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

2

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26 physiology

27 **Abstract**

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

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

40 Physiological mechanisms optimizing feeding behaviors have been selected during  
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 ubiquitous availability of palatable and energy-dense diets challenges the  
44 highly conserved and sophisticated systems controlling food intake. It is clear that,  
45 although inheritable genetic traits might contribute as risk factors for the development of  
46 metabolic disorders, the consumption of calorie-dense food beyond metabolic needs  
47 arises as a primary culprit in the obesity pandemic.

48 During the last decades, the brain has emerged as the master regulator of energy  
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)  
62 (**Figure 1**). This multimodal integration has been recently highlighted in humans where  
63 immediate orosensory and subsequent post-ingestive signals derived from a palatable  
64 food (milkshake) led to two temporally separated waves of DA release in the ventral and  
65 dorsal striatum, respectively [5].

66 Among nutrients (e.g. glucose, amino acids), dietary and circulating lipids have emerged  
67 as critical modulators of brain functions. Indeed, foods rich in fat are highly reinforcing.  
68 Despite orosensory perception and organoleptic components of food are known to be  
69 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

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

77 Triglyceride (TG)-rich lipoproteins and free fatty acids (FFA) bound to albumin represent  
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  
83 lipoprotein lipase (LPL) hydrolyses TG to provide lipids to metabolically active tissues,  
84 CM evolve towards intermediate (IDL) and high-density lipoproteins (HDL) (**Figure 1**). In  
85 physiological conditions plasma FFA and TG levels fluctuate in opposite directions.  
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].

92 How TG-rich particles access the brain is still debated. CM are likely too large to cross  
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  
95 lipoprotein (LDL), oxidized HDL or LDL receptor-related protein (LRP) [6]. Thus, the  
96 presence of membrane and mitochondrial machineries dedicated respectively to the  
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

101 brain during pre- or post-prandial periods, dietary lipids under either forms seem good  
102 candidates to regulate feeding behaviors through a continuum process embedding  
103 signals starting 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  
108 driving either consumption or avoidance. Although five taste modalities are commonly  
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  
114 and rodents [15,16]. Importantly, fat sensing requires complex inter-organized  
115 mechanisms since FFA of different chains length can elicit different behavioral responses  
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  
123 complex and dynamic inter-TBC networks of transmitters (ATP, acetylcholine,  
124 endocannabinoids, serotonin, GABA and norepinephrine), represent the main  
125 chemosensory processors [18].

126 Ingestion of very-low concentration of LCFA elicits DA release in the nucleus accumbens  
127 (NAc) [19] and fat consumption is rapidly accompanied by the activation of limbic, hedonic  
128 and motivational circuits in rodents and humans [12,20–22]. Therefore, it is unsurprising  
129 that a preference for high-fat foods is a widely shared and conserved trait in mammals.

130 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  
134 proteins, notably: GPR40 (or FFA1), GPR120 (or FFA4), CD36 and TRPM5 [17,25–27]  
135 (**Figure 2**). While Gq-coupled receptors GPR40/FFA1 (rodent TBCs) and GPR120/FFA4  
136 (human and rodent TBCs) have been reported to mediate fat-induced behavioral and  
137 cellular responses [25,28], other studies have not led to the same conclusions [29,30],  
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  $Ca^{2+}$  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  
145 turn, IP3, by binding to its endoplasmic reticulum receptor, promotes  $Ca^{2+}$  release. The  
146 rise in  $Ca^{2+}$  participates in activating the TRPM5 ion channel which, by  
147 depolarizing/activating TBCs, mediates the detection and transmission of gustatory  
148 signals [27,32].

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

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

157

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

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

163 reinforcement mechanisms can also derive, at least in part, from unconscious and  
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  
173 endocrine/paracrine networks, initiates several physiological processes (**Figure 3**).  
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  
176 intestinal lipases, TG-derived lipids (diacylglycerol, monoacylglycerol and FFA) stimulate  
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.

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

190 Beside EEC, dietary lipids are also sensed, absorbed and metabolized by enterocytes  
191 (**Figure 3**). In fact, after gastric TG hydrolysis, FFA and 2-monoacylglycerol (2-MAG) are  
192 transported into the enterocytes either by passive diffusion or by protein-dependent  
193 mechanisms (CD36, FATP4). Within the enterocytes, 2-MAG and the majority of LCFA

194 are re-esterified as TG, and either stored as cytosolic lipid droplets or packaged into  
195 lipoproteins (mostly CM). Lipoproteins are therefore secreted into the circulation through  
196 the lymphatic system to ultimately reach all organs [50].

