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Dietary triglycerides as signaling molecules that influence reward and motivation

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Abstract

The reinforcing and motivational aspects of food are tied to the release of the dopamine in the mesolimbic system (ML). Free fatty acids from triglyceride (TG)-rich particles are released upon action of TG-lipases found at high levels in peripheral oxidative tissue (muscle, heart), but also in the ML. This suggests that local TG-hydrolysis in the ML might regulate food seeking and reward. Indeed, evidence now suggests that dietary TG directly target the ML to regulate amphetamine-induced locomotion and reward seeking behavior. Though the cellular mechanisms of TG action are unresolved, TG act in part through ML lipoprotein lipase, upstream of dopamine 2 receptor (D₂R), and show desensitization in conditions of chronically elevated plasma TG as occur in obesity. TG sensing in the ML therefore represents a new mechanism by which chronic consumption of dietary fat might lead to adaptations in the ML and dysregulated feeding behaviors.

INTRODUCTION

The modern food environment is characterized by a radical increase in calorie-rich food as well as ubiquitous reminders of food palatability and accessibility. Hence, environmental variables that influence the energy balance equation have undergone a drastic change in

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

recent human history, in which the energy cost required for survival is often far exceeded by energy intake. This statement of fact is instrumental in the worldwide spreading of pathologies related to overfeeding including diabetes, obesity, cardiovascular disease and dyslipidemia - a constellation of pathophysiologicals referred to as metabolic syndrome [1].

Appropriate energy homeostasis is reached when energy intake and demands equilibrate around a defined metabolic set-point. Millennia of evolution have shaped a highly responsive system that integrates the various signals of hunger and satiety through a complex and redundant interplay of neural circuitry dedicated to long-term energy homeostasis. In the central nervous system (CNS) the hypothalamic-brainstem axis has been identified as a critical regulator of energy balance. Circulating energy-related signals such as leptin, ghrelin, insulin, as well as nutrients are detected by and alter the activity of discrete neuronal populations that in turn engage neuroendocrine, peripheral nervous, and ultimately behavioural systems to adapt nutrient intake to energy demands (**Figure 1**). This hypothalamus-brainstem system to regulate feeding and metabolism around a set point is therefore referred to as “homeostatic” [2,3]. The complex behavioural sequence that leads to food intake rely on hierarchical integrative processes encoding motivation, reward, habit, emotionality, and memory that are influenced by nutritional status and diverse hypothalamic and extrahypothalamic brain networks. Key among these are mesolimbic (ML) circuits, where the release of dopamine (DA) has been extensively shown to encode the reinforcing and motivational properties of high-fat and high-sugar (HFHS) foods [4,5]. In particular, midbrain projections from DA neurons of the ventral tegmental area (VTA) to the nucleus accumbens (NAc) represent a principal neural substrate upon which drugs of abuse exert their actions; and thus the ML is often referred to as the brain ‘reward circuit’. It is now well established that the ML is also a target for energy-related signals such as leptin, ghrelin, and insulin [6-8] ****[9]**.

Both the homeostatic and reward circuitries represent redundant yet complementary and interacting neural substrates participating in the control of energy balance under physiological conditions; but maladaptations in these circuits can be both a consequence of and contribute to nutrient overload [10-13]. Indeed, numerous lines of evidence have promoted the concept that compulsive/dysregulated food intake, as can occur in obesity, might be the result of adaptive responses of homeostatic and reward circuits in response to chronically increased exposure to calorie-dense food in susceptible individuals [10,14]. This review will focus particularly on recent developments in the field that point toward a direct connection between neural sensing of circulating lipids from nutritional origin and the function of the ML in the regulation of reward seeking.

High fat diet, obesity and the consequences on dopamine signaling

Hypothalamic structures lie close to circumventricular organs (CVO) and are regarded as a primary neural structure affected by nutrient overload [2]. Molecular underpinnings linking nutrient overconsumption and altered neural function involve hypothalamic FFA metabolism [15], nutrient-induced endoplasmic reticulum (ER) stress [16-19], inflammatory processes [20], or resistance to energy-related signals [18,21-23].

Besides the hypothalamus, there is now clear evidence that the DA signaling is also directly affected by high-fat feeding and obesity in both human and rodent. For instance, the abundance of dopamine D₂ receptor (D₂R) in the striatum is inversely correlated to body weight [11,24,25] and obese rats were shown to display compulsive eating as measured by palatable food consumption despite aversive conditioned stimulus [26]. Genetic silencing of D₂R in the dorsal striatum accelerates the development of a reward-deficit state and compulsive eating in rats exposed to high fat food [26]. In rats, individual variation in motivational response to food-related cues were also shown to predict body-weight gain and willingness to work for food rewards **[27]. Interestingly increased craving was associated with a rapid change in dorsal striatum DA signaling but not opioid signaling in the NAc **[27].

In human, striatal D₂R availability was initially found to be significantly lower in obese individuals and negatively correlated with body-mass index (BMI) [24,28]. BOLD signal assessed by brain functional Magnetic Resonance Imaging (fMRI) in striatal structures was decreased in obese versus lean subject [29], suggesting a defect in striatal neuron activity [29]. On the other hand obesity was associated with a greater BOLD response to food-related cues in brain regions associated with reward and motivation [12,28-30]. These data suggest that striatal neurons are underactive at baseline in obese individuals but show sensitized responses to food signals. A recent study implicates DA signalling in this process; using positron emission tomography (PET) to quantify striatal D₂R-like binding potential (D₂BP) identified an association between striatal DA binding in obesity. Body mass index (BMI) was negatively correlated with D₂BP in the ventral striatum (i.e., NAc) whereas in the dorsal striatum, both BMI and habitual/opportunistic eating behaviour positively correlated with D₂BP **[31]. It remains unclear whether altered DA signaling is a cause or a consequence of body weight gain, these studies draw a complex picture of DA signaling defects in obesity, where regionally distinct changes might create a state of both reward deficit and heightened habitual responding **[31].

Importantly, several studies highlight the fact that intrinsic defects in ML function developed independently of body weight gain and - although magnified by obesity states - might primarily be the result of dietary fat exposure. Although magnitude and direction of these changes sometimes vary according to diet, strain or anatomical region; exposure to high fat diet, independent of body weight gain, can promote change in D₂R abundance, DA turn-over rate, DA transporter (DAT) function, response to amphetamines, and operant responding for food reward [32,33]. Animals exposed to a restricted amount of calories from high-fat but not high-sugar diet exhibit decreased attention and increased impulsivity as assessed by 5-choice serial reaction task (5CSRT) **[34]. Limited exposure to a fat source also triggers binge-like eating behavior and increased sensitivity of ML activity, interestingly mice lacking ghrelin-receptor failed to escalate palatable food intake suggesting that energy-related signal such as ghrelin play also a role in ML response to energy-dense food **[35]. A recent study demonstrated that not all fat source are equivalent in their ability to temper with ML activity. Indeed exposure to amount of saturated but not unsaturated fat leads to change in D1R and DAT abundance in the ML **[36].

