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Dietary lipids and reward processes

1	Dietary lipids as regulators of reward processes: multimodal integration matters
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26	physiology

#### 27 Abstract

The abundance of energy-dense and palatable diets in the modern food environment 28 tightly contributes to the obesity pandemic. The reward circuit participates to the 29 30 regulation of body homeostasis by integrating energy-related signals with neural substrates encoding cognitive and motivational components of feeding behaviors. 31 32 Obesity and lipids-rich diets alter dopamine (DA) transmission leading to reward dysfunctions and food overconsumption. Recent reports indicate that dietary lipids can 33 34 act, directly and indirectly, as functional modulators of the DA circuit. This raises the possibility that nutritional or genetic conditions affecting "lipid sensing" mechanisms might 35 lead to maladaptations of the DA system. Here, we discuss the most recent findings 36 connecting dietary lipid sensing with DA signaling and its multimodal influence on circuits 37 38 regulating food-reward processes.

#### 39 Dietary signals: all roads lead to the brain

Physiological mechanisms optimizing feeding behaviors have been selected during 40 41 evolution. This is exemplified by the natural tropism of mammals toward energy-dense 42 food (rich in lipids and sugar) which represents a promise of maturation and survival. 43 Nowadays, the ubiguitous availability of palatable and energy-dense diets challenges the highly conserved and sophisticated systems controlling food intake. It is clear that, 44 although inheritable genetic traits might contribute as risk factors for the development of 45 metabolic disorders, the consumption of calorie-dense food beyond metabolic needs 46 47 arises as a primary culprit in the obesity pandemic.

During the last decades, the brain has emerged as the master regulator of energy 48 49 homeostasis by integrating metabolic demands with the reinforcing nutritional properties 50 of food [1]. In fact, while the hypothalamic melanocortin circuit ensures the homeostatic 51 control of ingestive behaviors and metabolism, the mesocorticolimbic dopamine (DA) 52 system integrates and translates metabolic signals into reward values [2] so that 53 associated cues are imbued with incentive salience and the power to drive choices and 54 behaviors [3]. Thus metabolic and reinforcing systems are dynamically integrated so that 55 metabolic requirement is translated into motivated behaviors to obtain nutrients [4]. The 56 ability of organisms to store energy extends this process beyond current needs, making 57 overconsumption adaptive throughout most of history.

58 Dietary signals can modulate brain circuits and functions in distinct ways. In fact, nutrients 59 sensing chemosensory mechanisms operate in compartmentalized cellular elements 60 located throughout our body, notably in the mouth, gastrointestinal (GI) tract and brain, 61 thereby playing a key role in the multimodal regulation and control of ingestive behavior(s) (Figure 1). This multimodal integration has been recently highlighted in humans where 62 63 immediate orosensory and subsequent post-ingestive signals derived from a palatable food (milkshake) led to two temporally separated waves of DA release in the ventral and 64 65 dorsal striatum, respectively [5].

Among nutrients (e.g. glucose, amino acids), dietary and circulating lipids have emerged as critical modulators of brain functions. Indeed, foods rich in fat are highly reinforcing. Despite orosensory perception and organoleptic components of food are known to be intimately associated with the reinforcing values of food, novel physiological routes are

- 70 emerging as instrumental in conveying the reinforcing aspects of dietary lipids through
- 71 direct and/or indirect connections with the mesolimbic DA circuit. However, dietary lipids-
- 72 related functions seem to strongly depend on the nature and source of circulating lipids
- 73 (pre- to post-prandial availability of circulating lipids, **Box 1**).
- 74