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

201 (1) Luminal TG-hydrolyzed oleic acid is transported into enterocytes via a CD36-  
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  
205 receptors- $\alpha$  (PPAR- $\alpha$ ) and the mediation of the vagus nerve [51–54]. However, some  
206 studies have also suggested alternative mechanisms by which LCFA and byproducts of  
207 TG (FFA and 2-MAG), rather than OEA, may function as immediate signals of feeding  
208 onto the DA system [35], while non-vagal afferent mechanisms could relay OEA-induced  
209 satiety effects [55].

210 (2) The inhibition of gastric emptying by lipids-triggered GPCRs-dependent  
211 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  
213 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*  $Ca^{2+}$  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  
221 vagal afferents transmitted intestinal lipid detection and spinal gut-brain inputs from the  
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

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

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

231 Beside their endocrine actions, gut hormones released upon intestinal lipid sensing can  
232 also act on sensory vagal afferents which highly express receptors for GLP-1, CCK and  
233 PYY [62]. Interestingly, in addition to detecting hormonal and mechanical signals [63],  
234 vagal sensory afferents can be directly modulated by dietary signals. In fact, vagal  
235 neurons express the molecular machinery required to sense circulating lipids, notably  
236 long- and medium-chain fatty acids [64,65], and through a polysynaptic gut-brain circuit  
237 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 (satiogenic  
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 PPAR $\alpha$ -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  
246 intraperitoneal administration of fat emulsions also trigger DA activity [34,36,61,67]. This  
247 indicates that dietary and diet-derived lipids engage vagus-dependent periphery-to-brain  
248 circuits which regulate dopamine release and reward events.

249 Although the detailed mechanisms underlying how gut sensing of dietary lipids may  
250 dampen food intake despite promoting reinforcement-like events are not fully elucidated,  
251 it is worth to mention that both vagal and spinal sensory afferents may collaborate in  
252 detecting food constituents through heterogeneous neuronal networks [68–70].  
253 Therefore, according to their intrinsic cell type-specificity, regionalized arborization into  
254 NTS territories and specific synaptic contacts onto distinct NTS cell types, they may  
255 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  
260 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  
278 to increased body weight and glucose intolerance [81,82]. Beyond LPL, the hormone-  
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,  
281 HSL deficiency triggers sustained food intake in [high-fat diet \(HFD\)](#)-fed mice, resulting in  
282 increased body weight gain [83]. Overall, these results strongly indicate that lipids-  
283 sensing functions of hypothalamic cells are pivotal in regulating energy homeostasis as  
284 their silencing exacerbates pro-obesity features.

285 Beside the hypothalamus, recent studies have clearly pointed to the [midbrain](#) dopamine  
286 system as a central target where circulating dietary TG may act by influencing molecular,

287 cellular and behavioral reinforcement features [11,84–86]. [This dopamine \(reward\)](#) circuit,  
288 consists of midbrain nuclei, notably the ventral tegmental area (VTA) and the substantia  
289 nigra *pars compacta* (SNc), densely projecting to dopaminoceptive structures such as the  
290 nucleus accumbens (NAc) and the dorsal striatum (DS). This brain circuit is strongly  
291 impaired by both short- and long-term exposure to HFD [87–89] as well as by perinatal  
292 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),  
312 are anatomically and functionally segregated into two major families according to the  
313 expression of either DA D1 or D2 receptors (D1R- and D2R-SPNs) [93–95]. Recently,  
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

318 DS/NAc territories. In addition, TG were shown to reduce the excitability of D2R-SPNs,  
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 dopaminergic 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-  
331 SPNs excitability [11]. In line with that view, cognitive impairments caused by PUFAs  
332 deficiency could be corrected by restoring PUFAs balance in D2R-SPNs but not D1R-  
333 SPNs [99].

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  
336 investigations aimed at unbiasedly studying the impact of dietary lipids on the cellular  
337 physiology of distinct striatal cell types are definitely needed.

338 Overall, these recent studies suggest an evolutionary acquired ability of D2R-SPNs to  
339 directly respond to circulating dietary lipids. This hypothesis nicely fits with other studies  
340 indicating that D2R-neurons are highly susceptible substrates for central maladaptations  
341 induced by obesogenic environments and altered cognitive functions. In fact, the D2R is  
342 commonly pointed as a molecular culprit potentially involved in the development and/or  
343 maintenance of food-related reward deficits and associated metabolic alterations [101–  
344 106].