Among the different consequence of high fat feeding, special attention was recently drawn to circulating TG metabolism as strong predictor of compulsive overeating propensity. Sprague-Dawley rats can be subdivided into obesity prone (OP) and resistant (OR) based on metabolic features and body weight gain during a short 5-day high fat challenge; among which altered circulating TG, fat partitioning characterized by increased Lipoprotein lipase (LPL) activity in the adipose tissue, and decreased muscle lipid transport were identified as signatures of OP rats [37]. Plasma TG levels after a meal were a strong predictor of future body weight gain in OP rats, that is larger TG excursion after a meal (high-TG responders) correlated with a propensity to overeat [38]. In OP high-TG responders, extracellular DA levels assessed by microdialysis in the NAc was reduced at both basal condition and in response to high fat feeding or peripheral injection of a fat emulsion (intralipid). Moreover, when orosensory reward was bypassed through systemic administration, TG emulsion but not sucrose led to increased DA release in the NAc as measured by microdialysis [39]. Along the same line, cognitive impairment in obese mice was improved by pharmacologically lowering plasma TG, while central injection of TG impaired cognition in lean mice [40].

Finally, a recent study in humans using fMRI demonstrated that plasma TG and ghrelin correlated with the magnitude of whole brain BOLD response to food reward. The larger post-prandial decrease in ghrelin or increase in TG were associated with a reduced BOLD response to palatable milkshake in limbic circuitry including the midbrain, pallidum, amygdala medial orbitofrontal cortex and hippocampus ****[41]**. Importantly, circulating albumin-bound FFA, glucose, or insulin did not correlate with brain responses to food reward.

Altogether these results suggest that among the nutrients that could affect brain function, dietary TG, independently of other energy-related signals such as insulin, glucose or FFA), could act on neural substrates regulating cognition and reward. This specificity might originate from both the physiology and biochemistry of meal-related TG-particle appearance and metabolism both at peripheral and central level.

Triglycerides or free-fatty-acids: a question of timing?

Lipids are the major component of the brain [42] and originate from both endogenous production and dietary inputs [43]. Plasma lipids can be found as free-fatty acids (FFA) bound to albumin and triglycerides (TG)-rich lipoproteins [44]. Lipoproteins are complex associations of apolipoproteins and phospholipids that create a polar environment for lipid transport. LPL expressed in peripheral tissues catalyze the hydrolysis of TG from TG-rich particles such as very-low-density lipoprotein (VLDL) and gut-borne chylomicron (CM) to give rise to particles with reduced lipid content such as high density lipoprotein (HDL) (**Figure 1**).

But how do lipids get into the brain? Tracing studies using positron emission tomography (PET) coupled with radiolabelled fatty acids injected peripherally have shown dynamic incorporation of arachidonic or palmitic acids in the brain [43,45,46]. Importantly, metabolic syndrome was shown to be associated with an increase in whole brain FFA uptake-and especially an 88% increase in hypothalamic FFA uptake [47]. Among FFA, essential

polyunsaturated fatty acids (PUFA) can cross the blood-brain barrier (BBB) through mechanisms that were poorly defined until the very recent discovery of Mfsd2a (major facilitator superfamily domain-containing 2a) as the main carrier for absorption of the essential fatty acids docosahexaenoic acid (DHA) in the brain *[48]. While free DHA was initially believed to be the major source of brain DHA [49], this recent study shows that DHA, together with long chain fatty acids (LCFA) are transported through Mfsd2a in the form of lysophosphatidylcholine (LPC) but not FFA. This result highlights the complex and redundant mechanisms for brain LCFA and DHA homeostasis *[48].

Circulating apolipoproteins range in size from less than 10 nm for HDL, 20-30 nm for LDL, 30-40 nm for IDL, and 5-80 nm for VLDL and CM. It is known that some small HDL can cross the BBB [44,50,51], but the question of brain-accessibility to larger TG-rich particles such as VLDL or CM is still debated based on previous tracer studies [44] and on the assumption that the brain is devoid of a lymphatic system. After a meal lipids are packaged in CM, secreted into the lymphatic system, and then to the general circulation where large particles would have to cross the BBB at the level of fenestrated capillaries in order to access the CNS. However the recent discovery of a lymphatic system in the mouse brain suggests a new route by which TG-rich particles may be available for cerebrospinal-fluid (CSF) exchange [52].

Indeed, brain cells express high levels of several lipoprotein receptors such as the VLDLR, LDLR, oxidized HDL receptors, and accessory proteins such as LDL receptor-related protein (LRP) [44]. These receptors bind selective apolipoprotein components and genetic and pharmacological approaches have highlighted the role for apolipoprotein signalling in brain development and function including learning and memory [53] and synaptic plasticity [54]. For instance apolipoprotein E, present in circulating chylomicrons and IDL, binds to LDLR and is recognized as a major genetic risk factor for common forms of late-onset Alzheimer disease (AD) [55], while brain-specific overexpression of LDLR enhances β -amyloid clearance and may be protective in AD [56]. Moreover the brain also produces apolipoproteins [44], primarily synthesized by astrocytes, and particles approximating the size and density of HDL can be measured in CSF [51].

Altogether these observations suggest that both endogenously (astrocyte produced) and peripherally generated (postprandial) lipoprotein particles can affect brain function. The precise mechanisms by which lipoprotein signalling is initiated in the brain is unclear and could potentially involve canonical cascades, local lipid delivery, or/and changes in cell metabolism which in turn might modulate neuron activity.

TG-lipases which catalyse the hydrolysis of TG into free fatty acids and mono- or diacylglycerol are abundantly expressed in the brain and particularly enriched in the ML [44] [57-59]. Accumulating evidence suggests that brain lipases act upon TG to mediate lipid delivery within discrete brain nuclei with important functional consequences *[60] [61]**[62]. Among these the LPL has been best studied with regard to its role in energy balance [59]. Pan neuronal LPL knock out animals (NEXLPL^{-/-}) display altered brain FFA and PUFA levels, develop late onset obesity [63], and show age-related declines in cognitive function and increases in anxiety *[60]. More restricted gain or loss of function approaches

have allowed for more precise determinations of the role of LPL in sub-structures of the brain. For example, hippocampal LPL regulates energy expenditure and autonomic tone through synthesis along the ceramide-based signalling pathway ****[64]**.

