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Dietary triglycerides as signaling molecules that influence reward and motivation

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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 (D_2R), 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.

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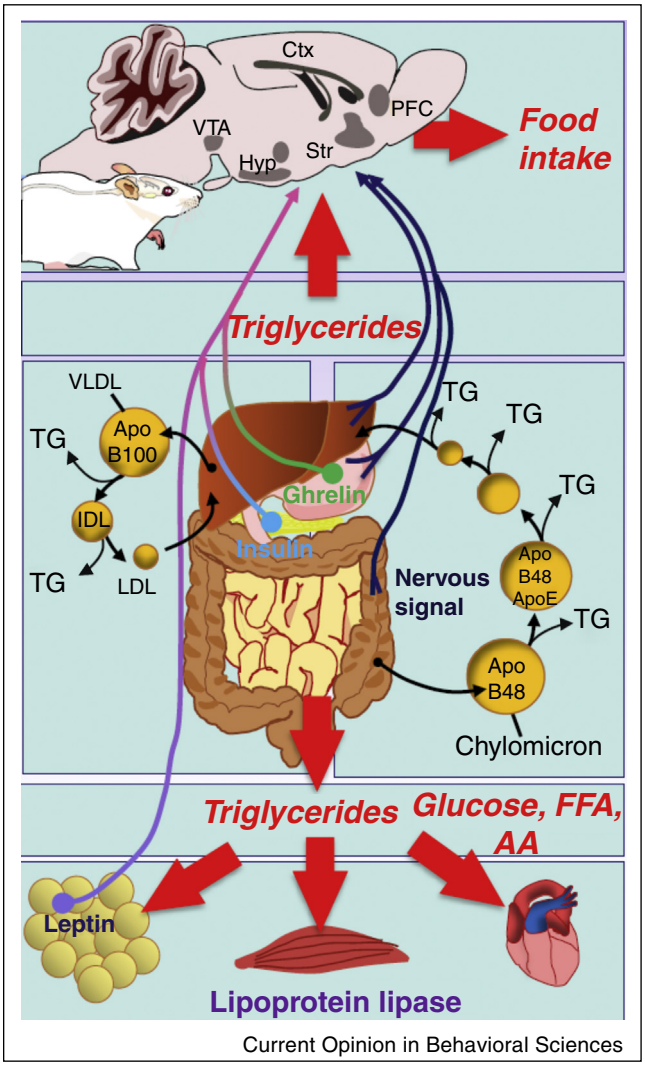
Introduction

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 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 pathophysiologies 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 behavioral 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 behavioral 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 [6–9••].

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

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), PYY_{3-36}, 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.

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 D_2 receptor (D_2R) 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 D_2R 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 was 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 D_2R 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 signaling in this process; using positron emission tomography (PET) to quantify striatal D_2R-like binding potential (D_2BP) identified an association between striatal DA binding in obesity. Body mass index (BMI) was negatively correlated with D_2BP in the

ventral striatum (i.e., NAc) whereas in the dorsal striatum, both BMI and habitual/opportunistic eating behavior positively correlated with D_2BP [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 D_2R 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 propensy. 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 was 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 signaling 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 signaling 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 catalyze the hydrolysis of TG into free fatty acids and mono-glycerol or diacyl-glycerol 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 substructures of the brain. For example, hippocampal LPL regulates energy expenditure and autonomic tone through synthesis along the ceramide-based signaling 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 behavior.

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

We have developed a model in which TG emulsion (intralipid^{TM}) 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 were 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-κB)-dependent pathways [3,18,70,71], 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].