345 D2R abundance predicts compulsive susceptibility in rats [103] and exposure to lipid-rich  
346 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 [showing](#) that TG metabolism  
350 correlates with brain responses to food cues in a direction that is influenced by genetic  
351 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  
364 related to whether and how dietary lipids control ingestive behavior. Overall, dietary lipids,  
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  
369 neuromodulatory actions of dietary TG/FFA on cell type-specific neurons of the  
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  
373 mechanisms ranging from GPCR signaling, direct and indirect allosteric regulation of  
374 receptors and channels, release of byproduct messengers from mitochondrial lipid  
375 oxidation and transcriptional regulation via lipid sensing transcription factors. This is  
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 lipids-  
393 induced molecular and synaptic responses may occur within the reward system during  
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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- 663

664 **Figure legends**

665

666 **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-to-  
671 brain communication and/or enter into the gut-liver transformative cycles. In the latter,  
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  
677 signal to the brain. This figure was created using BioRender.

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  
685 (PLC), the increase of intracellular  $\text{Ca}^{2+}$  and the activation of ERK1/2 through the  
686 calmodulin activated kinase (CaMKII). PLC promotes the release of intracellular  $\text{Ca}^{2+}$   
687 through inositol 3 phosphate (IP3). Delayed Rectifying  $\text{K}^+$ (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  
 696 enteroendocrine cells (EEC) (1, yellow circles). While TG-derived FFA can initiate  
 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.

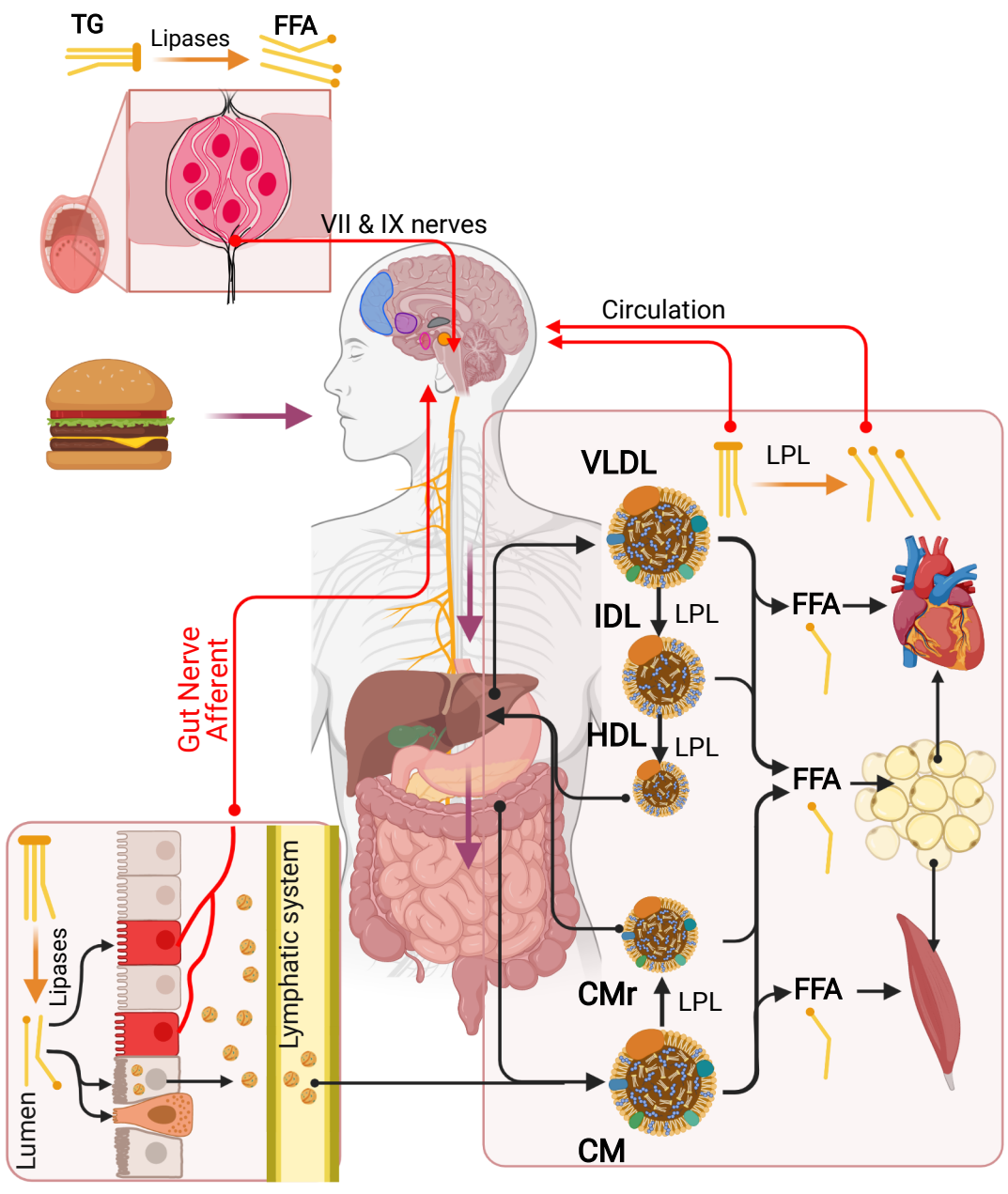
702 Within the enterocytes, FFA are re-esterified and packaged into chylomicrons (CM) to  
 703 ultimately reach the lymphatic system (4, green circles). A portion of FFA entering the  
 704 enterocytes can serve either as substrate for the synthesis of N-acylethanolamines and  
 705 produce the bioactive 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.