While a role for lipases during brain development could potentially account for the deficits observed in LPL knock out models, their continued expression in discrete nuclei in adulthood makes it tempting to speculate that brain TG-lipases regulate local TG breakdown and LCFA availability. In that regard, although TG and LCFAs are both circulating lipid species, their appearance in the blood stream occur at opposite time points with respect to feeding. TG-rich particles accumulate after a meal; whereas LCFA are released by fasting-induced adipose lipolysis and are thus elevated during periods of food abstinence [65]. In addition, while LCFA can readily be transported through fatty-acid transporters abundant in most brain structures, TG must first be broken-down by TG-lipases severely limiting central availability. Hence, brain structures equipped with TG-lipases might be uniquely disposed to detect post-prandial changes in dietary lipids. Indeed, the presence of LPL in the ML strongly suggests a role for TG sensing in post-prandial TG-mediated changes in reward valence. In that view TG breakdown in the ML and downstream adaptive changes occurring once FFA are released could directly affect DA or other ML signaling pathways to regulate reward-seeking behaviour.

Triglycerides sensing in the reward ML system: bridging dietary inputs and reward

We have developed a model in which TG emulsion (intralipid™) is perfused through the carotid artery in the direction of the brain at a rate and concentration that mimics the post-prandial increase in TG and that does not affect systemic lipids. Using this model we found that TG can act directly in the brain to regulate locomotor activity, food preference, and food seeking behaviors. Brain TG delivery dampened operant responding for rewards on a progressive ratio schedule, and preference for a palatable HFHS food in a food choice paradigm. Direct brain TG delivery decreased by ~50% nocturnal locomotor activity and amphetamine-induced locomotion. TG delivery also opposed D2R agonist-induced locomotion, suggesting a TG-evoked modulation of the dopaminergic circuitry. Selective knock-down of LPL in the NAc had the opposite consequences - leading to increased motivation to work for food rewards and increased consumption of palatable diet ****[62]**.

Plasma TG transiently increases after a meal [65]. However, plasma TG is chronically elevated in obesity and is obviously not associated with decreased tropism for calorie-dense food, suggesting adaptive mechanisms occur. In order to mimic the brains response to chronic hypertriglyceridemia we used sustained TG perfusion in lean animals and compared with a model of diet-induced obesity.

We modeled hypertriglyceridemia using a model of diet-induced obesity or with chronic (7-days) TG perfusion toward the brain that increases brain TG sensing without effect on plasma TG levels. Both these treatments led to behavior-specific desensitization, in which central TG sensing was no longer able to modulate tropism for palatable food but still led to a decrease in locomotor activity. This adaptive mechanism, induced by chronic elevations in circulating TG or brain TG sensing, may explain how sustained consumption of high-fat foods overwhelm regulatory systems to promote weight gain. Central TG sensing could

directly operate the acute decrease in locomotor activity that precedes metabolic changes when animals are presented with a western diet [66]. When brain TG sensing occurs acutely it might have a beneficial (or homeostatic) effect to reduce the desire for food reward. But when chronically elevated, TG-sensing mechanisms may desensitize or lead to compensatory adaptations such that reductions in physical activity persist, but motivation for high fat food becomes resistant to TG-mediated homeostatic control. The combination of both reduced physical activity and sustained motivation for high fat foods will inevitably lead to body weight gain.

These data support the concept that local TG hydrolysis in brain structures equipped with TG processing enzymes might have differential impacts. Circulating albumin-bound LCFAs may principally act in the hypothalamus and function to regulate feeding and glucose production [15]-specifically in time of scarcity when adipose lipolysis release of FFA is high-whereas LPL-mediated hydrolysis of TG-particles accumulated after a meal in ML structures might participate in the encoding of incentive and motivational properties of food. Acute exposure to TG-in the general framework of a meal-will decrease both rewarding and motivational aspect of food while chronic exposure would lead to desensitization and uncontrolled feeding behavior **[62].

Molecular basis for ML lipid sensing and source of vulnerability?

In the hypothalamus the existence of lipid sensing was pioneered by Oomura and colleagues. [67] and extensively studied during the last decade [22]. LCFA metabolisms was shown to regulate neuronal activity, autonomic control of insulin release, food intake, and liver glucose production [15,22,68]. Hypothalamic sensing of LCFA encompasses several cellular mechanisms including direct entry into the tricarboxylic acid cycle (TCA cycle), amino-acid mediated activation of mTOR [69], autophagy, inflammation through nuclear enhancer of kappa-light-chain-enhancer of activated B cells (IKK/NF- κ B)-dependent pathways [18,70] [3] [71], increased mitochondrial lipid beta-oxidation [68,72], adaptations in mitochondrial respiration and radical oxygen species (ROS) scavenging [73], accumulation of lipid metabolites such as acetyl-CoA and malonyl-CoA [15], direct modulation of protein-kinase C activity [74] [75], lipid-mediated activation of membrane receptors, eicosanoids-dependent signaling [46], and lipid-activated transcriptional adaptations [76,77].

Although high calorie food is virtually ubiquitous, uncontrolled feeding and obesity does not affect every individual suggesting that the modern food environment might directly interact with genetic or epigenetic elements of susceptibility. The *TaqIA* A1 allele is an excellent candidate in that regard. Affecting 30-40% of the population, homozygous dosage of the A1 allele correlates with a 30~40% reduction of striatal D₂R abundance [78] [79] **[80] [81,82] and is strongly associated with addiction and compulsive behavior, impacting both drugs of abuse as well as feeding [13,28]. The A1 allele results from a single-nucleotide polymorphism (SNP) located at the gene that encodes Ankyrin repeat and kinase domain containing 1 (ANKK1) near the gene encoding D₂R [83]. ANKK1 is a receptor-interacting protein (RIP) kinase: a structurally related family of factors that integrates various stimuli including inflammation, innate immune response downstream of Tumor-necrosis factor

alpha (TNF α -R1) receptor and Toll-like receptor (TLR), and converge upon c-jun N-terminal kinase (JNK), MAPK activity or NF- κ B [84] signaling pathways.

In silico analysis of human protein-protein interaction reveals that among the ~30 predicted partners for human ANKK1 [85] half are found in the NF- κ B, JNK or MAPK pathway (Table I). In the brain ANKK1 is uniquely expressed in astrocytes [83]. Astrocytes integrate various metabolic signals to coordinate neuronal activity and are direct targets for lipids; especially saturated fat-induced inflammatory responses and ER-stress mediated through TLR and IKK/NF- κ B signaling ****** [86] [87].