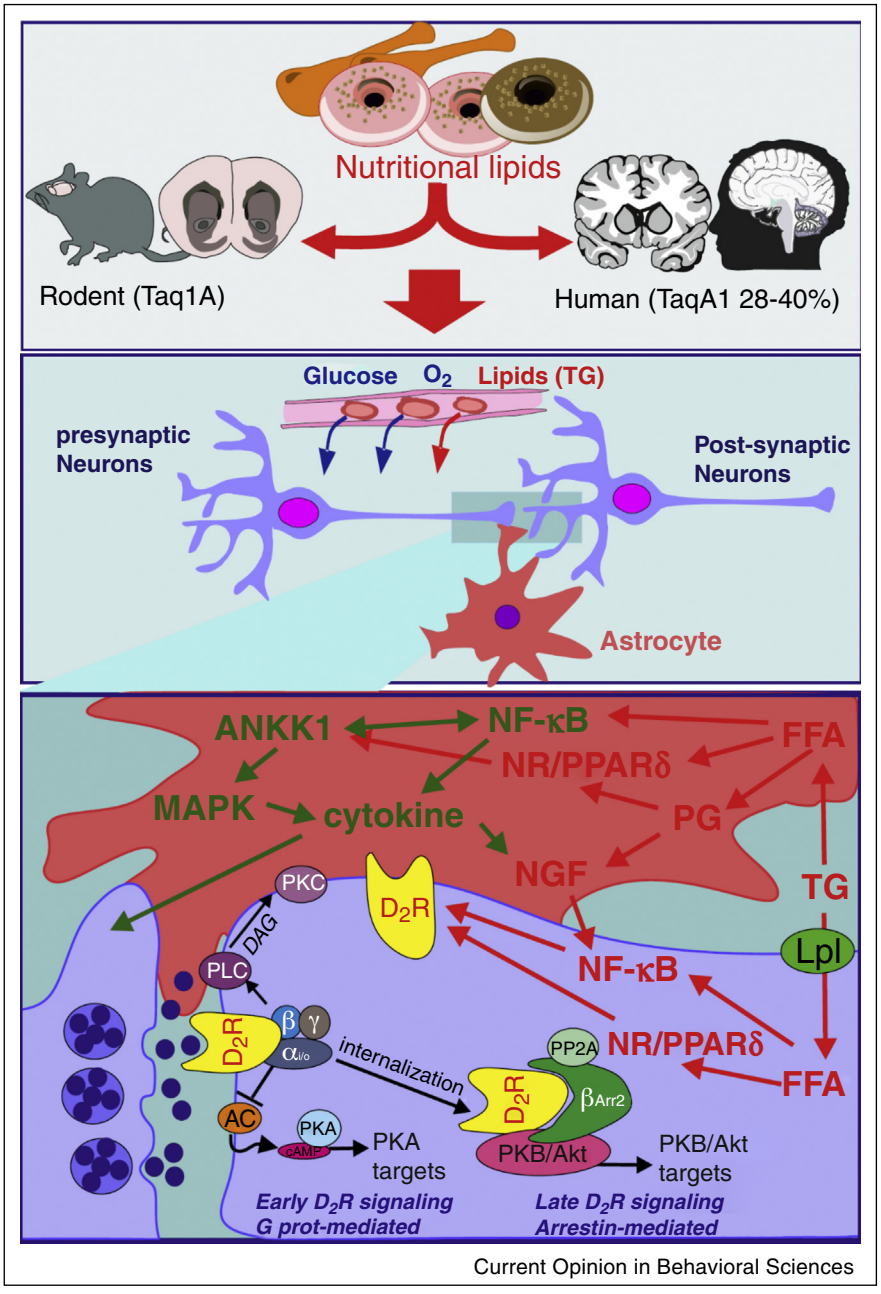
Although high calorie food is virtually ubiquitous, uncontrolled feeding and obesity does not affect every individual suggesting that the modern food environment might directly interact with genetic or epigenetic elements of susceptibility. The *TaqI*A A1 allele is an excellent candidate in that regard. Affecting 30–40% of the population, homozygous dosage of the A1 allele correlates with a 30∼40% reduction of striatal D_2R abundance [78,79••,80–82] 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 D_2R [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 (TNFα-R1) receptor and Toll-like receptor (TLR), and converge upon c-jun N-terminal kinase (JNK), MAPK activity or NF-κB [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≡, JNK or MAPK pathway. 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-κB signaling [86••,87].

How astrocyte ANKK1 activity could ultimately relate to the reduced D_2R abundance is still an open question but, here again, fatty acid metabolism might provide several potential mechanisms. For example the D_2R and ANKK1 promoters possess NF-κB 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 D_2R mRNA transcription through the NF-κB signaling pathway [89].

Finally, while increased feeding as a consequence of acute high fat diet exposure was recently shown to

Figure 2



Potential mechanism associating central TG sensing and reward. Nutritional lipids lead to increased synthesis of TG-rich particles and export by the gut. At the level of the brain, the tripartite synapse composed of neurons and astrocytes will detect changes in nutrient availability. Free fatty acids (FFA) enter astrocytes or neurons through lipid receptors/transporters or via lipoprotein lipase (LPL) mediated breakdown of lipoprotein. Once in the cell FFA can enter the TCA-cycle but can also directly activate lipid-activated nuclear receptors (NR) including proliferated activated receptors delta (PPARδ) or the nuclear enhancer of kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathways, or through indirect pathways involving Toll-like receptor activation, inflammatory processes, ER-stress, or prostaglandin (PG) synthesis. In turn, activated NR and NF-κB exert a direct regulation at the transcriptional level on dopamine D2 receptor (D_2R). At the level of the astrocyte, NF-κB activation leads to increased cytokine production which promotes the release of the neural-growth factor (NGF). NGF released by astrocyte directly regulates neural D_2R abundance. The astrocyte-specific Ankyrin repeat and kinase domain containing 1 (ANKK1) directly interacts with NF-κB and MAP kinases. In that regard, mutation of ANKK1 (*TaqI*A A1) would directly impact most FFA-induced cellular responses. At the level of DA neuron signaling, early D_2R response and late β-arrestin mediated responses could both be affected by a FFA/ANKK1 initiated pathway.

involve activation of astrocytic NF-κB [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). PPARδ belongs to a family of ligand-activated transcription factors, involved in a variety of cellular metabolic adaptations, which primarily respond to LCFA and prostaglandin. PPARδ has also emerged as an important regulator of the ML. For example, activation of PPARδ 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 PPARδ is directly regulated by TLR/NF-κB 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-κB/PPARs triad to effect the expression or function of D_2R (Figure 2). While the ML response to short term high fat exposure could be mediated by a NF-κB/NGF action on D_2R, PPARδ 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.

Conflict of interest

Nothing declared.

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Papers of particular interest, published within the period of review, have been highlighted as:

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- •• of outstanding interest

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