# BOX 1: Triglycerides or free fatty acids: the physiology of timing and nutritional states.

- Triglyceride (TG)-rich lipoproteins and free fatty acids (FFA) bound to albumin represent 77 78 the two main sources of circulating lipids in the body [6]. While FFA are released upon 79 adipose tissue lipolysis during periods of nutrients deficiency, lipoproteins are particles 80 released from the liver and the gut to serve as hydrophobic carriers of TG, which are 81 glycerol-esterified long chain fatty acids (LCFA) [7]. TG-rich lipoproteins arise from the 82 gut as chylomicrons (CM) or from the liver as very-low-density lipoproteins (VLDL). As lipoprotein lipase (LPL) hydrolyses TG to provide lipids to metabolically active tissues, 83 CM evolve towards intermediate (IDL) and high-density lipoproteins (HDL) (Figure 1). In 84 physiological conditions plasma FFA and TG levels fluctuate in opposite directions. 85 86 Indeed, plasma FFA drop in post-prandial periods due to the antilipolytic action of insulin 87 onto adipose tissue. On the other hand, plasma TG rise due to lipid re-esterification and 88 complexification into CM in enterocytes after a meal [7].
- 89 Both FFA and TG-particles were shown to access the brain. The transport of FFA in the
- 90 brain was demonstrated using radiolabeled lipids [8] and an increased in brain FFA
- 91 transport was found associated to metabolic disease [9]
- How TG-rich particles access the brain is still debated. CM are likely too large to cross 92 93 the blood brain barrier (BBB), but smaller HDL and remnant CM (rCM) were shown to 94 access the brain [6]. The brain expresses high levels of receptors for VLDL, low-density lipoprotein (LDL), oxidized HDL or LDL receptor-related protein (LRP) [6]. Thus, the 95 presence of membrane and mitochondrial machineries dedicated respectively to the 96 97 transport and oxidation of lipids in neurons suggest a role for FFA as signaling molecules 98 [10]. For example, the TG-processing enzyme LPL is expressed in very defined brain 99 structures [6,11] suggesting that LPL-expressing neurons are selectively equipped to 100 detect and respond to TG-rich particles. Since circulating FFA and TG can access the

brain during pre- or post-prandial periods, dietary lipids under either forms seem good
 candidates to regulate feeding behaviors through a continuum process embedding
 signals staring from taste buds, gut-brain axis and/or through direct actions on brain cells

- 104 (neurons and astrocytes).
- 105

### 106 From the mouth to the brain: a taste for fat

107 Taste is a sense assessing the nature, quality, texture and composition of food, thereby driving either consumption or avoidance. Although five taste modalities are commonly 108 109 recognized (sour, salty, sweet, bitter, and umami), several studies have shown that 110 dietary LCFA can trigger brain responses and affect digestive functions and feeding 111 behavior [12,13] through the interaction with dedicated receptors located on taste bud 112 cells (TBC) [14] (Figure 2). The ability of TG to be locally and rapidly hydrolyzed into FFA 113 represents the major stimulus for the perception of fat-containing food in both humans and rodents [15,16]. Importantly, fat sensing requires complex inter-organized 114 mechanisms since FFA of different chains length can elicit different behavioral responses 115 116 (consumption vs avoidance/irritation) [17].

- 117 In the lingual epithelium, taste buds are highly specialized bulb-like structures composed 118 of 50-100 TBC organized into cell types-assembled clusters functionally connected to 119 sensory afferent fibers of cranial nerves VII and IX, also known as the chorda tympani 120 (CT) and glossopharyngeal (GL) nerves (Figure 2). At the cytoarchitectural level, the 121 nutrients-exposed apical region of taste buds is mainly composed of type I (glia-like cells), 122 II (gustatory receptors-expressing cells) and III (neuron-like cells) TBC which, through a complex and dynamic inter-TBC networks of transmitters (ATP, acetylcholine, 123 124 endocannabinoids, serotonin, GABA and norepinephrine), represent the main 125 chemosensory processors [18].
- Ingestion of very-low concentration of LCFA elicits DA release in the nucleus accumbens (NAc) [19] and fat consumption is rapidly accompanied by the activation of limbic, hedonic and motivational circuits in rodents and humans [12,20–22]. Therefore, it is unsurprising that a preference for high-fat foods is a widely shared and conserved trait in mammals. How do TBCs sense fat? During the prandial period, although TG are the major
- 131 components of dietary fats, TG-hydrolyzed LCFA seem to drive the oral chemosensory

