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Mesolimbic lipid sensing and the regulation of feeding behaviour

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Abstract – In both developed and emerging countries, sedentary life style and over exposition to high energy dense foods has led to a thermodynamic imbalance and consequently obesity. Despite genetic predisposition, obesity often involves a behavioral component in which, similar to drugs of abuse, compulsive consumption of palatable food rich in lipids and sugar drives energy intake far beyond metabolic demands. Food intake is modulated by sensory inputs, such as tastes and odours, as well as by affective or emotional states. The mesolimbic pathway is well established as a main actor of the rewarding aspect of feeding. Particularly, the hedonic and motivational aspects of food are closely tied to the release of the neurotransmitter dopamine (DA) in striatal structure such as the Nucleus Accumbens (Nacc). In both rodent and humans several studies shows an attenuated activity of dopaminergic signal associated with obesity and there is evidence that consumption of palatable food per se leads to DA signalling alterations. Furthermore impaired cognition in obese mice is improved by selectively lowering triglycerides (TG) and intracerebroventricular administration of TG induces by itself acquisition impairment in several cognitive paradigms in normal body weight mice. Together, these observations raise the possibility that nutritional lipids, particularly TG, directly affect cognitive and reward processes by modulating the mesolimbic pathway and might contribute to the downward spiral of compulsive consumption of palatable and obesity. This review is an attempt to capture recent evolution in the field that might point toward a direct action of nutritional lipid in the mesolimbic pathway.

Keywords: Obesity / tryglicerides / feeding behavior / reward / lipoprotein lipase

Résumé – La détection des lipides par le système mésolimbique et la régulation des comportements alimentaires. Dans les pays développés et en voie de développement la sédentarisation des populations et la sur-exposition aux nourritures riche en énergie conduisent à la mise en place d'un déséquilibre énergétique et à l'obésité. Bien qu'il existe des prédispositions génétiques, l'obésité implique souvent des comportements compulsifs face à la nourriture, similaires aux drogues d'abus, qui entraînent une consommation de nourriture supérieure aux besoins énergétiques de l'organisme. L'hypothalamus est le premier site d'intégration des facteurs circulants qui reflètent le statut énergétique de l'organisme, il est donc considéré comme un des acteurs principaux dans la régulation centrale de la balance énergétique. Cependant, la prise alimentaire est également régulée par des facteurs sensoriels ou affectifs et le système mesolimbique est reconnu pour être un des systèmes majeurs dans la régulation de récompense associée à la prise alimentaire. Plus spécifiquement, les aspects motivationnels et hédoniques de la prise alimentaire sont étroitement liés à la libération de dopamine (DA) notamment dans le noyau accumbens. Plusieurs études montrent qu'à la fois chez l'homme et le rongeur, l'obésité est associée à une altération du système dopaminergique et certaines études suggèrent que la consommation d'un régime palatable en lui-même pourrait être directement la cause de cette altération. De plus, chez les individus obèses, la normalisation des triglycérides (TG) circulants améliore les troubles cognitifs associés à l'obésité et l'injection de TG en intracérébroventriculaire entraîne une diminution des performances dans différents tests cognitifs. L'ensemble de ces observations suggère que les lipides nutritionnels et plus spécifiquement les TG pourraient directement affecter les processus cognitifs et de récompense en modifiant l'activité du système mésolimbique et entraîner ainsi la mise en place de comportements alimentaires compulsifs et donc de l'obésité. Dans cette revue, nous tenterons de rassembler les récentes évolutions du domaine qui mettent en avant la possibilité d'une action directe des lipides nutritionnels dans le système de la récompense.

Mots clés : Obésité / triglycéride / comportement alimentaire / système de la récompense / lipoprotéine lipase

