Central lipid detection and the regulation of feeding behavior

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Abstract: *The modern abundance of energy-rich foods combined with a shift to more sedentary lifestyles has led to a thermodynamic imbalance in which excessive caloric intake and reduced energy expenditure account for the prevalence of obesity. In particular, exposure to lipid-rich diet is thought to promote metabolic alteration in peripheral tissue associated with obesity-related diseases. The regulation of energy balance depends on the ability of the brain to provide an adaptive response to change in circulating factors of hunger and satiety. The hypothalamus is particularly regarded as key integrative structure but, aside from hypothalamic-mediated homeostatic control, feeding behavior is also modulated by sensory inputs, such as tastes and odors, as well as by affective or emotional states. The reinforcing and motivational aspects of food are closely tied to the release of the neurotransmitter dopamine by the mesolimbic system, which is stimulated by calorie-dense foods as well as by most other objects of desire. Therefore feeding behavior is regulated by homeostatic as well as non-homeostatic inputs from the hypothalamus and the mesolimbic region. Interestingly, these structures expresses several enzymes involved in the processing of triglyceride and fatty acid and the recent literature provide growing evidence that fatty acid metabolism within discrete brain regions can function as sensor of nutrient availability directly control the hedonic and the homeostatic aspect of feeding.*

Key words: *Free fatty acid, triglycerides, lipoprotein lipase, mesolimbic system, reward, hypothalamus*

The modern abundance of energy-rich foods combined with a shift to more sedentary lifestyles has led to a thermodynamic imbalance, and consequently, excessive caloric intake and reduced energy expenditure are the main causes for the prevalence of obesity. According to the World Health Organization (WHO)[1]. The obesity worldwide obesity has more than doubled since 1980. In 2008, 1.5 billion adults, 20 and older, were overweight. Obesity is now also considered as an epidemic by the French Health system. A recent report from the French SENAT pinpoints the dramatic progression of obesity in France[2] and a ''Plan Obésité'' has been launched in 2011 under the highest authorities. According to the WHO, the fundamental cause of obesity and overweight is an energy imbalance between calories consumed and calories expended. And it is a fact that globally, there has been both an increased intake of energy-dense foods that are high in fat, salt and a decrease in physical activity.

In adult mammals energy homeostasis is finely regulated. Blood glucose levels, body weight, and fat content remain within narrow ranges and experimentally-induced perturbations (e.g., food restriction) invariably result in a rapid return to ''set point'' when normal conditions are restored. To accomplish this, circulating peripheral factors such as hormones (e.g., insulin, leptin, ghrelin) and nutrients (e.g., glucose, lipids) activate discrete neural circuits in the brain that trigger changes in the basal metabolic rate and/or feeding behaviour. Disruption of these neural circuits can give rise to life-threatening conditions that include metabolic diseases such as obesity and diabetes in both humans and rodent models. Therefore it is crucial to understand the mechanism that insures the proper equilibrium between energy intake and expenditure.

Several observations led to the identification of the hypothalamus as a major

[1] http://www.who.int/mediacentre/factsheets/fs311/en/

[2] http://www.senat.fr/rap/r10-158/r10-1580.html#toc0

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integration site for inputs related to energy homeostasis (Schwartz and Porte, 2005). The hypothalamus contains specialized neurons that monitor circulating factors of hunger and satiety in order to provide an integrated adaptive response at both the metabolic and behavioral levels. This homeostatic control of energy homeostasis relies primarily on the so called melanocortin system which encompasses several molecular actors involved in body weight regulation (Schwartz *et al.*, 2000; Cone, 2005).

However, aside from hypothalamic-mediated homeostatic control, feeding behavior is also modulated by sensory inputs, such as tastes and odors, as well as by affective or emotional states. For example, stress or anxiety can stimulate reward seeking and consumption of highly palatable food independent of metabolic demand (Dallman *et al.*, 2005). The reinforcing and motivational aspects of food are closely tied to the release of the neurotransmitter dopamine, which is stimulated by high-fat/high-sugar foods as well as by most other objects of desire (e.g., sex, drugs) (Gunstad *et al.*, 2007).

In particular, the projection of midbrain dopamine neurons in the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and other limbic brain regions is a crucial neural substrate upon which drugs of abuse (e.g., cocaine, nicotine, morphine) exert their effect; and thus this projection is often referred to as the brain ''reward circuit''. This immediately suggests that compulsive consumption of high-fat/high-sugar foods and the consequent chronic spiking of brain reward circuitry may produce molecular changes similar to those that lead to drug addiction. Thus, as with drug addiction, repeated exposure to high-fat/high-sugar foods may lead to heightened craving for and dependence on these calorie-rich foods resulting in a downward spiral of compulsive over-consumption and ultimately obesity.

In the brain, both the hypothalamus and the brain reward circuit expresses several enzymes involved in the transport, manipulation and metabolism of both free fatty acid and triglyceride rich particles (TG). Elevated circulating levels of long-chain fatty acids (LCFAs), which are often elevated in obese and diabetic individuals, have recently been demonstrated to be an important signaling molecule acting in the hypothalamus to control food intake and energy expenditure (Kim *et al.*, 2002; Ronnett *et al.*, 2005; Ronnett *et al.*, 2006). In addition, component of the reward circuitry also expresses several enzymes involved in the processing of triglyceride and fatty acid including lipoprotein lipase (LPL) (Ben-Zeev *et al.*, 1990; Paradis *et al.*, 2004), an enzyme responsible for triglyceride hydrolysis. Recent studies have provided have highlighted a role for neuronal LPL-mediated hydrolysis of TG particles in the regulation energy balance (Wang *et al.*, 2011; Wang and Eckel, 2012).

High fat feeding and in general lipid & sugar rich diet in both human and rodent has been associated with the progressive loss in spontaneous locomotor activity, and it has been shown that an acute reduction in locomotor activity in a major contributor to western diet-induced obesity in mice (Bjursell and Gerdin *et al.*, 2008). Moreover high fat/high sucrose diet were also link to the establishment of an addictive-like reward dysfunction and compulsive eating in obese rats (Johnson and Kenny, 2010). Therefore it is tempting to speculate that TG-rich particles, accumulated during high fat feeding and in obese state could directly affect the mesolimbic reward/goal directed dopaminergic circuitry.