How astrocyte ANKK1 activity could ultimately relate to the reduced D₂R abundance is still an open question but, here again, fatty acid metabolism might provide several potential mechanisms. For example the D₂R and ANKK1 promoters possess NF- κ B cis regulatory elements [83,88]; and lipid-derived prostaglandins are powerful inducers of Neural Growth Factor (NGF) secretion by astrocytes, NGF in turn has been shown to directly regulate neuronal D₂R mRNA transcription through the NF- κ B signaling pathway [89].

Finally, while increased feeding as a consequence of acute high fat diet exposure was recently shown to involve activation of astrocytic NF- κ B ****** [86], adaptations occurring upon long-term exposure to high-fat diet might involve a third partner of the triad: the peroxisome proliferated activated receptors delta (PPARs). PPAR δ belongs to a family of ligand-activated transcription factors, involved in a variety of cellular metabolic adaptations, which primarily respond to LCFA and prostaglandin. PPAR δ has also emerged as an important regulator of the ML. For example, activation of PPAR δ by LCFA or synthetic agonist decreases opioid synthesis in forebrain neurons [90] and protects from methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP)-induced loss of DA neurons. Striatal PPAR δ is directly regulated by TLR/NF- κ B pathway [91] and a PPAR responsive element exists in the ANKK1 promoter [83].

LCFA signaling in the ML could potentially be integrated at the level of the tripartite synapse composed of striatal DA neurons and astrocytes engaged in a coordinated activation of the ANKK1/NF- κ B/PPARs triad to effect the expression or function of D₂R (**Figure 2**). While the ML response to short term high fat exposure could be mediated by a NF- κ B/NGF action on D₂R, PPAR δ activation by LCFA could lead to long-term transcriptional adaptations in striatal structures with chronic high fat consumption. In that view, altered lipid sensing in the ML along with heightened exposure to food-related cues – both consequences of the modern food environment - would reveal and magnify the consequence of the ANKK1 polymorphism on compulsive behavior.

CONCLUSION

How TG enter the brain and affect central function is still unclear, as are the molecular underpinnings by which local FFA delivery via TG hydrolysis affects neural responses and reward. However both human and rodent studies provide direct and indirect evidence for an action of dietary TG on reward and motivation. TG hydrolyzed locally in the striatum could inhibit locomotor activity and transiently reduce the incentive properties of calorie-rich

HFHS foods. However, in the face of chronic elevation in plasma TG, a hallmark of the modern food environment and obesity, the homeostatic mechanisms that normally decrease the hedonic impact of HFHS foods fails **[62]. In that view, a positive feedback loop whereby chronically high plasma TG, such as occur in obesity, will damage homeostatic mechanisms that limit food intake resulting in altered reward encoding, uncontrolled caloric consumption, and reduced physical activity. Such a mechanism will inevitably drive body weight gain. Further studies will be required to understand the physiology and molecular mechanism of central TG sensing and if/how inheritable susceptibility loci such as the TaqA1 allele could exacerbate the adaptive mechanisms associated with brain TG sensing and, ultimately, the downward spiral that drives compulsive eating dissociated from metabolic needs.

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BIBLIOGRAPHIE

1. Reaven GM. The metabolic syndrome: is this diagnosis necessary? *Am J Clin Nutr.* 2006; 83:1237–1247. [PubMed: 16762930]
2. Blouet C, Schwartz GJ. Hypothalamic nutrient sensing in the control of energy homeostasis. *Behav Brain Res.* 2010; 209:1–12. [PubMed: 20035790]
3. Thaler JP, Yi CX, Schur EA, Guyenet SJ, Hwang BH, Dietrich MO, Zhao X, Sarruf DA, Izgur V, Maravilla KR, et al. Obesity is associated with hypothalamic injury in rodents and humans. *J Clin Invest.* 2012; 122:153–162. [PubMed: 22201683]
4. Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci U S A.* 1988; 85:5274–5278. [PubMed: 2899326]
5. Dallman MF, Pecoraro NC, la Fleur SE. Chronic stress and comfort foods: self-medication and abdominal obesity. *Brain Behav Immun.* 2005; 19:275–280. [PubMed: 15944067]
6. Fulton S, Woodside B, Shizgal P. Modulation of brain reward circuitry by leptin. *Science.* 2000; 287:125–128. [PubMed: 10615045]
7. Skibicka KP, Hansson C, Alvarez-Crespo M, Friberg PA, Dickson SL. Ghrelin directly targets the ventral tegmental area to increase food motivation. *Neuroscience.* 2011; 180:129–137. [PubMed: 21335062]
8. 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; 964:107–115. [PubMed: 12573518]
- **9. Stouffer MA, Woods CA, Patel JC, Lee CR, Witkovsky P, Bao L, Machold RP, Jones KT, de Vaca SC, Reith ME, et al. Insulin enhances striatal dopamine release by activating cholinergic interneurons and thereby signals reward. *Nat Commun.* 2015; 6:8543. This study demonstrates that insulin can regulate dopamine release in the striatum through direct action on cholinergic interneurons expressing the insulin receptor. [PubMed: 26503322]
10. Volkow ND, Wang GJ, Tomasi D, Baler RD. Obesity and addiction: neurobiological overlaps. *Obesity reviews : an official journal of the International Association for the Study of Obesity.* 2013; 14:2–18. [PubMed: 23016694]
11. Kenny PJ, Voren G, Johnson PM. Dopamine D2 receptors and striatopallidal transmission in addiction and obesity. *Current opinion in neurobiology.* 2013