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1 Introduction

Between 1980 and 2008 the mean BMI of the world's population has increased dramatically. Globally, in 2008, around 35% of adults aged 20 and over were overweight and around 12% were obese (World Health Organization (WHO) estimations). Obesity is a risk factor for chronic diseases like cardiovascular diseases, diabetes, degenerative joint diseases and cancers. Overweight and obesity are the fifth worldwide mortality factor (WHO estimation). Monogenic form of obesity shows that genetic factors can be involved in the establishment of this disease (Xia and Grant, 2013). However in many cases, obesity results from interaction between genetic predisposition and negative environment. In fact, maintenance of a healthy body weight is possible through a fine regulation of energy balance which coordinates energy intake, food consumption, and energy release, activity and thermogenesis. In both developed and emerging countries, sedentary life style and over exposition to high energy dense foods has led to a thermodynamic imbalance, and consequently, excessive caloric intake and reduced energy expenditure are the main causes for the prevalence of obesity (Hill *et al.*, 2003). The central regulator of food intake and energy expenditure is the brain and particularly the hypothalamus which is the primary site of circulating energy-related signals integration like leptin, ghrelin, or lipids and glucose (Schwartz and Porte, 2005). Imbalance in this regulatory process invariably leads to metabolic diseases such as obesity and diabetes in both humans and rodent models (Denis *et al.*, 2014; Schwartz and Porte, 2005). Especially, hypothalamus lipids sensing has emerged as a key component in brain regulation of energy balance (Blouet and Schwartz, 2010; Moulle *et al.*, 2014). Alteration of hypothalamic lipid sensing appears to be involved in several brain response to nutrient oversupply (*i.e.* inflammation, ER stress...) that leads to obesity (Velloso and Schwartz, 2011). Food intake is also modulated by sensory inputs, such as tastes and odours, 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.*, 2003). Among several brain circuits, the mesolimbic pathway is well established as a main actor of the rewarding aspect of feeding. In fact, the hedonic and motivational aspects of food are closely tied to the release of the neurotransmitter dopamine (DA) in striatal structure such as the Nucleus Accumbens (Nacc). DA release is stimulated by high-fat/high-sugar (HFHS) foods as well as by various desirable stimuli (*e.g.*, sex, drugs) (Palmiter, 2007; Volkow *et al.*, 2011; Wise, 2006). HFHS diet consumption 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 is a major contributor to western diet-induced obesity in mice (Bjursell *et al.*, 2008). Moreover HFHS diet were also link to the establishment of an addictive-like reward dysfunction and compulsive eating in obese rats (Johnson and Kenny, 2010) and depressive like behaviour (Hryhorczuk *et al.*, 2013). Interestingly, obesity-associated cognitive impairment can be improved by selective lowering of circulating triglyceride (TG) (Farr *et al.*, 2008). Altogether, those observations raise the possibility that nutritional lipids, and specifically triglycerides, directly act on brain

structure-through mechanism similar as hypothalamic lipid sensing to affect cognitive and reward processes and contribute to the downward spiral of compulsive food consumption.

In this review, we will focus on mechanism by which brain regulates rewarding component of food intake and then expose recent evolution in the field that might point toward a direct action of nutritional lipid in the mesolimbic pathway.

2 Hedonic and motivational aspect of feeding: a focus on the mesolimbic pathway

Hypothalamic integration of orexigenic and anorexigenic circulating signals allow the brain to adapt food intake according to energy needs, however, the food palatability is a powerful determinant of feeding and characterize the rewarding aspect of food intake. Palatability defines food properties which induce animal sensitive response for this food and so induce a desire more or less important for this food (Greenhalgh and Reid, 1971). Food palatability is characterized by the smell, the taste, the texture, the temperature and the appearance of the food. Nevertheless, it is not only an inherent property of food as it is also defined by experience, metabolic demands and other environmental factors like stress (de Castro *et al.*, 2000). The mesolimbic pathway is one of neural networks which encode the different aspect of food intake: "liking", "wanting" and "learning" (Berridge, 2009; Wise, 2006). The mesolimbic pathway is a dopaminergic pathway. Although, DA is a neurotransmitter well studied in reward processes, opioids, endocannabinoids, serotonin and others are also involved in the rewarding aspect of food intake but we will not discuss it in this review (Kelley *et al.*, 2002; Le Merrer *et al.*, 2009). It has been shown that DA antagonists increase appetite, energy intake and weight gain, whereas DA agonists reduce energy intake and produce weight loss (Leddy *et al.*, 2004; de Leon *et al.*, 2007). DA binds to several G-protein-coupled DA receptors-D1 and D5 coupled to G α ; D2, D3 and D4 coupled to G α -which activate intracellular signalling pathways in postsynaptic neurons. DA neurons are mainly located in the Ventral Tegmental Area (VTA) and innervate limbic regions like the Nacc, the prefrontal cortex (PFC), the amygdala (AG) and the hippocampus (HP). During regular circumstances, DA neurons are firing continuously causing tonic DA release; salient environmental stimuli induce burst-firing of DA neurons resulting in a burst of DA release (Palmiter, 2007). Palatable food ingestion is associated with DA release in Nacc, and the degree of pleasure from eating correlates with amount of DA released (Small *et al.*, 2003; Szczyepka *et al.*, 2001). DA is also involved with the motivation to perform behaviours necessary to procure and consume the food. In fact, DA-deficient mice are hypophagic, fail to engage in goal-directed feeding behaviours, and will die of starvation (Palmiter, 2008; Szczyepka *et al.*, 1999). Moreover, it was found that chemical lesions of the DA system (pharmacological antagonists of DA receptor), sufficient to inhibit food-seeking behaviour, did not affect the pleasure reactions to sucrose placed in the mouth (Berridge and Robinson, 1998; Tyrka *et al.*, 1992). This finding was interpreted as indicating that the neural systems mediating the pleasure impact