This review is an attempt to provide the neuro-anatomic framework together with recent update in the literature supporting the hypothesis in which nutritional lipids could be detected in different area of the brain and could serve as nutritional signal to regulate food intake in its rewarding and homeostatic component.

Hypothalamic regulation of feeding: the Melanocortin-Signaling Pathway

The hypothalamus consists of several nuclei involved in food intake, including the arcuate nucleus (ARC), the paraventricular nucleus (PVN), the lateral hypothalamic area (LHA), the ventromedial nucleus (VMH), and the dorsomedial nucleus (DMH). ARC neurons are located at the bottom of the hypothalamus around the third ventricle. They are called ''first order neurons'' because they directly contact the bloodstream and, thus, circulating satiety factors like insulin, ghrelin or leptin. This is due to an anatomical property of the ARC to be surrounded by the Median Eminence (ME) where the Brain Blood Barrier (BBB) is less developed. Two distinct groups of ARC neurons are directly controlling energy balance, the neurons containing orexigenic neuropeptides, agouti-gene-related protein (AgRP) and neuropeptide Y (NPY) (NPY/AgRP Neurons), and the neurons containing anorexigenic neuropeptides, pro-opiomelanocortin (POMC) and cocaine-and amphetamine-related transcript (CART). Both groups also express leptin receptors and insulin receptors. ARC neurons project to 'second order neurons' in the PVN, VMH, DMH and LHA which, in turn, project to other brain areas, essential for the long-term regulation of energy homeostasis, like Nucleus of the Solitary Tract (NTS). The ARC-PVN axis defines the so-called melanocortin-signalling pathway and is a key neuro-circuit for the regulation of feeding, any mutation of the melanocortin system leads to obesity and hyperphagia in both human and rodent (Kalra *et al.*, 1991; Beck, 2001).

Hypothalamic sensing of LCFAs and metabolic syndrome

Plasma fatty acids (FA) as informative molecules acting on brain have been poorly studied for long time, as they were thought unable to cross the blood-brain barrier. However, growing amount of data attest that cerebral lipids come from both local synthesis and plasma origin (Rapoport, 2001). Furthermore, it must be pointed that structure and function of the BBB within hypothalamus – especially the ME and associated circumventricular organs (CVO) – is quite different from other part of the brain (review in (Abbott *et al.*, 2006). In particular, CVO are characterized by their small size, high permeability and fenestrated capillaries (Abbott *et al.*, 2006). Thus, substances that do not cross BBB in other part of the brain may be imported in hypothalamus and it has been demonstrated using brain uptake index (BUI) method that palmitate uptake in hypothalamus is about 10 to 15% whereas less than 2% in other brain areas (Rapoport, 2001).

There is now growing amount of evidence that ''central lipid sensing sensing'' is involved in the control of feeding behavior.

Central infusion of LCFAs such as oleate physiologically inhibits both hepatic glucose production and food intake (Obici *et al.*, 2002) and it was demonstrated that neuronal subpopulations of the arcuate nucleus could be either excited or inhibited by LCFAs (Wang *et al.*, 2005). Genetic or pharmacological inhibition of enzymes involved in lipid metabolism like the Fatty Acid Synthase (FAS) or the Carnitine Palmitoyltransferase 1 (CPT-1) leads to a decrease in food intake, hepatic glucose production and are often associated with decreased expression of NPY and AgRP (Lam *et al.*, 2005; Lam *et al.*, 2005; Pocai *et al.*, 2005). The molecular mechanisms relaying fatty acid action involve metabolites such as acylCoA or malonylCoA, which could be major fuel sensors and most of the enzymes involved in lipid metabolism are detected at high level in the hypothalamic nucleus that control feeding behavior like the ARC, DMN and VMN (Kim *et al.*, 2002; Sorensen *et al.*, 2002). Moreover, central administration of C75, a potent inhibitor of FAS, also increases malonyl-CoA concentration in the hypothalamus, suppresses food intake and leads to profound weight loss (Gao and Lane, 2003). It has been proposed that centrally, C75 and cerulenin – another inhibitor of FAS – alter the expression profiles of feeding-related neuropeptides (such as NPY), often inhibiting the expression of orexigenic peptides (Gao and Lane, 2003). C75 also increases energy consumption, which contributes to weight loss. *In vitro* and *in vivo* studies demonstrate that at least part of C75's effects are mediated by the modulation of AMP kinase (AMPK), a known peripheral energy-sensing kinase (Ronnett *et al.*, 2005). Indeed, ICV. Administration of AICAR (5-aminoimidazole-4-carboxamide ribonucleoside), a 5'-AMP kinase activator, rapidly lowers hypothalamic malonyl-CoA concentration and increases food intake (Hu *et al.*, 2005). These effects correlate closely with the phosphorylation and thus inactivation of the Acyl-CoA Carboxylase (ACC), an established target of AMPK. Collectively, these data suggest a role for fatty acid metabolism in the perception and regulation of food intake (Tu *et al.*, 2005).

Thus, LCFAs appeared to modulate neuronal activities in hypothalamic areas playing a critical role in the control of energy homeostasis.

However, it must be pointed out that, unlike plasma triglyceride-rich particle which rise after a meal, plasma level of LCFAs actually decrease due to the combined action of lipolysis inhibition and hyperinsulinemia (Ruge *et al.*, 2009). Indeed, during a meal the hydrolysis and absorption by the gut leads to triglycerides packaging and through chylomicrons synthesis. Moreover the liver also produces very low density lipoprotein (VLDL). Thus TG-rich particles, accumulating after a meal, could also pretend to be a physiologically relevant satiety signal acting in the brain to regulate feeding behavior and energy expenditure. One would have to assume that TG particle are entering the brain and can be locally hydrolyzed into areas mentioned above (hippocampus, striatum, and hypothalamus).