132 stimulation and its associated behavioral outputs [23,24]. This chemosensory 133 detection/reception of dietary lipids relies, at least in part, on TBC-expressing membrane proteins, notably: GPR40 (or FFA1), GPR120 (or FFA4), CD36 and TRPM5 [17,25-27] 134 135 (Figure 2). While Gg-coupled receptors GPR40/FFA1 (rodent TBCs) and GPR120/FFA4 (human and rodent TBCs) have been reported to mediate fat-induced behavioral and 136 cellular responses [25,28], other studies have not led to the same conclusions [29,30], 137 138 thus complicating the molecular view of fat taste. More is known about the functions of 139 lingual CD36 (also known as fatty acid translocase (FAT)), a transmembrane glycoprotein 140 with high affinity for FFA and whose single nucleotide polymorphism (rs1761667) lowers 141 CD36 expression and fat gustatory perception in humans [24]. At the transductional level, 142 LCFA-activated CD36 and GPR120 both lead to increased Ca<sup>2+</sup> levels, through two 143 different but complementary intracellular signaling paths [31]. In particular, activation of 144 CD36 promotes PLC-dependent hydrolysis of PIP2 which gives rise to IP3 and DAG. In turn, IP3, by binding to its endoplasmic reticulum receptor, promotes Ca<sup>2+</sup> release. The 145 rise in Ca<sup>2+</sup> participates in activating the TRPM5 ion channel which, by 146 147 depolarizing/activating TBCs, mediates the detection and transmission of gustatory 148 signals [27,32].

Fat signal transduction also relies on the activation of MAP kinase cascade (MEKs-ERKs) via a mechanism requiring Ca<sup>2+</sup> signaling [33]. Importantly, down-regulation of ERK1/2 signaling cascade significantly decreased fat preference in mice [33], thereby indicating that chemosensory oral detection of fat requires both Ca<sup>2+</sup> and ERK dynamics.

Once stimulated, TBCs activate sensory afferent fibers conveying fat-taste information to the rostral nucleus tractus solitarius (NTS) which in turn relays such information to secondary brain structures, allowing integration and elaboration of fat signals and encoding of their rewarding/reinforcement values.

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#### 158 From the gut to the brain: interoceptive and integrative fat-sensing mechanisms

Food palatability, which promotes positive reinforcement and overeating, is traditionally described in terms of sensory (smell, taste) pleasantness, thereby embracing into the definition of "reward" conscious features such as liking, wanting, predictive value and insensitive salience [3]. However, it is of paramount importance to mention that

reinforcement mechanisms can also derive, at least in part, from unconscious and 163 164 interoceptive processes which rely on the detection of "reinforcers" (nutrients, energy 165 contents, circulating signals) from specialized internal detectors/sensors usually 166 inaccessible to conscious palatable features [2]. This can be easily summarized by the 167 fact that food consumption, preference and/or seeking, although facilitated by sensory 168 pleasantness, tightly depend on energy availability and contents which, by acting as 169 secondary reinforcers, represent conditioned signals predictive of the metabolic effects 170 of ingested nutrients [34–36].

171 The gastrointestinal (GI) tract, a highly heterogeneous chemosensory organ, is 172 specialized in sensing and absorbing nutrients, and, in virtue of its complex endocrine/paracrine networks, initiates several physiological processes (Figure 3). 173 174 Dietary lipids occupy a key place in the complex GI functions that control energy 175 homeostasis and feeding behaviors. Once in the GI lumen and upon the action of intestinal lipases, TG-derived lipids (diacylglycerol, monoacylglycerol and FFA) stimulate 176 177 specialized gut cells [37], notably enteroendocrine cells (EEC), which initiate hormonal 178 and gut-to-brain responses [38]. Indeed, EEC types are well-equipped with dietary fat 179 cellular sensors as they express FFA1, FFA4, GPR119 and CD36 [39-42] (Figure 3). In 180 line with this evidence, post-oral delivery of dietary lipids triggers the release of GLP-1 181 and CCK [35,43]. Such capability of EEC to detect dietary lipids contributes to their 182 modulatory functions.

Originally believed to be specific to distinct secretory mediators (CCK, GLP-1, GIP, secretin, PYY), recent breakthroughs have shown that this "*one mediator-one cell type*" theory is outdated as EEC located throughout the GI tract express and actively co-release a combination of different hormonal mediators and neurotransmitters [44–47] and even signal using specialized entero-neuronal synapses named neuropods [48,49]. Overall, these recent evidence indicate that fat-sensing at EEC level may trigger multiple modulatory responses.

Beside EEC, dietary lipids are also sensed, absorbed and metabolized by enterocytes (**Figure 3**). In fact, after gastric TG hydrolysis, FFA and 2-monoacylglycerol (2-MAG) are transported into the enterocytes either by passive diffusion or by protein-dependent mechanisms (CD36, FATP4). Within the enterocytes, 2-MAG and the majority of LCFA are re-esterified as TG, and either stored as cytosolic lipid droplets or packaged into
lipoproteins (mostly CM). Lipoproteins are therefore secreted into the circulation through
the lymphatic system to ultimately reach all organs [50].