of preferred tastes was distinct from that mediating the ability of incentives to elicit goal-directed behaviour; these two processes were termed “liking” and “wanting”, respectively. With regard to neurochemical mediation, it was proposed that “wanting” is governed by DA whereas “liking” depends upon opioid transmission (Kelley *et al.*, 2005).

In summary the rewarding aspect of food intake elicited by the mesolimbic pathway activation is well established as a main actor of feeding regulation however the neurochemical characterization of this process is still discussed (Maldonado *et al.*, 2006; Palmiter, 2007; Will *et al.*, 2006).

3 Mesolimbic lipid sensing and feeding behaviour

3.1 Brain lipid sensing

Cerebral lipids are an essential component of both membranes and intracellular signalling pathways. They represent 50% of brain dry weight – the highest organ lipid content after adipose tissue (Edmond, 2001; Watkins *et al.*, 2001). A growing body of evidence suggests that cerebral lipids are derived from both local synthesis and uptake from the blood. In fact, in human, brain signal of radiolabelled arachidonic acid (AA) has been shown by Positron Emission Tomography (PET) scan imaging following the intravenous injection of radiolabeled AA (Esposito *et al.*, 2007). PET scan imaging also demonstrates Palmitate and AA brain incorporation in primate and rats (Arai *et al.*, 1995; Chang *et al.*, 1997a, 1997b). Although their transport mechanism across the BBB are still not clear, several studies show that some polyunsaturated FA (PUFA) have the ability to cross the BBB (Rapoport *et al.*, 2001; Smith and Nagura, 2001). Once across the BBB, it is probable that neurons can take up FA as some neurons do appear to have FA transporters. For example, dissociated neurons from the hypothalamic ventromedial nucleus (VMN) of rats express mRNAs for FA transport proteins (FATP)-1 and 4, and the FA transporter/receptor FAT/CD36 mRNAs (Le Foll *et al.*, 2009, 2013). Lipoproteins are also a major source of lipids for the brain (Giovacchini *et al.*, 2002) and low-density lipoprotein (LDL) and high-density lipoprotein (HDL) transport across the BBB has been demonstrated *in vitro* (Balazs *et al.*, 2004; Candela *et al.*, 2008) and *in vivo* in *Drosophila* (Brankatschk and Eaton, 2010). Regarding their transport mechanism it has been suggested that lipoproteins could be detected by specific receptors in endothelial cells and then transported and metabolised in the brain (Chen *et al.*, 2008; Edmond, 2001). Another model suggests that TG contained in lipoproteins could be hydrolysed at the level of BBB by the LPL; liberated FA could then be transported in the brain (Chen *et al.*, 2008; Rapoport, 2001) *via* passive transport, the flip-flop (Mitchell and Hatch, 2011) or active transport *via* transport proteins described above (Mitchell and Hatch, 2011).

Hypothalamic lipid sensing is involved in the central regulation of different aspect of energy balance like food intake, pancreatic hormones secretion, hepatic glucose production, lipids metabolism and energy expenditure (Blouet and Schwartz, 2010; Mouille *et al.*, 2014; Picard *et al.*, 2014). Most of studies about brain lipid sensing focused on FA, however

TG are also involved in the central regulation of energy balance. In fact, TG are able to change BBB permeability to Ghrelin and so participates to the regulation of food intake (Kumar *et al.*, 2002). Moreover a recent study has shown that the central inhibition of TG hydrolysis by the LPL induces hyperphagia and obesity (Wang *et al.*, 2011). Although fatty acid have been shown to regulate food intake through hypothalamic network (Lam *et al.*, 2005) it must be pointed out that, unlike plasma TG-rich lipoproteins which rise after a meal, plasma level of FA 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 TG packaging and finally chylomicrons synthesis. Moreover the liver also produces very low density lipoprotein (VLDL). Thus TG-rich lipoproteins, accumulating after a meal, could also pretend to be a physiologically relevant satiety signal acting in the brain to regulate feeding behaviour and energy expenditure (Blouet and Schwartz, 2010; Migrenne *et al.*, 2011; Wang *et al.*, 2011).