The Mesolimbic system: a brain circuits encoding the motivational and hedonic aspects of food intake

Palatability and pleasantness are powerful determinant of food intake. Ingestion of food provides subjective pleasure, particularly if the food is rich in sugar or fat, and eating can be a source of comfort in depression or stressful states (Dallman *et al.*, 2003). The positive emotion or pleasure of tasting sugar or fat foods may have evolved to guarantee sufficient intake of varied food and high-energy foods (Kelley *et al.*, 2002). A feeding induced hedonic response is positively reinforcing, and driving an organism to repeat ingestion of calorically dense food. Dopamine (DA) is involved in the reinforcing effects of food (Comings and Blum, 2000). Dopamine antagonist increase appetite, energy intake and weight gain, whereas dopamine agonist reduce energy intake and produce weight loss (Leddy *et al.*, 2004; de Leon *et al.*, 2007). DA binds to several G-protein-coupled dopamine receptors-D1 and D5 coupled to $G_{\alpha s}$; D2, D3 and D4 coupled to $G_{\alpha i}$-which activate intracellular signaling pathways in postsynaptic neurons. DA neurons in the Ventral Tegmental Area (VTA) and the Substancia Nigra innervate the Nucleus Accumbens (Nacc), Caudate Putamen (Cpu), cortical regions (prefrontal cortex (PFC), orbitofrontal cortex (OFC)) and limbic regions (amygdala (AG), hippocampus). During regular circumstances, DA neurons are firing continuously causing tonic DA release; salient environmental stimuli induce burst-firing of DA neurons resulting in DA release (Palmiter, 2007). Feeding is associated with DA release in the dorsal striatum (St), and the degree of pleasure from eating correlates with amount of dopamine released (Szczypka *et al.*, 2001; Small *et al.*, 2003). DA is also involved with the motivation to perform the behaviors necessary to procure and consume the food. In fact, Dopamine-deficient mice are hypophagic, fail to engage in goal-directed feeding behaviors, and will die of starvation (Szczypka *et al.*, 1999; Palmiter, 2008). If DA signaling is restored only to the Cpu, mice will eat sufficiently for survival, whereas restoration of DA in the Nacc is not sufficient to sustain long-term feeding (Szczypka *et al.*, 2001; Palmiter, 2008). These results show that Cpu has a role in mediating motivational aspect of feeding whereas Nacc does not. Moreover, it was found that chemical lesions of the DA system (pharmacological antagonists of DA receptor), sufficient to render the animals completely incapable of initiating behavior aimed at obtaining food, did not affect the hedonic-like reactions to sucrose placed in the mouth (Tyrka *et al.*, 1992; Berridge and Robinson, 1998). This finding was interpreted as indicating that the neural systems mediating the hedonic impact of preferred tastes was distinct from that mediating the ability of incentives to elicit goal-directed behavior; these two processes were termed ''liking'' and ''wanting'', respectively. With regard to neurochimical mediation, it was proposed that liking depends upon opioid transmission and wanting is governed by the mesolimbic DA system (Kelley *et al.*, 2005). Opioid peptides that are produced in the body include: endorphins, enkephalins, dynorphins, endomorphins. The striatum contains enkephalin and β-endorphin (Pickel *et al.*, 1980; Sweep *et al.*, 1989). Opioid receptors are found throughout the brain including Striatum, VTA and HT (Mansour *et al.*, 1987). There are also found in neural pathways thought to

relay taste information (Nucleus Tractus Solitarius (NTS), the parabrachial nucleus (PB) and the AG) (Mansour *et al.*, 1987; Xia and Haddad, 1991). Opioid receptor agonist enhance food intake by increasing the hedonic valence of food (Kotz *et al.*, 1997; Echo *et al.*, 2002; Wilson *et al.*, 2003; Levine *et al.*, 2004; Kelley *et al.*, 2005). Local injection of the selective μ-opioid receptor agonist DAMGO into the nucleus accumbens results in increased intake of both fat and carbohydrate-rich diets when either are presented alone (Zhang and Kelley, 1997; Zhang *et al.*, 1998). Interestingly, if rats were given a choice between both diets, DAMGO treatment strongly increased their intake of the fat diet without affecting carbohydrate consumption, suggesting that the fat diet is inherently more palatable (Kelley *et al.*, 2005).

With sensorial or emotional signals, circulating factors like hormones or nutrients which encoding nutritional status of the organism, influence brain regions that regulate the motivation to consume high-calorie foods.

Circulating factors also provide signals to the mesolimbic system: implication for the regulation of feeding behavior

A variety of hormones, such as leptin, insulin and ghrelin can directly modulate DA neuron activity. The role of these hormones in regulating homeostatic circuits in the hypothalamus has been examined extensively, but studying their effects on the DA reward circuit is a new direction.

Leptin, insulin and ghrelin receptors are expressed in the VTA (Figlewicz *et al.*, 2003; Abizaid *et al.*, 2006; Fulton *et al.*, 2006; Hommel *et al.*, 2006; Pardini *et al.*, 2006). Intracerebroventricular (i.c.v.) insulin administration increased the mRNA levels and the functional activity of DA transporter (DAT). Authors suggested that this increase would facilitate clearing DA from synapse and hence reduce DA signaling (Figlewicz *et al.*, 1994; Figlewicz *et al.*, 2003). Moreover, the firing rate of DA neurons in anesthetized rats decreased in response to an intravenous infusion of leptin (Hommel *et al.*, 2006) and i.c.v. leptin infusion reduced extracellular dopamine in the Nacc (Krugel *et al.*, 2003). Inversely, ghrelin increased the firing rate of VTA DA neurons and i.c.v. and systemic administration of ghrelin induced a DA over-flow in the Nacc (Abizaid *et al.*, 2006; Jerlhag *et al.*, 2006; Quarta *et al.*, 2009). In humans, a functional MRI experiment revealed that ghrelin injection activates brain regions associated with reward processing of appetitive behaviors including AG and Striatum (Malik *et al.*, 2008). Behavioral evidences showed that these hormones, by modulating DA system, directly affect feeding behavior. In fact, i.c.v. insulin or leptin administration reduced sucrose self administration, suppressed the conditioned place preference (CPP) for sucrose pellets and reversed CPP for high-fat (HF) food (Figlewicz *et al.*, 2003; Figlewicz *et al.*, 2004; Figlewicz *et al.*, 2006). Moreover, leptin administration to the VTA decreased food intake (Hommel *et al.*, 2006; Morton *et al.*, 2009). Authors proposed that a reduction in CPP by these hormones suggested that they interfere with subjective reward value, and associative learning of food. Moreover, i.c.v. leptin and insulin infusion or more specifically in the VTA decreases the feeding and sucrose intake induced by opioid receptor agonist (μ and k) (Sipols *et al.*, 2002; Figlewicz *et al.*, 2007). On the other hand, ghrelin delivery to the VTA or to the Nacc stimulated food intake in a dose dependant manner (Naleid *et al.*, 2005; Abizaid *et al.*, 2006). Thus insulin and leptin provide inhibitory inputs fo DA neurons in the VTA which can decrease dopaminergic tone in postsynaptic areas and ghrelin activates DA neurons activity, stimulates DA turnover and release in the Nacc. Food restriction lower serum levels of insulin and leptin while increasing level of ghrelin; each of these individual effects predicted to enhance DA neuron activity. Thus is consistent with the idea that food restriction enhanced the subjective value of food (Carr, 2002). However there is disconnection between DA signaling and eating behavior, thus it is premature to ascribe feeding and reward behaviors exclusively to DA release (Palmiter, 2007).