Aside of FFA transport and metabolism, lipids can directly signal onto specialized receptors. In that regards, studies using intragastric fat infusions have highlighted several redundant mechanisms through which dietary lipid sensing in the gut regulates feeding (**Figure 3**):

- (1) Luminal TG-hydrolyzed oleic acid is transported into enterocytes via a CD36-201 202 dependent mechanism and converted into oleoylethanolamide (OEA). OEA acts as a 203 satiety signal through a mechanism that is still not fully elucidated, mostly via the 204 activation of the lipid-activated transcription factor peroxisome proliferator-activated receptors- $\alpha$  (PPAR- $\alpha$ ) and the mediation of the vagus nerve [51–54]. However, some 205 206 studies have also suggested alternative mechanisms by which LCFA and byproducts of TG (FFA and 2-MAG), rather than OEA, may function as immediate signals of feeding 207 onto the DA system [35], while non-vagal afferent mechanisms could relay OEA-induced 208 209 satiety effects [55].
- (2) The inhibition of gastric emptying by lipids-triggered GPCRs-dependent
   enteroendocrine release of GLP-1, CCK and PYY [39,42,56].
- 212 (3) The action of lipid oxidation byproducts from enterocytes or microbiota, such as ketone
- bodies/beta-hydroxy butyrate (BHB), which signal through spinal afferent fibers [57].
- 214

215 Lipid sensing in the gut-brain axis can shape how hypothalamic hunger-activated neurons 216 respond to food cues. A recent study using cell type-specific in vivo Ca2+ dynamics in 217 Agouti-related protein (AgRP)-expressing neurons provides evidence that glucose- and 218 lipids-dependent signals initiated in the gut are routed through redundant and segregated 219 nervous afferent routes to impinge on hypothalamic responses to food cues [58]. This 220 selectivity to nutrients was ascribed to distinct nervous routes of the gut-brain axis where vagal afferents transmitted intestinal lipid detection and spinal gut-brain inputs from the 221 222 intestinal and hepatic portal vein signaled glucose detection. Both paths serve as 223 modulators of AgRP-neurons activity, thereby promoting fullness and satiation [58]. Of 224 note, obesity and exposure to high-fat have been shown to selectively impair lipids, but

not carbohydrates, signaling from gut $\rightarrow$ AgRP-neurons [59,60]. These results suggest that gut-brain fat sensing represents a privileged substrate for obesity-induced maladaptations.

Interestingly, despite promoting satiation, intragastric infusion of lipids elicits dopamine
 release [35,61], suggesting that reward/reinforcement encoding and satiation are not
 functional antagonists.

Beside their endocrine actions, gut hormones released upon intestinal lipid sensing can also act on sensory vagal afferents which highly express receptors for GLP-1, CCK and PYY [62]. Interestingly, in addition to detecting hormonal and mechanical signals [63], vagal sensory afferents can be directly modulated by dietary signals. In fact, vagal neurons express the molecular machinery required to sense circulating lipids, notably long- and medium-chain fatty acids [64,65], and through a polysynaptic gut-brain circuit they may convey signals that are translated into reinforcement by DA-neurons [66].

238 One would therefore argue that the blunting action of OEA over food intake (satietogenic 239 signal) may also reduce the hedonic drive to food consumption. However, recent 240 breakthroughs have elegantly shown that OEA promotes DA release in the striatum, 241 through a PPARα-mediated vagus-dependent action [61]. This DA release depends on 242 metabolic states (low-fat vs high-fat fed mice), and rerouting of the GI tract by Roux-en-243 Y Gastric Bypass (RYGB) mobilized small intestine OEA, an affect associated with a 244 vagus-dependent and diet-mediated enhancement in striatal dopamine release [53]. 245 Beside the peripheral OEA-mediating actions onto central DA release, intra-gastric or intraperitoneal administration of fat emulsions also trigger DA activity [34,36,61,67]. This 246 247 indicates that dietary and diet-derived lipids engage vagus-dependent periphery-to-brain 248 circuits which regulate dopamine release and reward events.

