: α-melanocyte-stimulating hormone
AgRP: agouti-related peptide
AMY: amygdala
ARC: arcuate nucleus of the hypothalamus
BED: binge eating disorder
BMI: body mass index
CCK: cholecystokinin
D1-D5: dopamine 1-5 (receptors)
D2R: dopamine 2 receptor
DAT: dopamine reuptake transporter
DMH: dorsomedial hypothalamus
DS: dorsal striatum
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition (book with criteria to classify mental disorders)
fMRI: functional magnetic resonance imaging
GABA: gamma-aminobutyric acid
GLP-1: glucagon like peptide-1
HCRTR1: hypocretin receptor 1
HF: high-fat
HFHS: high-fat and high-sugar
HIPPO: hippocampus
HS: high-sugar
IRS-PI3K: insulin receptor substrate- phosphatidylinositol 3-kinase
LH: Lateral hypothalamus
MC3R and MC4R: melanocortin 3 and 4 receptors
MCH: melanocortin
mPFC: medial prefrontal cortex
mRNA: messenger ribonucleic acid
NAc: nucleus accumbens
NPY: neuropeptide Y
NTS: nucleus tractus solitarus
ob/ob gene: defect in lleptin receptor gene
OFC: orbitofrontal cortex
PFC: prefrontal cortex
POMC: pro-opiomelanocortin
Prader Willi syndrome: genetic hyperghrelinemia
PVN: paraventricular nucleus of the hypothalamus
PYY3-36: peptide YY3-36
SN: substantia nigra
SOCS-3: suppressor of cytokine signalling-3
STAT3: signal transducer activator of transcription-3
VMH: ventromedial hypothalamus
VTA: ventral techmental area