We have seen that circulating hormones can modulate mesolimbic system by modulating dopaminergic tonus essentially. Other circulating parameters like plasmatic glucose encoding nutritional status can also influence mesolimbic system. In fact systemic glucose administration suppressed the firing of dopaminergic neurons within the SN (Saller and Chiodo, 1980) and local glucose in the SN increased GABA release (During *et al.*, 1995). Authors suggested that glucose acts as a signaling molecule in DA neurons which played an important role in maintaining motivated feeding behaviors especially in response to abrupt decreases in glucose use (Saller and Chiodo, 1980). However, in this study, insulin was not measured and authors put forward a potential role of insulin in dopaminergic transmission changing. Interestingly, a recent study, succeed to isolated the physiological stimulus glycemic state in humans. By using, functional MRI combined with a stepped hyperinsulinemic euglycemic-hypoglycemic clamp and behavioral measures of interest in food, they shown that hypoglycemia activates limbic striatal brain regions (Nacc, Insula, Ht, Thalamus and Cpu) in response to food cues to produce a greater desire for high-calorie foods.

Thus, hormones and nutrients that regulate energy balance through the hypothalamus also modulate the activity of dopamine cells and their projections into regions involve in the rewarding aspect of food intake. Hypothalamic signaling disruption is now recognized as a major component in metabolic syndrome development (Schwartz *et al.*, 2000; Prodi and Obici, 2006). However, accumulating evidences show that disruptions in brain circuits, other than those regulate hunger and satiety, are involved in feeding behavior disorders and, consequently, obesity development.

Disruptions of mesolimbic system activity associated with obesity and high circulating lipids

Growing evidences show that obesity is associated with deficits in mesolimbic system.

In rats, striatal levels of D2R were inversely related to body weight (Johnson and Kenny, 2010). Importantly, in this study, authors liked the

decrease of striatal D2R to compulsive food intake by lentivirus-mediated knockdown of striatal D2R which rapidly accelerated the development of addiction-like reward deficits in rats with extended access to palatable HF food (Johnson and Kenny, 2010). Moreover, another study showed that D2R activation (subcutaneous pellet of bromocriptine/i.p. bromocriptine injection) partly redirected HF diet induced metabolic anomalies in obesity-prone mice (Davis *et al.*, 2009; de Leeuw van Weenen *et al.*, 2011). Conversely, blocking D2R (subcutaneous pellet of haloperidol) induces an adverse metabolic profile in mice that are inherent resistant to the deleterious effect of HF food (de Leeuw van Weenen *et al.*, 2011). Besides D2R alteration, D1R and μ-opiod receptor mRNA was down-regulated after long-term (5 weeks) high fat high sucrose (HFHS) access in obesity-prone rats compared with obesity resistant rats (Alsio *et al.*, 2010). In human, striatal D2R availability was significantly lower in obese individuals and the body mass index (BMI) correlated negatively with measures of D2R; the individuals with the lowest D2 values had the largest BMI (Wang *et al.*, 2001; Volkow *et al.*, 2008). Obese versus lean humans showed less activation of striatal DA target regions in response to palatable food intake (Stice *et al.*, 2008) whereas they showed greater activation of regions that process palatability and motivation (Nacc, St, orbitofrontal cortex (OFC), AG…) when they anticipated consumption (stimulated with pictures of high-calorie food) (Rothemund *et al.*, 2007; Stice *et al.*, 2008; Stoeckel *et al.*, 2008). Thus suggests that an enhanced activity of regions that process palatability could make obese subjects favor food over other natural reinforcers (Volkow *et al.*, 2011). Taken together, rats and humans data suggest that an attenuated activity of dopaminergic would reduce the hedonic response associated with feeding, a deficit that obese individuals might strive to compensate by overeating (Geiger *et al.*, 2008; Stice *et al.*, 2008; Volkow *et al.*, 2011).

However, there is evidence that consumption of palatable food *per se* leads to DA signaling alterations. 40 days of cafeteria diet consumption decreased striatal D2R expression and induced brain reward dysfunctions (Johnson and Kenny, 2010). However, at the early stage of obesity, HF diet consumption (20 days) significantly increased D2 receptor (D2R) binding in the Cpu and the Nacc, but decreased DAT binding in the Cpu. Authors suggest that combination of higher levels of D2 and low levels of DAT binding suggest they may have had lower striatal dopaminergic activity compared to a low-fat fed group (South and Huang, 2008). What is consistent with the fact that electrically evoked DA release from Nacc slice preparations and extracellular DA level in the Nacc (microdialysis) was markedly reduced in cafeteria diet induced obesity animals (15 weeks) compared with chow fed animals (Geiger *et al.*, 2009). Moreover, some studies showed that sucrose intake by itself influence dopamine signaling in the brain (Colantuoni *et al.*, 2001; Bello *et al.*, 2002).

As it has been shown in the hypothalamus (Arase *et al.*, 1988), HF diet can also alter mesolimbic insulin action. In fact, HF consumption (28 days) induced impairment in striatal activation of the insulin-activated signaling kinase (Akt). HF-induced Akt impairment reduced DAT cell surface expression and function, thereby decreasing DA homeostasis and DA-related behaviors such as AMPH-induced locomotion and increase caloric intake. Restoration of nigro-striatal Akt phosphorylation using recombinant viral vector induced a rescue of DAT expression in HF fed rats which was associated with a normalization of HF-diet induced hyperphagia (Speed *et al.*, 2011). All these data imply that overeating palatable food *per se* may contribute to a further attenuation reward circuitry. In humans, a fMRI study indicated that weight gain in overweigh and obese young women was associated with a reduction in striatal activation in response to palatable food intake relative to baseline response six month before. As we discussed above, the attenuation of reward circuitry induced by palatable food consumption could reduce the rewarding and hedonic value of food. Consisting with this hypothesis, it has been shown that animal consuming HF diet, independent of the development of obesity, exhibit decreased dopamine turnover in the OFC and Nacc, what is associated with behavioral defaults like a reduced preference for an amphetamine cue, and an attenuated operant responding for sucrose (Davis *et al.*, 2008).