Although the detailed mechanisms underlying how gut sensing of dietary lipids may dampen food intake despite promoting reinforcement-like events are not fully elucidated, it is worth to mention that both vagal and spinal sensory afferents may collaborate in detecting food constituents through heterogeneous neuronal networks [68–70]. Therefore, according to their intrinsic cell type-specificity, regionalized arborization into NTS territories and specific synaptic contacts onto distinct NTS cell types, they may convey different integrative information to the brainstem. In turn, NTS cell types, by

- 256 projecting to second order brain regions [71-73], may signal to different downstream
- 257 structures involved in the regulation of homeostatic (hypothalamus) and hedonic feedings
- 258 (mesolimbic and nigrostriatal dopamine circuits). Finally, the precise timing by which lipids
- 259 (and glucose) pass through and signal into digestive segments, might directly account for
- the different phases by which each nutrient triggers specific brain responses.
- 261

#### 262 Central action of dietary lipids: between reward and satiety

263 Dietary and diet-derived signals can also directly act on distinct brain circuits and discrete 264 cell types which regulate hunger/satiety and reinforcement. In fact, although the 265 mechanisms underlying their entry into the brain remain largely unknown, pioneering 266 studies have indicated that circulating lipids can reach the brain and be uptaken by 267 neurons by crossing the BBB [8,74] (Figure 4). Moreover, although not specifically 268 demonstrated for lipids, new evidence highlight the key role of the lymphatic system in 269 allowing brain access to large and small molecules [75]. Neurons are fully equipped with 270 the molecular components capable of recognizing and metabolizing dietary lipids [76].

- 271 Indeed, among central brain regions, the hypothalamus has been long recognized as a 272 key sensor of circulating lipids [10]. Notably, hypothalamic cells (neurons and/or 273 astrocytes) express a variety of membrane proteins capable of detecting and handling 274 extracellular FFAs [77,78] and also respond to circulating TG [79]. Importantly, 275 hypothalamic cells also contain the lipoprotein lipase LPL which, by locally hydrolyzing 276 TG into 2-MAG and FFAs, contributes to the regulation of food intake and energy balance 277 [80,81]. In fact, downregulation of LPL in hypothalamic astrocytes and/or neurons leads to increased body weight and glucose intolerance [81,82]. Beyond LPL, the hormone-278 279 sensitive lipase (HSL), hydrolyzing tri- and diglycerides within the hypothalamus, may 280 also play a fundamental role in regulating food intake and body homeostasis [83]. In fact, HSL deficiency triggers sustained food intake in high-fat diet (HFD)-fed mice, resulting in 281 increased body weight gain [83]. Overall, these results strongly indicate that lipids-282 283 sensing functions of hypothalamic cells are pivotal in regulating energy homeostasis as 284 their silencing exacerbates pro-obesity features.
- Beside the hypothalamus, recent studies have clearly pointed to the midbrain dopamine
  system as a central target where circulating dietary TG may act by influencing molecular,

cellular and behavioral reinforcement features [11,84–86]. This dopamine (reward) circuit, consists of midbrain nuclei, notably the ventral tegmental area (VTA) and the substantia nigra *pars compacta* (SNc), densely projecting to dopaminoceptive structures such as the nucleus accumbens (NAc) and the dorsal striatum (DS). This brain circuit is strongly impaired by both short- and long-term exposure to HFD [87–89] as well as by perinatal dietary exposure to maternal HFD feeding [90,91].

- 293 Although the consequences of HFD exposure on the dopaminergic system are well-294 studied, whether and how dietary lipids as such can modulate the activity of the dopamine 295 circuit is still a matter of intense investigations. Interestingly, VTA DA-neurons contain 296 FFA-associated proteins, such as the fatty acid transport proteins (FATP1 and FATP4), 297 fatty acid-binding proteins (FABP3) [86], as well as LPL [11], thereby highlighting the 298 capacity of DA-neurons to detect and metabolize circulating lipids. In fact, LCFA, such as 299 the oleic and palmitic acids (OA, PA), and/or long-term central delivery of TG, modulate 300 the activity of VTA DA-neurons by reducing their neuronal firing rate and therefore by 301 modulating reward-associated events [11,85,86]. Hence, the presence of LPL in 302 dopamine and dopaminoceptive neurons might represent an additional arsenal to 303 selectively respond to postprandially released TG. It is interesting to note that while 304 sensory information routed by the vagus nerve was shown to modulate DA release from 305 SNc DA-neurons [66], Lpl mRNA was found to be among the 5 most robust markers 306 differentially expressed in the VTA compared to the SNc [92], thereby suggesting that 307 VTA could directly detect postprandial circulating TG while SNc DA-neurons would rather 308 respond to gut-borne stimuli routed by vagal afferents.
- 309