12. Rothemund Y, Preuschhof C, Bohner G, Bauknecht HC, Klingebiel R, Flor H, Klapp BF. Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. *Neuroimage*. 2007; 37:410–421. [PubMed: 17566768]
13. 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; 322:449–452. [PubMed: 18927395]
14. DiLeone RJ, Taylor JR, Picciotto MR. The drive to eat: comparisons and distinctions between mechanisms of food reward and drug addiction. *Nature neuroscience*. 2012; 15:1330–1335. [PubMed: 23007187]
15. Lam TK, Schwartz GJ, Rossetti L. Hypothalamic sensing of fatty acids. *Nat Neurosci*. 2005; 8:579–584. [PubMed: 15856066]
16. Velloso LA, Schwartz MW. Altered hypothalamic function in diet-induced obesity. *Int J Obes (Lond)*. 2011; 35:1455–1465. [PubMed: 21386802]
17. Arruda AP, Milanski M, Coope A, Torsoni AS, Ropelle E, Carvalho DP, Carnevali JB, Velloso LA. Low-grade hypothalamic inflammation leads to defective thermogenesis, insulin resistance, and impaired insulin secretion. *Endocrinology*. 2011; 152:1314–1326. [PubMed: 21266511]
18. Milanski M, Degasperi G, Coope A, Morari J, Denis R, Cintra DE, Tsukumo DM, Anhe G, Amaral ME, Takahashi HK, et al. Saturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamus: implications for the pathogenesis of obesity. *J Neurosci*. 2009; 29:359–370. [PubMed: 19144836]
19. Lee BC, Lee J. Cellular and molecular players in adipose tissue inflammation in the development of obesity-induced insulin resistance. *Biochim Biophys Acta*. 2014; 1842:446–462. [PubMed: 23707515]
20. Gao Y, Ottaway N, Schriever SC, Legutko B, Garcia-Caceres C, de la Fuente E, Mergen C, Bour S, Thaler JP, Seeley RJ, et al. Hormones and diet, but not body weight, control hypothalamic microglial activity. *Glia*. 2014; 62:17–25. [PubMed: 24166765]
21. Lockie SH, Dinan T, Lawrence AJ, Spencer SJ, Andrews ZB. Diet-induced obesity causes ghrelin resistance in reward processing tasks. *Psychoneuroendocrinology*. 2015; 62:114–120. [PubMed: 26292268]
22. Lopez M, Tovar S, Vazquez MJ, Nogueiras R, Senaris R, Dieguez C. Sensing the fat: fatty acid metabolism in the hypothalamus and the melanocortin system. *Peptides*. 2005; 26:1753–1758. [PubMed: 15979207]
23. Kleinridders A, Schenten D, Konner AC, Belgardt BF, Mauer J, Okamura T, Wunderlich FT, Medzhitov R, Bruning JC. MyD88 signaling in the CNS is required for development of fatty acid-induced leptin resistance and diet-induced obesity. *Cell Metab*. 2009; 10:249–259. [PubMed: 19808018]
24. Volkow ND, Wang GJ, Telang F, Fowler JS, Thanos PK, Logan J, Alexoff D, Ding YS, Wong C, Ma Y, et al. Low dopamine striatal D2 receptors are associated with prefrontal metabolism in obese subjects: possible contributing factors. *Neuroimage*. 2008; 42:1537–1543. [PubMed: 18598772]
25. Alsio J, Olszewski PK, Norback AH, Gunnarsson ZE, Levine AS, Pickering C, Schiöth HB. 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; 171:779–787. [PubMed: 20875839]
26. Johnson PM, Kenny PJ. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nat Neurosci*. 2010; 13:635–641. [PubMed: 20348917]
- **27. Robinson MJ, Burghardt PR, Patterson CM, Nobile CW, Akil H, Watson SJ, Berridge KC, Ferrario CR. Individual Differences in Cue-Induced Motivation and Striatal Systems in Rats Susceptible to Diet-Induced Obesity. *Neuropsychopharmacology*. 2015; 40:2113–2123. This paper uses a model of individual susceptibility to assess whether there are pre-existing or diet-induced increases in incentive salience for sucrose reward. The study shows that an increased susceptibility for food craving exists prior to obesity in animals that are obesity-prone, and is not due to preexisting changes in opioid signaling. Further, that exposure to a western-diet promotes the downregulation of D₂R independent of obesity. [PubMed: 25761571]

28. Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, Netusil N, Fowler JS. Brain dopamine and obesity. *Lancet*. 2001; 357:354–357. [PubMed: 11210998]
29. Stice E, Spoor S, Bohon C, Veldhuizen MG, Small DM. Relation of reward from food intake and anticipated food intake to obesity: a functional magnetic resonance imaging study. *J Abnorm Psychol*. 2008; 117:924–935. [PubMed: 19025237]
30. Michaelides M, Thanos PK, Volkow ND, Wang GJ. Dopamine-related frontostriatal abnormalities in obesity and binge-eating disorder: emerging evidence for developmental psychopathology. *International review of psychiatry*. 2012; 24:211–218. [PubMed: 22724642]
- **31. Guo J, Simmons WK, Herscovitch P, Martin A, Hall KD. Striatal dopamine D2-like receptor correlation patterns with human obesity and opportunistic eating behavior. *Mol Psychiatry*. 2014; 19:1078–1084. This study measures striatal D₂R-like binding potential (D₂BP) and highlighted an inverted association between ventral and dorsal striatal DA binding in obesity. Body mass index (BMI) was negatively correlated with D₂BP in the ventral striatum while both BMI and habitual/opportunistic eating positively correlated with D₂BP in the dorsal striatum. [PubMed: 25199919]
32. Davis JF, Tracy AL, Schurdak JD, Tschop MH, Lipton JW, Clegg DJ, Benoit SC. Exposure to elevated levels of dietary fat attenuates psychostimulant reward and mesolimbic dopamine turnover in the rat. *Behav Neurosci*. 2008; 122:1257–1263. [PubMed: 19045945]
33. South T, Huang 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. [PubMed: 17940894]
- **34. Adams WK, Sussman JL, Kaur S, D'Souza AM, Kieffer TJ, Winstanley CA. Long-term, calorie-restricted intake of a high-fat diet in rats reduces impulse control and ventral striatal D2 receptor signaling: two markers of addiction vulnerability. *European Journal of Neuroscience*. 2015:n/a–n/a. This paper demonstrates that short-term equicaloric exposure to high-fat diet, but not high sucrose diet, reduces impulse control as measured in 5-choices serial reaction time task.
35. Valdivia S, Cornejo MP, Reynaldo M, De Francesco PN, Perello M. Escalation in high fat intake in a binge eating model differentially engages dopamine neurons of the ventral tegmental area and requires ghrelin signaling. *Psychoneuroendocrinology*. 2015; 60:206–216. [PubMed: 26186250]
- **36. Hryhorczuk C, Florea M, Rodaros D, Poirier I, Daneault C, Des Rosiers C, Arvanitogiannis A, Alquier T, Fulton S. Dampened Mesolimbic Dopamine Function and Signaling by Saturated but not Monounsaturated Dietary Lipids. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2015 This work studies the effect of saturation degree (saturated versus mono-unsaturated) of dietary lipids on mesolimbic dopamine signaling. The authors demonstrate that equicaloric amounts of saturated fat but not monounsaturated fat, lead to reduced D₁R abundance and dopamine transporter expression resulting in altered dopamine signalling independent of total caloric intake, body weight gain, insulin, or leptin.
37. Dourmashkin JT, Chang GQ, Hill JO, Gayles EC, Fried SK, Leibowitz SF. Model for predicting and phenotyping at normal weight the long-term propensity for obesity in Sprague-Dawley rats. *Physiol Behav*. 2006; 87:666–678. [PubMed: 16513148]
38. 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; 1298:111–122. [PubMed: 19666014]
39. Rada P, Avena NM, Barson JR, Hoebel BG, Leibowitz SF. A high-fat meal, or intraperitoneal administration of a fat emulsion, increases extracellular dopamine in the nucleus accumbens. *Brain Sci*. 2012; 2:242–253. [PubMed: 24962774]
40. Farr SA, Yamada KA, Butterfield DA, Abdul HM, Xu L, Miller NE, Banks WA, Morley JE. Obesity and hypertriglyceridemia produce cognitive impairment. *Endocrinology*. 2008; 149:2628–2636. [PubMed: 18276751]
- **41. Sun X, Veldhuizen MG, Wray AE, de Araujo IE, Sherwin RS, Sinha R, Small DM. The neural signature of satiation is associated with ghrelin response and triglyceride metabolism. *Physiol Behav*. 2014; 136:63–73. This manuscript uses functional magnetic resonance (fMRI) to demonstrate that, in humans, post-prandial decreases of ghrelin and increases of TG correlate with greater attenuation of palatable food-induced BOLD signals in ML structures. [PubMed: 24732416]