We have seen that palatable food consumption could directly alters rewarding system, causing inappropriate feeding behavior and leading to obesity. Because the palatability of food is typically a function of its fat and sugar composition (Drewnowski *et al.*, 1989), we can suppose that these nutrients, particularly lipids, could act directly on mesolimbic system to modulate the motivational and rewarding aspect of food intake.

Lipids consumption could induce a disruption of the mesolimbic system

It is important to note that independently of weight gain, at the early stage of obesity development, fat consumption lead to dopamine system dysfunction. In fact, animals consuming high fat diet diet prior to obesity development exhibit a decreased in dopamine turnover (Davis *et al.*, 2008), restricted access to cafeteria diet decreased striatal expression of D2R (Johnson and Kenny, 2010), and HFHS pair fed decreased D1R and D1R Nacc expression, relative to chow fed controls (Alsio *et al.*, 2010). Above, we have discussed the fact that circulating factors like hormones or nutrients (glucose) could modulate mesolimbic system by modulating dopaminergic tonus essentially. We can suppose that nutritional lipids present in HF, HFHS and cafeteria diet could directly modulate mesolimbic system and may contribute to a further attenuation of mesolimbic responsivity to food, as it is suspected in other brain areas. In fact, there is increasing evidence that obesity is associated with impairment on certain cognitive function, such as executive function, attention and memory (Gunstad *et al.*, 2007; Bruce-Keller *et al.*, 2009; Bruehl *et al.*, 2009). Although co-morbid medical conditions (cerebrovascular pathology, hypertension and diabetes) are known to affect cognition adversely, there is also evidence that high BMI, by itself, might impair various cognitive domains particularly executive function (Gunstad *et al.*, 2007) which could be explain by a lower baseline prefrontal (OFC included) metabolism (Volkow *et al.*, 2009). Even though the correlation between lipid levels and cognitive function is still debated, a recent study has shown that impaired cognition in obese mice was

improved by selectively lowering triglycerides with gemfibrozil (Farr *et al.*, 2008). Moreover it was shown that i.c.v injection of the triglyceride triolein impaired acquisition in several cognitive paradigms in normal body weight mice. Authors suggested that triglycerides, by itself, mediate cognitive impairment as seen in obesity such as food reward lever press (Farr *et al.*, 2008). In agreement with this hypothesis, when the orosensory reward of fat is bypassed with i.p. injection of triglycerides (TG) the increase in TG levels rats leads to an increase in both DA and and DA metabolites in the Nacc, similar what is observed after the fat consumption (Rada *et al.*, 2010). These result suggest that, as glucose, TG could act as a signaling molecule in dopamine system and could be part of the reinforcing effects of palatable food. Interestingly, obesity prone rats still at normal weight (based on their weight gain during 5 days of access to HF diet) had levels of TG consistently higher in response to high-fat meal or injection of Intralipid compared to obesity-resistant rats. We can suppose that brain overexposure to TG could induce desensitization to TG signaling in the dopamine system. This could in turn reduce DA responsiveness to circulating lipids which may contribute to the failure of obesity-prone rats to properly regulate their intake of a high-fat diet. This is consistent with the observation that high-TG responders showed an increased propensity to overeat and gain weight on a chronic HF diet (Karatayev *et al.*, 2009).

Conclusion

Several observations led to the identification of the hypothalamus as a major integration site for inputs related to energy homeostasis (Schwartz and Porte, 2005). The hypothalamus contains specialized neurons that monitor circulating factors of hunger and satiety in order to provide an integrated adaptive response at both the metabolic and behavioral levels. This homeostatic control of energy homeostasis tends to keep body weight within a narrow range.

However, aside from hypothalamic-mediated homeostatic control, feeding behaviour is also modulated by sensory inputs, such as tastes and odors, as well as by affective or emotional states. For example, stress or anxiety can stimulate reward seeking and consumption of highly palatable food independent of metabolic demand (Dallman *et al.* 2005). The reinforcing and motivational aspects of food are closely tied to the release of the neurotransmitter dopamine, which is stimulated by high-fat/high-sugar foods as well as by most other objects of desire (e.g., sex, drugs) (Wise, 2006). In particular, the projection of midbrain dopamine neurons in the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and other limbic brain regions is a crucial neural substrate upon which drugs of abuse (e.g., cocaine, nicotine, morphine) exert their effect; and thus this projection is often referred to as the brain ''reward circuit''. Strong evidence indicates that chronic exposure to drugs of abuse leads to molecular changes in the neurons of the brain reward circuit which underlie key aspects of the addictive state such as craving and dependence (Wise, 2006).

A widely accepted conceptual framework sees food intake as the result of a complex behavioral sequence that entail both ''homeostatic'' inputs, arising from the hypothalamus and emotional-cognitive inputs encode by the mesolimbic system. The two components integrate several circulating factors of hunger and satiety and communicate with one another to adapt both metabolic demands and the hedonic and motivational aspect of food intake. Although it is generally accepted that the brain does not uses lipids as a primary source of energy, it expresses several enzymes involved in the transport, hydrolysis and manipulation of TG-rich particle and LCFAs (Kim *et al.*, 2002; Ronnett *et al.*, 2005; Ronnett *et al.*, 2006). Central LCFAs sensing in the hypothalamus was recently demonstrated to be a key mechanism for the homeostatic regulation of food intake (Lam *et al.*, 2005; Migrenne *et al.*, 2011). Beside LCFAs that only increase in the bloodstream during fasting condition, TG-rich particle are found to be elevated in most obese and high fat condition. TG hydrolyses involved lipoprotein lipase activity, and the genetic invalidation of the gene encoding the Lpl, selectively in neurons translate into obesity and feeding alteration (Wang *et al.*, 2011; Wang and Eckel, 2012). This result strongly suggests a key role for TG-rich particle detection and hydrolysis in brain areas involved in feeding. Both the hypothalamus and the reward neurocircuitry express high level of LPL (Ben-Zeev *et al.*, 1990; Paradis *et al.*, 2004), and could therefore relay the action of TG-rich particle, and in general high fat associate hypertriglycemia, in the long-term alteration of both homeostatic regulation of food intake as well as the cognitive and emotional aspect of feeding

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Conflict of interest: none.