310 At the postsynaptic level and throughout the rostro-caudal axis, DS and NAc 311 dopaminoceptive neurons, also known as GABAergic spiny projection neurons (SPNs), are anatomically and functionally segregated into two major families according to the 312 expression of either DA D1 or D2 receptors (D1R- and D2R-SPNs) [93-95]. Recently, 313 314 striatal and accumbal SPNs, in both humans and rodents, have been shown to express 315 the LPL and respond to circulating TG [11]. Notably, central delivery of dietary TG resulted 316 in a blunted activity of DA-dependent intracellular signaling pathways (MAPK, PKA and 317 mTOR) and concomitant increase of  $\beta$ -arrestin-dependent signaling (GSK3- $\beta$ ) within the

DS/NAc territories. In addition, TG were shown to reduce the excitability of D2R-SPNs, 318 319 sparing D1R-SPNs [11] (Figure 4). Importantly, cell type-specific deletion of LPL in D2R-320 SPNs increased neuronal excitability [11], thereby indicating that local metabolism of TG 321 may be critical in gating the neuronal activity of dopaminoceptive neurons. Of interest, 322 central delivery of dietary TG, although associated to dampened food intake and reduced 323 responses to psychostimulants [11,84], was accompanied by enhanced reward sensitivity 324 and positive reinforcement [11], indicating that circulating TG may possess reward-like 325 properties. This evidence suggests that dietary TG, and eventually their TG-derived FFA, 326 may inhibit D2R-SPNs, therefore bypassing the inhibitory action of endogenous DA onto 327 D2R of D2R-SPNs and disinhibiting D2R-SPNs-downstream targets. Such dietary 328 inhibition of D2R-SPNs may then participate in promoting reinforcement as reported by 329 cell type-specific manipulation of D2R-SPNs [96–98]. Of note, D1R-SPNs also express 330 LPL but they do not seem to respond to TG concentrations capable of modulating DRD2-SPNs excitability [11]. In line with that view, cognitive impairments caused by PUFAs 331 332 deficiency could be corrected by restoring PUFAs balance in D2R-SPNs but not D1R-SPNs [99]. 333

334 It is worth to mention that D2R is also expressed in DS/NAc cholinergic interneurons

335 (ChINs [100]) but that this cell type seems to lack Lpl mRNA [11]. Nevertheless, future

investigations aimed at unbiasedly studying the impact of dietary lipids on the cellular

337 physiology of distinct striatal cell types are definitely needed.

- Overall, these recent studies suggest an evolutionary acquired ability of D2R-SPNs to directly respond to circulating dietary lipids. This hypothesis nicely fits with other studies indicating that D2R-neurons are highly susceptible substrates for central maladaptations induced by obesogenic environments and altered cognitive functions. In fact, the D2R is commonly pointed as a molecular culprit potentially involved in the development and/or maintenance of food-related reward deficits and associated metabolic alterations [101– 106].
- 345 D2R abundance predicts compulsive susceptibility in rats [103] and exposure to lipid-rich
- diet triggers impulsive feeding independently from body weight changes [101]. Moreover,
- 347 knock down of striatal D2R expression leads to compulsive eating in rats exposed to high-
- 348 fat food [103].

349 This observation is also supported by studies in humans showning that TG metabolism

correlates with brain responses to food cues in a direction that is influenced by genetic
 traits affecting D2R signaling [11,107].

352 Whether dietary lipids as such may directly and causally be involved in promoting the 353 dysfunctions of D2R-SPNs and D2R-coupled signaling remains to be fully established. It 354 is interesting to note that central increase of circulating TG counteracts D2R-dependent 355 signaling pathways but does not impact D1R-coupled signaling events [11]. Although 356 molecular mechanistic insights are still under investigation, it is worth to mention that a 357 role for the fatty acid binding protein FABP3 has been highlighted in modulating D2R 358 striatal functions [108]. Indeed, how striatal SPNs compute lipids-carried information at 359 the cellular and circuit level represent the next step in the understanding of neuronal lipid 360 sensing mechanisms.