42. Edmond J. Essential polyunsaturated fatty acids and the barrier to the brain: the components of a model for transport. *J Mol Neurosci*. 2001; 16:181–193. discussion 215-121. [PubMed: 11478373]
43. Rapoport SI, Chang MC, Spector AA. Delivery and turnover of plasma-derived essential PUFAs in mammalian brain. *J Lipid Res*. 2001; 42:678–685. [PubMed: 11352974]
44. Wang H, Eckel RH. What are lipoproteins doing in the brain? *Trends Endocrinol Metab*. 2014; 25:8–14. [PubMed: 24189266]
45. Arai T, Wakabayashi S, Channing MA, Dunn BB, Der MG, Bell JM, Herscovitch P, Eckelman WC, Rapoport SI, Chang MC. Incorporation of [1-carbon-11]palmitate in monkey brain using PET. *J Nucl Med*. 1995; 36:2261–2267. [PubMed: 8523117]
46. Rapoport SI. In vivo fatty acid incorporation into brain phospholipids in relation to plasma availability, signal transduction and membrane remodeling. *J Mol Neurosci*. 2001; 16:243–261. discussion 279-284. [PubMed: 11478380]
47. Karmi A, Iozzo P, Viljanen A, Hirvonen J, Fielding BA, Virtanen K, Oikonen V, Kempainen J, Viljanen T, Guiducci L, et al. Increased brain fatty acid uptake in metabolic syndrome. *Diabetes*. 2010; 59:2171–2177. [PubMed: 20566663]
- **48. Nguyen LN, Ma D, Shui G, Wong P, Cazenave-Gassiot A, Zhang X, Wenk MR, Goh EL, Silver DL. Mfsd2a is a transporter for the essential omega-3 fatty acid docosahexaenoic acid. *Nature*. 2014; 509:503–506. This study identify Mfsd2a as the transporter for the long-chain omega-3 essential unsaturated fatty acid Docosahexaenoic acid (DHA) through the blood-brain barrier. The authors reveal also a new and unexpected role for plasma lysophosphatidylcholine (LPC) as a source for brain DHA via Mfsd2a. [PubMed: 24828044]
49. Ouellet M, Emond V, Chen CT, Julien C, Bourasset F, Oddo S, LaFerla F, Bazinet RP, Calon F. Diffusion of docosahexaenoic and eicosapentaenoic acids through the blood-brain barrier: An in situ cerebral perfusion study. *Neurochem Int*. 2009; 55:476–482. [PubMed: 19442696]
50. Ladu MJ, Reardon C, Van Eldik L, Fagan AM, Bu G, Holtzman D, Getz GS. Lipoproteins in the central nervous system. *Ann N Y Acad Sci*. 2000; 903:167–175. [PubMed: 10818504]
51. Koch S, Donarski N, Goetze K, Kreckel M, Stuerenburg HJ, Buhmann C, Beisiegel U. Characterization of four lipoprotein classes in human cerebrospinal fluid. *J Lipid Res*. 2001; 42:1143–1151. [PubMed: 11441143]
52. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, Derecki NC, Castle D, Mandell JW, Lee KS, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature*. 2015; 523:337–341. [PubMed: 26030524]
53. Evola M, Hall A, Wall T, Young A, Grammas P. Oxidative stress impairs learning and memory in apoE knockout mice. *Pharmacol Biochem Behav*. 2010; 96:181–186. [PubMed: 20457176]
54. de Oliveira J, Moreira EL, dos Santos DB, Piermartiri TC, Dutra RC, Pinton S, Tasca CI, Farina M, Prediger RD, de Bem AF. Increased susceptibility to amyloid-beta-induced neurotoxicity in mice lacking the low-density lipoprotein receptor. *J Alzheimers Dis*. 2014; 41:43–60. [PubMed: 24577472]
55. Borroni B, Grassi M, Agosti C, Costanzi C, Archetti S, Franzoni S, Caltagirone C, Di Luca M, Caimi L, Padovani A. Genetic correlates of behavioral endophenotypes in Alzheimer disease: role of COMT, 5-HTTLPR and APOE polymorphisms. *Neurobiol Aging*. 2006; 27:1595–1603. [PubMed: 16257094]
56. Kim J, Castellano JM, Jiang H, Basak JM, Parsadanian M, Pham V, Mason SM, Paul SM, Holtzman DM. Overexpression of low-density lipoprotein receptor in the brain markedly inhibits amyloid deposition and increases extracellular A beta clearance. *Neuron*. 2009; 64:632–644. [PubMed: 20005821]
57. Eckel RH, Robbins RJ. Lipoprotein lipase is produced, regulated, and functional in rat brain. *Proc Natl Acad Sci U S A*. 1984; 81:7604–7607. [PubMed: 6594703]
58. Paradis E, Clavel S, Julien P, Murthy MR, de Bilbao F, Arsenijevic D, Giannakopoulos P, Vallet P, Richard D. 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; 15:312–325. [PubMed: 15006701]
59. Wang H, Eckel RH. Lipoprotein lipase in the brain and nervous system. *Annu Rev Nutr*. 2012; 32:147–160. [PubMed: 22540257]