REFERENCES

Abbott NJ, Ronnback L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. *Nat Rev Neurosci* 2006; 7: 41-53.

Abizaid A, Liu ZW, Andrews ZB, *et al.* Ghrelin modulates the activity and synaptic input organization of midbrain dopamine neurons while promoting appetite. *J Clin Invest* 2006; 116: 3229-39.

Alsio J, Olszewski PK, Norback AH, *et al.* Dopamine D1 receptor gene expression decreases in the nucleus accumbens upon long-term exposure to palatable food and differs depending on diet-induced obesity phenotype in rats. *Neuroscience* 2010; 171: 779-87.

Arase K, Fisler JS, Shargill NS, York DA, Bray GA. Intracerebroventricular infusions of 3-OHB and insulin in a rat model of dietary obesity. *Am J Physiol* 1988; 255: R974-81.

Beck B. KO's and organisation of peptidergic feeding behavior mechanisms. *Neurosci Biobehav Rev* 2001; 25: 143-58.

Bello NT, Lucas LR, Hajnal A. Repeated sucrose access influences dopamine D2 receptor density in the striatum. *Neuroreport* 2002; 13: 1575-8.

Ben-Zeev O, Doolittle MH, Singh N, Chang CH, Schotz MC. Synthesis and regulation of lipoprotein lipase in the hippocampus. *J Lipid Res* 1990; 31: 1307-13.

Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res Brain Res Rev* 1998; 28: 309-69.

Bruce-Keller AJ, Keller JN, Morrison CD. Obesity and vulnerability of the CNS. *Biochim Biophys Acta* 2009; 1792: 395-400.

Bruehl H, Wolf OT, Sweat V, Tirsi A, Richardson S, Convit A. Modifiers of cognitive function and brain structure in middle-aged and elderly individuals with type 2 diabetes mellitus. *Brain Res* 2009; 1280: 186-94.

Carr KD. Augmentation of drug reward by chronic food restriction: behavioral evidence and underlying mechanisms. *Physiol Behav* 2002; 76: 353-64.

Colantuoni C, Schwenker J, Mccarthy J, *et al.* Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain. *Neuroreport* 2001; 12: 3549-52.

Comings DE, Blum K. Reward deficiency syndrome: genetic aspects of behavioral disorders. *Prog Brain Res* 2000; 126: 325-41.

Cone RD. Anatomy and regulation of the central melanocortin system. *Nat Neurosci* 2005; 8: 571-8.

Dallman MF, Pecoraro N, Akana SF, *et al.* Chronic stress and obesity: a new view of ''comfort food''. *Proc Natl Acad Sci U S A* 2003; 100: 11696-701.

Dallman MF, Pecoraro NC, La Fleur SE. Chronic stress and comfort foods: self-medication and abdominal obesity. *Brain Behav Immun* 2005; 19: 275-80.

Davis JF, Tracy AL, Schurdak JD, *et al.* Exposure to elevated levels of dietary fat attenuates psychostimulant reward and mesolimbic dopamine turnover in the rat. *Behav Neurosci* 2008; 122: 1257-63.

Davis LM, Michaelides M, Cheskin LJ, *et al.* Bromocriptine administration reduces hyperphagia and adiposity and differentially affects dopamine D2 receptor and transporter binding in leptin-receptor-deficient Zucker rats and rats with diet-induced obesity. *Neuroendocrinology* 2009; 89: 152-62.

De Leeuw Van Weenen JE, Parlevliet ET, Schröder-van der Elst JP, *et al.* Pharmacological modulation of dopamine receptor D2-mediated transmission alters the metabolic phenotype of diet induced obese and diet resistant C57Bl6 mice. *Exp Diabetes Res* 2011; 2011: 928523.

De Leon J, Diaz FJ, Josiassen RC, Cooper TB, Simpson GM. Weight gain during a double-blind multidosage clozapine study. *J Clin Psychopharmacol* 2007; 27: 22-7.

Drewnowski A, Shrager EE, Lipsky C, Stellar E, Greenwood MR. Sugar and fat: sensory and hedonic evaluation of liquid and solid foods. *Physiol Behav* 1989; 45: 177-83.

During MJ, Leone P, Davis KE, Kerr D, Sherwin RS. Glucose modulates rat substantia nigra GABA release in vivo via ATP-sensitive potassium channels. *J Clin Invest* 1995; 95: 2403-8.

Echo JA, Lamonte N, Ackerman TF, Bodnar RJ. Alterations in food intake elicited by GABA and opioid agonists and antagonists administered into the ventral tegmental area region of rats. *Physiol Behav* 2002; 76: 107-16.

Farr SA, Yamada KA, Butterfield DA, *et al.* Obesity and hypertriglyceridemia produce cognitive impairment. *Endocrinology* 2008; 149: 2628-36.

Figlewicz DP, Bennett J, Evans SB, Kaiyala K, Sipols AJ, Benoit SC. Intraventricular insulin and leptin reverse place preference conditioned with high-fat diet in rats. *Behav Neurosci* 2004; 118: 479-87.

Figlewicz DP, Bennett JL, Naleid AM, Davis C, Grimm JW. Intraventricular insulin and leptin decrease sucrose self-administration in rats. *Physiol Behav* 2006; 89: 611-6.

Figlewicz DP, Evans SB, Murphy J, Hoen M, Baskin DG. Expression of receptors for insulin and leptin in the ventral tegmental area/substantia nigra (VTA/SN) of the rat. *Brain Res* 2003; 964: 107-15.

Figlewicz DP, Macdonald Naleid A, Sipols AJ. Modulation of food reward by adiposity signals. *Physiol Behav* 2007; 91: 473-8.

Figlewicz DP, Szot P, Chavez M, Woods SC, Veith RC. Intraventricular insulin increases dopamine transporter mRNA in rat VTA/substantia nigra. *Brain Res* 1994; 644: 331-4.

Fulton S, Pissios P, Manchon RP, *et al.* Leptin regulation of the mesoaccumbens dopamine pathway. *Neuron* 2006; 51: 811-22.

Gao S, Lane MD. Effect of the anorectic fatty acid synthase inhibitor C75 on neuronal activity in the hypothalamus and brainstem. *Proc Natl Acad Sci U S A* 2003; 100: 5628-33.