361

#### 362 **Concluding remarks and future perspectives**

363 In this review, we have highlighted and discussed the most recent discoveries related to whether and how dietary lipids control ingestive behavior. Overall, dietary lipids, 364 365 notably TG and their derived FFA, can govern appetite and reinforcement through the 366 modulation of DA release/signaling by multimodal mechanisms of lipid sensing. These 367 mechanisms involve nervous inputs arising from the oral cavity and from various 368 compartments of digestive tract (mouth-to-brain and gut-to-brain signals) as well as direct neuromodulatory actions of dietary TG/FFA on cell type-specific neurons of the 369 370 mesolimbic circuit (central detection). Traditionally believed to solely serve as energy 371 substrates, dietary lipids are nowadays also functionally involved in regulating brain 372 systems. Dietary lipid-dependent actions encompass a variety of intracellular mechanisms ranging from GPCR signaling, direct and indirect allosteric regulation of 373 374 receptors and channels, release of byproduct messengers from mitochondrial lipid oxidation and transcriptional regulation via lipid sensing transcription factors. This is 375 376 ensured by the presence of lipids-associated molecular detectors in key cellular elements 377 located at different strategic levels: mouth, gut, brain. Such complexity of integrative 378 mechanisms reveals a highly sophisticated regulation of pre-prandial, prandial and post-379 prandial fat signals which collectively contribute to the reinforcing aspects of food, and

380 most probably also to cognitive functions associated with the encoding of food cues. It is 381 interesting to highlight that at the physiological level dietary lipid sensing mechanisms 382 may follow a time-dependent process: fast (mouth-to-brain, taste), intermediate (gut-to-383 brain, interoception) and slow (neuronal sensing) actions. Moreover, this may strongly 384 depend on nutritional/metabolic states and endogenous/exogenous sources of lipids as 385 during postprandial and fed states circulating TG represent the main source of lipids, 386 whilst in fasting and energy-deprived conditions circulating FFAs are increased. However, 387 in conditions of abnormal circulating lipids including (but not restricted to) obesity, neural 388 substrates involved in reward and cognitive processing are altered.

389 It is therefore tempting to hypothesize that dietary lipid sensing mechanisms within neural 390 circuits supporting appetite and reinforcing behaviors may undergo functional 391 maladaptations during obesity, as already observed in the tongue [109], gut [110] and 392 hypothalamic arcuate nucleus [59,60]. In fact, whether long-term maladaptive lipidsinduced molecular and synaptic responses may occur within the reward system during 393 394 obesity remain to be established. In line with this hypothesis we have shown that short-395 term binge consumption of palatable diet was able to downregulate the expression of LPL 396 mRNA in the nucleus accumbens [11]. Future studies are now warranted to unveil in-397 depth mechanisms of cellular lipid sensing in physiological and pathological contexts. 398 Moreover, the emerging field of lipid sensing could also pave the way to explore the 399 etiopathology of other reward-related psychiatric and metabolic disorders such as 400 anorexia nervosa, bulimia and binge eating [111]. Indeed, recent discoveries and current 401 hypotheses also raise new interesting challenges that need to be tackled to fully depict a 402 novel conceptual framework that sees dietary lipids as key modulators of integrative 403 functions (see Outstanding Questions).

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## 414 **Declaration of Interests**

415 The authors declare no conflicts of interest.

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#### 664 **Figure legends**

665

# **Figure 1. The physiology of fat sensing throughout the body.**

667 Oral perception of dietary fat requires the action of lingual lipases which hydrolyze TG 668 into free fatty acids (FFA) whose presence is detected by taste bud cells. Encoded 669 information is then rapidly sent toward the brain via the chorda tympani (VII) and 670 glossopharyngeal (IX) nerves. After ingestion/digestion, dietary lipids can promote gut-tobrain communication and/or enter into the gut-liver transformative cycles. In the latter, 671 672 FFA transported and re-esterified by enterocytes are packaged into TG-rich chylomicrons 673 (CM) and released into the lymphatic and circulatory systems. The breakdown of 674 lipoproteins through the action of lipoprotein lipase (LPL) allows the extraction of TG from 675 large CM/VLDL leading to intermediate or high-density particles (IDL, HDL) and 676 chylomicron remnants (rCM) recaptured by the liver. FFA and TG directly or indirectly signal to the brain. This figure was created using BioRender. 677