- **60. Yu T, Taussig MD, DiPatrizio NV, Astarita G, Piomelli D, Bergman BC, Dell'Acqua ML, Eckel RH, Wang H. Deficiency of Lipoprotein Lipase in Neurons Decreases AMPA Receptor Phosphorylation and Leads to Neurobehavioral Abnormalities in Mice. *PLoS one*. 2015; 10:e0135113. This work shows that neuron-specific deletion of the gene encoding the triglyceride-hydrolyzing enzyme lipoprotein lipase (LPL) leads to cognitive decline and a drastic reduction of AMPA receptor; associated with a marked deficit in brain polyunsaturated fatty acid (PUFA) content in hippocampus that could be restored by feeding with a diet enriched with PUFA. [PubMed: 26263173]
61. Pellinen J, Wang H, Eckel RH. Mice with altered brain lipoprotein metabolism display maladaptive responses to environmental challenges that may predispose to weight gain. *Metab Syndr Relat Disord*. 2014; 12:339–346. [PubMed: 24730656]
- **62. Cansell C, Castel J, Denis RG, Rouch C, Delbes AS, Martinez S, Mestivier D, Finan B, Maldonado-Aviles JG, Rijnsburger M, et al. Dietary triglycerides act on mesolimbic structures to regulate the rewarding and motivational aspects of feeding. *Mol Psychiatry*. 2014; 19:1095–1105. This study provide the first demonstration that striatal structures can detect circulating triglycerides through a lipoprotein-lipase dependent mechanism; and that TG sensing in the Nucleus accumbens regulates food reward seeking and response to amphetamine. [PubMed: 24732670]
63. Wang H, Astarita G, Taussig MD, Bharadwaj KG, DiPatrizio NV, Nave KA, Piomelli D, Goldberg IJ, Eckel RH. Deficiency of lipoprotein lipase in neurons modifies the regulation of energy balance and leads to obesity. *Cell Metab*. 2011; 13:105–113. [PubMed: 21195353]
- **64. Picard A, Rouch C, Kassiss N, Moulle VS, Croizier S, Denis RG, Castel J, Coant N, Davis K, Clegg DJ, et al. Hippocampal lipoprotein lipase regulates energy balance in rodents. *Molecular metabolism*. 2014; 3:167–176. This manuscript provides novel evidence that lipoprotein-lipase detection of triglyceride in the hippocampus regulates body weight through autonomic regulation and via de novo synthesis along the ceramide signaling pathway. [PubMed: 24634821]
65. Ruge T, Hodson L, Cheeseman J, Dennis AL, Fielding BA, Humphreys SM, Frayn KN, Karpe F. 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; 94:1781–1788. [PubMed: 19223522]
66. Bjursell M, Gerdin A-K, Lelliott CJ, Egecioglu E, Elmgren A, Törnell J, Oscarsson J, Bohlooly-Y M. Acutely reduced locomotor activity is a major contributor to Western diet-induced obesity in mice. *American journal of physiology. Endocrinology and metabolism*. 2008; 294:E251–260. [PubMed: 18029443]
67. Oomura Y, Nakamura T, Sugimori M, Yamada Y. Effect of free fatty acid on the rat lateral hypothalamic neurons. *Physiol Behav*. 1975; 14:483–486. [PubMed: 1135293]
68. Obici S, Feng Z, Morgan K, Stein D, Karkani G, Rossetti L. Central administration of oleic acid inhibits glucose production and food intake. *Diabetes*. 2002; 51:271–275. [PubMed: 11812732]
69. Proulx K, Cota D, Woods SC, Seeley RJ. Fatty acid synthase inhibitors modulate energy balance via mammalian target of rapamycin complex 1 signaling in the central nervous system. *Diabetes*. 2008; 57:3231–3238. [PubMed: 18776140]
70. Milanski M, Arruda AP, Coope A, Ignacio-Souza LM, Nunez CE, Roman EA, Romanatto T, Pascoal LB, Caricilli AM, Torsoni MA, et al. Inhibition of hypothalamic inflammation reverses diet-induced insulin resistance in the liver. *Diabetes*. 2012; 61:1455–1462. [PubMed: 22522614]
71. Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D. Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. *Cell*. 2008; 135:61–73. [PubMed: 18854155]
72. Cruciani-Guglielmacci C, Hervalet A, Douared L, Sanders NM, Levin BE, Ktorza A, Magnan C. Beta oxidation in the brain is required for the effects of non-esterified fatty acids on glucose-induced insulin secretion in rats. *Diabetologia*. 2004; 47:2032–2038. [PubMed: 15599702]
73. Andrews ZB, Liu ZW, Wallingford N, Erion DM, Borok E, Friedman JM, Tschop MH, Shanabrough M, Cline G, Shulman GI, et al. UCP2 mediates ghrelin's action on NPY/AgRP neurons by lowering free radicals. *Nature*. 2008; 454:846–851. [PubMed: 18668043]
74. Benoit SC, Kemp CJ, Elias CF, Abplanalp W, Herman JP, Migrenne S, Lefevre AL, Cruciani-Guglielmacci C, Magnan C, Yu F, et al. Palmitic acid mediates hypothalamic insulin resistance by