Geiger BM, Behr GG, Frank LE, *et al.* Evidence for defective mesolimbic dopamine exocytosis in obesity-prone rats. *FASEB J* 2008; 22: 2740-6.

Geiger BM, Haburcak M, Avena NM, Moyer MC, Hoebel BG, Pothos EN. Deficits of mesolimbic dopamine neurotransmission in rat dietary obesity. *Neuroscience* 2009; 159: 1193-9.

Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, Gordon E. Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. *Compr Psychiatry* 2007; 48: 57-61.

Hommel JD, Trinko R, Sears RM, *et al.* Leptin receptor signaling in midbrain dopamine neurons regulates feeding. *Neuron* 2006; 51: 801-10.

Hu Z, Dai Y, Prentki M, Chohnan S, Lane MD. A role for hypothalamic malonyl-CoA in the control of food intake. *J Biol Chem* 2005; 280: 39681-3.

Jerlhag E, Egecioglu E, Dickson SL, Andersson M, Svensson L, Engel JA. Ghrelin stimulates locomotor activity and accumbal dopamine-overflow via central cholinergic systems in mice: implications for its involvement in brain reward. *Addict Biol* 2006; 11: 45-54.

Johnson PM, Kenny PJ. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nature neuroscience* 2010; 13: 635-41.

Kalra SP, Dube MG, Sahu A, Phelps CP, Kalra PS, Neuropeptide. Y secretion increases in the paraventricular nucleus in association with increased appetite for food. *Proc Natl Acad Sci U S A* 1991; 88: 10931-5.

Karatayev O, Gaysinskaya V, Chang GQ, Leibowitz SF. Circulating triglycerides after a high-fat meal: predictor of increased caloric intake, orexigenic peptide expression, and dietary obesity. *Brain Res* 2009; 1298: 111-22.

Kelley AE, Bakshi VP, Haber SN, Steininger TL, Will MJ, Zhang M. Opioid modulation of taste hedonics within the ventral striatum. *Physiol Behav* 2002; 76: 365-77.

Kelley AE, Baldo BA, Pratt WE. A proposed hypothalamic-thalamic-striatal axis for the integration of energy balance, arousal, and food reward. *J Comp Neurol* 2005; 493: 72-85.

Kim EK, Miller I, Landree LE, *et al.* Expression of FAS within hypothalamic neurons: a model for decreased food intake after C75 treatment. *Am J Physiol Endocrinol Metab* 2002; 283: E867-79.

Kotz CM, Billington CJ, Levine AS. Opioids in the nucleus of the solitary tract are involved in feeding in the rat. *Am J Physiol* 1997; 272: R1028-32.

Krugel U, Schraft T, Kittner H, Kiess Willes P. Basal and feeding-evoked dopamine release in the rat nucleus accumbens is depressed by leptin. *Eur J Pharmacol* 2003; 482: 185-7.

Lam TK, Pocai A, Gutierrez-Juarez R, *et al.* Hypothalamic sensing of circulating fatty acids is required for glucose homeostasis. *Nat Med* 2005; 11: 320-7.

Lam TK, Schwartz GJ, Rossetti L. Hypothalamic sensing of fatty acids. *Nat Neurosci* 2005; 8: 579-84.

Leddy JJ, Epstein LH, Jaroni JL, *et al.* Influence of methylphenidate on eating in obese men. *Obes Res* 2004; 12: 224-32.

Levine AS, Olszewski PK, Mullett MA, *et al.* Intra-amygdalar injection of DAMGO: effects on c-Fos levels in brain sites associated with feeding behavior. *Brain Res* 2004; 1015: 9-14.

Malik S, Mcglone F, Bedrossian DDagher A. Ghrelin modulates brain activity in areas that control appetitive behavior. *Cell Metab* 2008; 7: 400-9.

Mansour A, Khachaturian H, Lewis ME, Akil H, Watson SJ. Autoradiographic differentiation of mu, delta, and kappa opioid receptors in the rat forebrain and midbrain. *J Neurosci* 1987; 7: 2445-64.

Migrenne S, Le Foll C, Levin BE, Magnan C. Brain lipid sensing and nervous control of energy balance. *Diabetes Metab* 2011; 37: 83-8.

Morton GJ, Blevins JE, Kim F, Matsen M, Figlewicz DP. The action of leptin in the ventral tegmental area to decrease food intake is dependent on Jak-2 signaling. *Am J Physiol Endocrinol Metab* 2009; 297: E202-210.

Naleid AM, Grace MK, Cummings DE, Levine AS. Ghrelin induces feeding in the mesolimbic reward pathway between the ventral tegmental area and the nucleus accumbens. *Peptides* 2005; 26: 2274-9.

Obici S, Feng Z, Morgan K, Stein D, Karkanias G, Rossetti L. Central administration of oleic acid inhibits glucose production and food intake. *Diabetes* 2002; 51: 271-5.

Palmiter RD. Is dopamine a physiologically relevant mediator of feeding behavior? *Trends Neurosci* 2007; 30: 375-81.

Palmiter RD. Dopamine signaling in the dorsal striatum is essential for motivated behaviors: lessons from dopamine-deficient mice. *Ann N Y Acad Sci* 2008; 1129: 35-46.

Paradis E, Clavel S, Julien P, *et al.* Lipoprotein lipase and endothelial lipase expression in mouse brain: regional distribution and selective induction following kainic acid-induced lesion and focal cerebral ischemia. *Neurobiol Dis* 2004; 15: 312-25.

Pardini AW, Nguyen HT, Figlewicz DP, *et al.* Distribution of insulin receptor substrate-2 in brain areas involved in energy homeostasis. *Brain Res* 2006; 1112: 169-78.

Pickel VM, Sumal KK, Beckley SC, Miller RJ, Reis DJ. Immunocytochemical localization of enkephalin in the neostriatum of rat brain: a light and electron microscopic study. *J Comp Neurol* 1980; 189: 721-40.

Pocai A, Lam TK, Gutierrez-Juarez R, *et al.* Hypothalamic K(ATP) channels control hepatic glucose production. *Nature* 2005; 434: 1026-31.

Prodi E, Obici S. Minireview: the brain as a molecular target for diabetic therapy. *Endocrinology* 2006; 147: 2664-9.

Quarta D, Di Francesco C, Melotto S, Mangiarini L, Heidbreder C, Hedou G. Systemic administration of ghrelin increases extracellular dopamine in the shell but not the core subdivision of the nucleus accumbens. *Neurochem Int* 2009; 54: 89-94.