3.2 Mesolimbic triglycerides sensing

Both mesolimbic and hypothalamic regions express enzymes involved in the transport, manipulation and metabolism of TG (Eckel and Robbins, 1984; Kim *et al.*, 2002; Paradis *et al.*, 2004; Rapoport, 2001; Ronnett *et al.*, 2005, 2006; Wang and Eckel, 2009, 2012). In particular, the HP and the Nacc express LPL, a key enzyme involved in TG hydrolysis (Ben-Zeev *et al.*, 1990). Recent studies have highlighted the importance of brain TG hydrolysis in the regulation of energy balance (Wang *et al.*, 2011). In fact neuronal deletion of LPL induces hyperphagia, energy expenditure and locomotor activity decrease, and finally obesity in mice on standard diet (Wang *et al.*, 2011). Moreover variation in circulating TG after a high-fat meal is a strong predictor for hyperphagia and obesity (Karatayev *et al.*, 2009) but until now a physiological model that allows for the study of TG action on the brain has been missing. In a recent study we have established a method to evaluate the behavioural and metabolic consequences of brain TG sensing by infusing TG *via* the natural route of access to the brain through the carotid artery in the direction of the brain, at a rate and concentration that closely recapitulate the postprandial increase in TG but without affecting systemic FA or TG concentrations. Our results provide the first experimental evidence that TG can directly target mesolimbic structures to modulate the rewarding component of food intake (Cansell *et al.*, 2014). Such TG infusion leads to a decrease in nocturnal and amphetamine (DA activator) induced locomotor activity and abolishes preference for palatable HFHS food in lean mice. As described before, the palatable property of food and its ability to induce pleasure are regulated by the reward system and particularly involved DA signalling. The action of central TG delivery on food preference, nocturnal activity and psychostimulant-induced locomotion suggested that brain TG signalling may directly influence motivated behaviour. We tested this hypothesis by first pretraining mice to lever press for high sucrose food reward pellets, and then following intra-carotid saline or TG infusion, assessing their performance on a Progressive Ratio (PR) task that measures the amount of effort an animal is

willing to exert to obtain food rewards. We demonstrated that brain TG delivery decreases the overall motivation to work for reward. We have also begun to define the neural circuitry and molecular mechanisms by which TG influence neural activity and behaviour. Indeed, in contrast to the effects of TG infusion, deletion of the gene encoding the TG-hydrolyzing enzyme LpL specifically in the Nacc leads to sensitization to the reinforcing properties of palatable food as revealed by the PR operant task and hyperphagia during a HFHS food preference task (Cansell *et al.*, 2014).

As previously enounced, plasma TG accumulate after a meal and gradually return to basal levels (Ruge *et al.*, 2009). However, plasma TG is often chronically elevated in obesity (Subramanian and Chait, 2012). During prolonged TG perfusion, designed to mimic chronic hypertriglyceridemia, we found that adaptive desensitization processes occur such that TG infusion no longer abolishes HFHS preference but continues to suppress locomotor activity. Consistent with this, using Diet Induced Obesity (DIO) mice to physiologically model chronic hypertriglyceridemia, central TG delivery still reduced locomotor activity but no longer was effective in modulating food preference. Together, these data suggest a model whereby postprandial increases in plasma TG are hydrolyzed locally in the Nacc where they alter the reward system to effect a reduction in locomotor activity and reduce the incentive properties of calorie-rich HFHS foods. Those findings are consistent with a recent study demonstrating that satiation-induced changes in brain response to a palatable food are strongly and specifically associated with changes in circulating ghrelin and TG (Sun *et al.*, 2014). However, in the face of sustained elevations in plasma TG, achieved either by intra-carotid perfusion or DIO, the mechanisms that normally serve to reduce the rewarding impact of HFHS foods is no longer operating (Cansell *et al.*, 2014). This model predicts a positive feedback loop whereby chronically high plasma TG, such as occurs in obesity, cripple the homeostatic mechanisms that curb food intake resulting in uncontrolled caloric consumption and reduced physical activity. Such a mechanism would serve to drive body weight gain, whereas making weight loss more difficult. Further studies will be required to uncover the cellular basis of mesolimbic TG sensing mediated by LpL, the downstream molecular events that occur following TG hydrolysis, and how these events alter the activity of rewarding circuits.