- altering PKC-theta subcellular localization in rodents. *J Clin Invest.* 2009; 119:2577–2589. [PubMed: 19726875]
75. Yue JT, Abraham MA, LaPierre MP, Mighiu PI, Light PE, Filippi BM, Lam TK. A fatty acid-dependent hypothalamic-DVC neurocircuitry that regulates hepatic secretion of triglyceride-rich lipoproteins. *Nat Commun.* 2015; 6:5970. [PubMed: 25580573]
76. Zhang L, Reith ME. Regulation of the functional activity of the human dopamine transporter by the arachidonic acid pathway. *Eur J Pharmacol.* 1996; 315:345–354. [PubMed: 8982675]
77. Aleshin S, Reiser G. Role of the peroxisome proliferator-activated receptors (PPAR)-alpha, beta/delta and gamma triad in regulation of reactive oxygen species signaling in brain. *Biol Chem.* 2013; 394:1553–1570. [PubMed: 24021597]
78. Jonsson EG, Nothen MM, Grunhage F, Farde L, Nakashima Y, Propping P, Sedvall GC. Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. *Mol Psychiatry.* 1999; 4:290–296. [PubMed: 10395223]
- **79. Stice E, Yokum S, Bohon C, Marti N, Smolen A. Reward circuitry responsivity to food predicts future increases in body mass: moderating effects of DRD2 and DRD4. *Neuroimage.* 2010; 50:1618–1625. This study shows that neural responses to receipt and anticipated receipt of food reward, but not monetary reward, predict body fat gain. In addition this works shows that increased dopamine-sensitive brain responses to food reward is modulated by gene dosage of TaqA1/A2 alleles. This study underscores the Gaussian relationship between dopamine signaling and vulnerability to body weight gain. [PubMed: 20116437]
80. Stice E, Burger KS, Yokum S. Reward Region Responsivity Predicts Future Weight Gain and Moderating Effects of the TaqIA Allele. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2015; 35:10316–10324. [PubMed: 26180206]
81. Ritchie T, Noble EP. Association of seven polymorphisms of the D2 dopamine receptor gene with brain receptor-binding characteristics. *Neurochem Res.* 2003; 28:73–82. [PubMed: 12587665]
82. Barnard ND, Noble EP, Ritchie T, Cohen J, Jenkins DJ, Turner-McGrievy G, Gloede L, Green AA, Ferdowsian H. D2 dopamine receptor Taq1A polymorphism, body weight, and dietary intake in type 2 diabetes. *Nutrition.* 2009; 25:58–65. [PubMed: 18834717]
83. Hoenicka J, Quinones-Lombrana A, Espana-Serrano L, Alvira-Botero X, Kremer L, Perez-Gonzalez R, Rodriguez-Jimenez R, Jimenez-Arriero MA, Ponce G, Palomo T. The ANKK1 gene associated with addictions is expressed in astroglial cells and upregulated by apomorphine. *Biol Psychiatry.* 2010; 67:3–11. [PubMed: 19853839]
84. Meylan E, Tschopp J. The RIP kinases: crucial integrators of cellular stress. *Trends Biochem Sci.* 2005; 30:151–159. [PubMed: 15752987]
85. Kotlyar M, Pastrello C, Pivetta F, Lo Sardo A, Cumbaa C, Li H, Naranian T, Niu Y, Ding Z, Vafae F, et al. In silico prediction of physical protein interactions and characterization of interactome orphans. *Nat Methods.* 2015; 12:79–84. [PubMed: 25402006]
- **86. Buckman LB, Thompson MM, Lippert RN, Blackwell TS, Yull FE, Ellacott KL. Evidence for a novel functional role of astrocytes in the acute homeostatic response to high-fat diet intake in mice. *Mol Metab.* 2015; 4:58–63. This work uses a conditional model for NF-kB expression to demonstrate that activation of NF-kB in astrocytes is determinant in the acute change in feeding behavior resulting from high fat diet exposure. [PubMed: 25685690]
87. Gupta S, Knight AG, Gupta S, Keller JN, Bruce-Keller AJ. Saturated long-chain fatty acids activate inflammatory signaling in astrocytes. *J Neurochem.* 2012; 120:1060–1071. [PubMed: 22248073]
88. Bontempi S, Fiorentini C, Busi C, Guerra N, Spano P, Missale C. Identification and characterization of two nuclear factor-kappaB sites in the regulatory region of the dopamine D2 receptor. *Endocrinology.* 2007; 148:2563–2570. [PubMed: 17317773]
89. Fiorentini C, Guerra N, Facchetti M, Finardi A, Tiberio L, Schiaffonati L, Spano P, Missale C. Nerve growth factor regulates dopamine D(2) receptor expression in prolactinoma cell lines via p75(NGFR)-mediated activation of nuclear factor-kappaB. *Mol Endocrinol.* 2002; 16:353–366. [PubMed: 11818506]
90. Poon K, Alam M, Karatayev O, Barson JR, Leibowitz SF. Regulation of the orexigenic neuropeptide, enkephalin, by PPARdelta and fatty acids in neurons of the hypothalamus and forebrain. *J Neurochem.* 2015

91. Chistyakov DV, Aleshin S, Sergeeva MG, Reiser G. Regulation of peroxisome proliferator-activated receptor beta/delta expression and activity levels by toll-like receptor agonists and MAP kinase inhibitors in rat astrocytes. *J Neurochem.* 2014; 130:563–574. [PubMed: 24806616]

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HIGHLIGHTS

- The mesolimbic system (ML) express triglyceride (TG) lipases
- Dietary TG can be hydrolyzed at the level of the ML
- TG sensing in the ML regulate reward seeking behavior
- Obesity-associated hypertriglyceridemia alters TG sensing

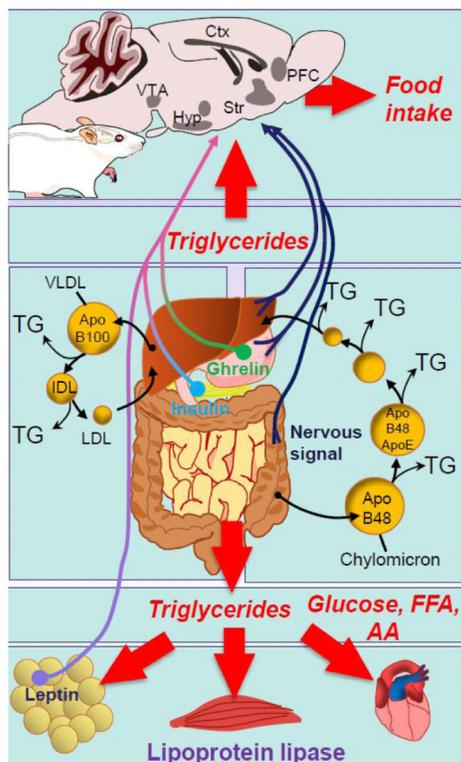


Figure 1. Peripheral signals regulating feeding

Central integration of peripheral nervous and hormonal inputs that regulate energy balance. Gut-derived nervous and circulating factors convey a satiety signal and include vagal inputs from stomach or digestive tracts as well as secreted peptides such as cholecystokinin (CCK), PYY₃₋₃₆, or glucagon-like peptide 1 (GLP-1). Ghrelin is secreted primarily by the stomach and positively regulates feeding while insulin or leptin act as long-term satiety factors. Ghrelin, leptin, and insulin have targets in the hypothalamus as well as the reward circuitry. Dietary lipids are esterified into triglycerides (TG) and packaged in nascent chylomicron (CM) at the level of the gut, secreted first in to the lymphatic system, and then the bloodstream. TG-rich CM gradually lose their lipid content upon action of tissue lipoprotein lipase (LPL) and ultimately recaptured as remnant CM by the liver. In the process CM exchange their native Apolipoprotein B48 (ApoB48) component for the apolipoprotein E (ApoE). Very-low density lipoprotein (VLDL), produced by the liver, represent another source of TG-rich particles which, upon action of LPL, give rise to intermediate-density (IDL) and low-density (LDL) lipoproteins. LPL is also expressed in the brain in both hypothalamic structures and ML structures including the prefrontal cortex (PFC), the hippocampus, ventral tegmental area, and throughout dorsal and ventral striatum. TG hydrolysis in the NAc regulates the rewarding and motivational aspects of food intake and could be an important mechanism linking dietary input with reward.