Rada P, Bocarsly ME, Barson JR, Hoebel BG, Leibowitz SF. Reduced accumbens dopamine in Sprague-Dawley rats prone to overeating a fat-rich diet. *Physiol Behav* 2010; 101: 394-400.

Rapoport SI. In vivo fatty acid incorporation into brain phosholipids in relation to plasma availability, signal transduction and membrane remodeling. *J Mol Neurosci* 2001; 16: 243-61; discussion 279-84.

Ronnett GV, Kim EK, Landree LE, Tu Y. Fatty acid metabolism as a target for obesity treatment. *Physiol Behav* 2005; 85: 25-35.

Ronnett GV, Kleman AM, Kim EK, Landree LE, Tu Y. Fatty acid metabolism, the central nervous system, and feeding. *Obesity (Silver Spring)* 2006; 14 (Suppl. 5): 201S-7S.

Rothemund Y, Preuschhof C, Bohner G, *et al.* Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. *Neuroimage* 2007; 37: 410-21.

Ruge T, Hodson L, Cheeseman J, *et al.* Fasted to fed trafficking of Fatty acids in human adipose tissue reveals a novel regulatory step for enhanced fat storage. *J Clin Endocrinol Metab* 2009; 94: 1781-8.

Saller CF, Chiodo LA. Glucose suppresses basal firing and haloperidol-induced increases in the firing rate of central dopaminergic neurons. *Science* 1980; 210: 1269-71.

Schwartz MW, Porte D Jr. Diabetes, obesity, and the brain. *Science* 2005; 307: 375-9.

Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature* 2000; 404: 661-71.

Sipols AJ, Bayer J, Bennett R, Figlewicz DP. Intraventricular insulin decreases kappa opioid-mediated sucrose intake in rats. *Peptides* 2002; 23: 2181-7.

Small DM, Jones-Gotman M, Dagher A. Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. *Neuroimage* 2003; 19: 1709-15.

Sorensen A, Travers MT, Vernon RG, Price NT, Barber MC. Localization of messenger RNAs encoding enzymes associated with malonyl-CoA metabolism in mouse brain. *Brain Res Gene Expr Patterns* 2002; 1: 167-73.

South THuang XF. High-fat diet exposure increases dopamine D2 receptor and decreases dopamine transporter receptor binding density in the nucleus accumbens and caudate putamen of mice. *Neurochem Res* 2008; 33: 598-605.

Speed N, Saunders C, Davis AR, *et al.* Impaired striatal Akt signaling disrupts dopamine homeostasis and increases feeding. *PLoS One* 2011; 6: e25169.

Stice E, Spoor S, Bohon C, Small DM. Relation between obesity and blunted striatal response to food is moderated by TaqIA A1 allele. *Science* 2008; 322: 449-52.

Stoeckel LE, Weller RE, Cook EW 3rd, Twieg DB, Knowlton RC, Cox JE. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. *Neuroimage* 2008; 41: 636-47.

Sweep CG, Wiegant VM, De Vry J. Van Ree JM. Beta-endorphin in brain limbic structures as neurochemical correlate of psychic dependence on drugs. *Life Sci* 1989; 44: 1133-40.

Szczypka MS, Kwok K, Brot MD, *et al.* Dopamine production in the caudate putamen restores feeding in dopamine-deficient mice. *Neuron* 2001; 30: 819-28.

Szczypka MS, Mandel RJ, Donahue BA, Snyder RO, Leff SE, Palmiter RD. Viral gene delivery selectively restores feeding and prevents lethality of dopamine-deficient mice. *Neuron* 1999; 22: 167-78.

Tu Y, Thupari JN, Kim EK, *et al.* C75 alters central and peripheral gene expression to reduce food intake and increase energy expenditure. *Endocrinology* 2005; 146: 486-93.

Tyrka A, Gayle C, Smith GP. Raclopride decreases sucrose intake of rat pups in independent ingestion tests. *Pharmacol Biochem Behav* 1992; 43: 863-9.

Volkow ND, Wang GJ, Baler RD. Reward, dopamine and the control of food intake: implications for obesity. *Trends Cogn Sci* 2011; 15: 37-46.

Volkow ND, Wang GJ, Telang F, *et al.* Inverse association between BMI and prefrontal metabolic activity in healthy adults. *Obesity (Silver Spring)* 2009; 17: 60-5.

Volkow ND, Wang GJ, Telang F, *et al.* Low dopamine striatal D2 receptors are associated with prefrontal metabolism in obese subjects: possible contributing factors. *Neuroimage* 2008; 42: 1537-43.

Wang GJ, Volkow ND, Logan J, *et al.* Brain dopamine and obesity. *Lancet* 2001; 357: 354-7.

Wang H, Astarita G, Taussig MD, *et al.* Deficiency of lipoprotein lipase in neurons modifies the regulation of energy balance and leads to obesity. *Cell Metab* 2011; 13: 105-13.

Wang H, Eckel RH. Lipoprotein Lipase in the Brain and Nervous System. *Annu Rev Nutr* 2012.

Wang R, Cruciani-Guglielmacci C, Migrenne S, Magnan C, Cotero VE, Routh VH. The effects of oleic-acid (OA) on distinct populations of neurons in the hypothalamic arcuate nucleus (ARC) are dependent on extracellular glucose levels. *J Neurophysiol* 2005.

Wilson JD, Nicklous DM, Aloyo VJ, Simansky KJ. An orexigenic role for mu-opioid receptors in the lateral parabrachial nucleus. *Am J Physiol Regul Integr Comp Physiol* 2003; 285: R1055-6.

Wise RA. Role of brain dopamine in food reward and reinforcement.. *Philosophical transactions of the Royal Society of London Series B Biological sciences* 2006; 361: 1149-58.

Xia Y, Haddad GG. Ontogeny and distribution of opioid receptors in the rat brainstem. *Brain Res* 1991; 549: 181-93.

Zhang M, Gosnell BA, Kelley AE. Intake of high-fat food is selectively enhanced by mu opioid receptor stimulation within the nucleus accumbens. *J Pharmacol Exp Ther* 1998; 285: 908-14.

Zhang M, Kelley AE. Opiate agonists microinjected into the nucleus accumbens enhance sucrose drinking in rats. *Psychopharmacology (Berl)* 1997; 132: 350-60.