4 Conclusion

Previous work on how circulating lipids affect the brain has focused chiefly on the effects of FA on brain metabolism and behavior. For instance, intracerebroventricular injection of oleic acid was shown to alter hypothalamic lipid metabolism and result in decreased food intake (Obici *et al.*, 2002). Furthermore, lipid metabolism in the hypothalamus has been repeatedly shown to be critical in mediating the central effects of FA (Lam *et al.*, 2005; Moulle *et al.*, 2014; Picard *et al.*, 2014). We therefore propose that the central availability of TG and FA differ (Fig. 1), that these lipid species influence neural circuit function through separate mechanisms, and that they have opposing effects on food-seeking behaviour. Although FA may principally act in the hypothalamus and func-

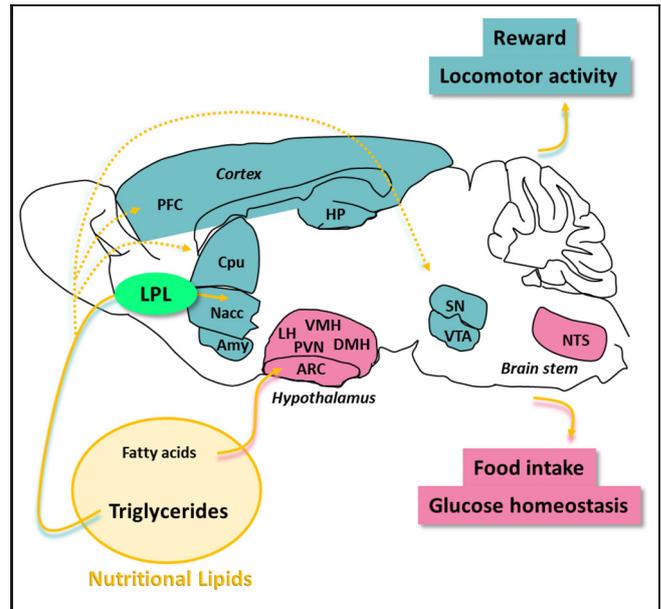


Fig. 1. Brain nutritional lipids sensing and the central regulation of energy balance. We therefore propose that the central availability of TG and FA differ, that these lipid species influence neural circuit function through separate mechanisms, and that they have opposing effects on food-seeking behaviour. Although FA may principally act in the hypothalamus and function to increase food intake in response to a fast, TG sensing may depend on local hydrolysis by LpL in the mesolimbic pathway where they decrease the rewarding or motivational properties of food. Amy, amygdala; ARC, arcuate nucleus; Cpu, caudate putamen; DMH, dorsomedial hypothalamus; HP, hippocampus; LH, lateral nucleus; LpL, Lipoprotein lipase; Nacc, nucleus accumbens; NTS, nucleus tractus solitarius; PFC, prefrontal cortex; PVN, para-ventricular nucleus; SN, substantia nigra; VMH, ventromedial hypothalamus; VTA, ventral tegmental area.

tion to increase food intake in response to a fast, TG sensing may depend on local hydrolysis by LpL in the mesolimbic pathway where they decrease the rewarding or motivational properties of food. Potential mechanisms could involve lipid-mediated activation of membrane receptors (Abumrad *et al.*, 2005; Moulle *et al.*, 2013) cellular energy-related pathways (Lage *et al.*, 2008; Lopez *et al.*, 2005) endoplasmic reticulum stress (Zhang *et al.*, 2008) eicosanoids-dependent inflammatory processes (Rapoport *et al.*, 2001), endocannabinoid signalling pathways (Lafourcade *et al.*, 2011; Solinas *et al.*, 2008) and lipid-activated transcriptional adaptations (Aleshin *et al.*, 2013).

It has been shown that hypothalamic FA sensing is involved in the central regulation of food intake and glucose homeostasis. In a recent study we demonstrated that TG acts on the mesolimbic pathway probably through a mechanism dependant on their hydrolysis by LpL (Lam *et al.*, 2005; Moulle *et al.*, 2014; Picard *et al.*, 2014).

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Disclosure

The authors declare no conflict of interest.

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