678

#### 679 Figure 2. Fat sensing by taste bud cells.

680 Type 3 taste bud cells (TBC) express gustatory receptors for sweet, umami and bitter 681 tastes. However, they also express receptors that can be activated by FFA released from 682 dietary TG by the action of lingual lipases. FFA can activate lipid sensor CD36 and G-683 coupled receptor 40 (GPR40/FFAR1) and 120 (GPR120/FFAR1). The activation of Src 684 kinase as a consequence of CD36 activation leads the recruitment of phospholipase C (PLC), the increase of intracellular Ca<sup>2+</sup> and the activation of ERK1/2 through the 685 calmodulin activated kinase (CaMKII). PLC promotes the release of intracellular Ca<sup>2+</sup> 686 687 through inositol 3 phosphate (IP3). Delayed Rectifying K+(DRK, Kv1.5) channels can 688 directly or indirectly respond to FFA. Once activated by the detection of dietary lipids, TBC 689 will release neurotransmitters and messengers allowing the transfer of lipids-associated 690 information to the nucleus tactus solitarius (NTS) through the cranial nerves VII et IX. This 691 figure was created using BioRender.

692

## 693 Figure 3. Gut lipid sensing: mechanisms and circuits.

694 During intestinal transit, dietary TG are hydrolyzed by luminal lipases. Released 2-695 monoacylglycerol (2-MAG) and FFA will act on lipid sensors expressed onto enteroendocrine cells (EEC) (1, yellow circles). While TG-derived FFA can initiate 696 697 signaling events by binding to CD36, G-coupled receptor 40 (GPR40/FFAR1) and 120 698 (GPR120/FFAR4), 2-MAG can signal by GPR119 (2, red circles). Upon activation of lipid 699 receptors located on EEC membranes, gut hormones and neurotransmitters can be 700 released from EEC (3, blue circles). In turn, gut hormones can enter the general 701 circulation or directly stimulate vagal afferents.

702 Within the enterocytes, FFA are re-esterified and packaged into chylomicrons (CM) to 703 ultimately reach the lymphatic system (4, green circles). A portion of FFA entering the 704 enterocytes can serve either as substrate for the synthesis of N-acylethanolamines and 705 produce the bioactive N-oleoylethanolamine (OEA) (5, grey circles), or enter lipid 706 oxidation processes whom beta-hydroxy butyrate (BHB) byproduct (6, brown circles) can 707 also signal through the circulation and/or afferent fibers. Vagal afferent fibers, ascending 708 through the nodose ganglia (NG), respond to OEA while spinal afferent fibers routed 709 through the dorsal root ganglia (DRG) respond to BHB produced by enterocytes and 710 microbiota. OEA, BHB, gut hormones and nutrients also signal through portal vein 711 metabolic sensors and liver-brain afferent fibers. This figure was created using 712 BioRender.

713

# Figure 4. Direct and indirect physiological routes of lipid sensing in the reward system.

716 (A) Dietary lipid sensing modulates dopamine (DA) release and signaling through 717 segregated direct and indirect physiological routes. Intestinal detection of lipids is conveyed to the striatum via a vagus→nucleus tractus solitarius (NTS)→parabrachial 718 719 nucleus (PBN)  $\rightarrow$  substantia nigra (SNc) path (blue). Circulating lipids can also directly 720 modulate DA-neurons in the ventral tegmental area (VTA) and dopaminoceptive neurons 721 in the dorsal striatum (DS) and nucleus accumbens (NAc). (B) The lipoprotein lipase (LPL) in the brain microvasculature releases free fatty acids (FFA) from triglyceride (TG)-722 723 rich circulating particles such as chylomicrons (CM). Smaller in size, high-density 724 lipoprotein (HDL) can cross the capillaries through transcytosis and via astrocyte endfeet. 725 (C) FFA can enter the neuron through membrane fatty acids transporter (FATP<sub>1/4</sub>) or via 726 the hydrolysis of TG from TG-particle docked on lipoprotein receptor (LDL-R). In the VTA, TG/FFA-mediated signaling was shown to decrease firing activity. In the striatum, 727 728 dopamine D2 receptor (D2R)-expressing spiny projection neurons (SPNs) respond to 729 TG/FFA through a mechanism that involves the LPL. TG/FFA modulate bona fide D2R-730 coupled intracellular signaling events and reduce neuronal excitability. Altogether, lipidsregulated circuits and neuronal responses concur in scaling reward-driven behaviors. 731 732 Abbreviations: protein kinase A (PKA), extracellular signal-regulated kinase (ERK), 733 ribosomal protein S6 (rpS6), ribosomal protein S6 kinase (S6K), mechanistic target of 734 rapamycin (mTOR), dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP-32), glycogen synthase kinase 3 beta (GSK-3b). This figure was created using 735 736 BioRender.