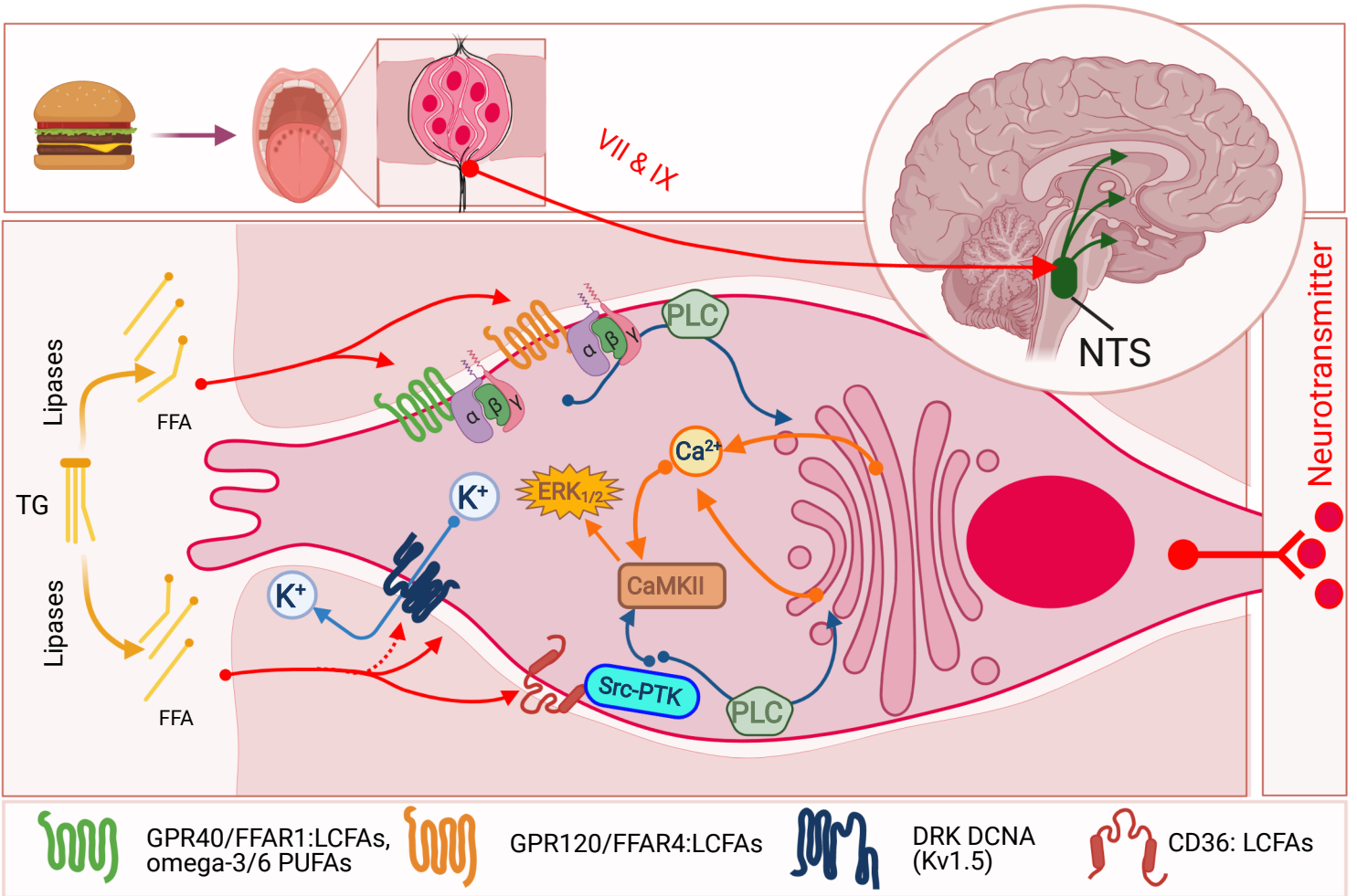
713

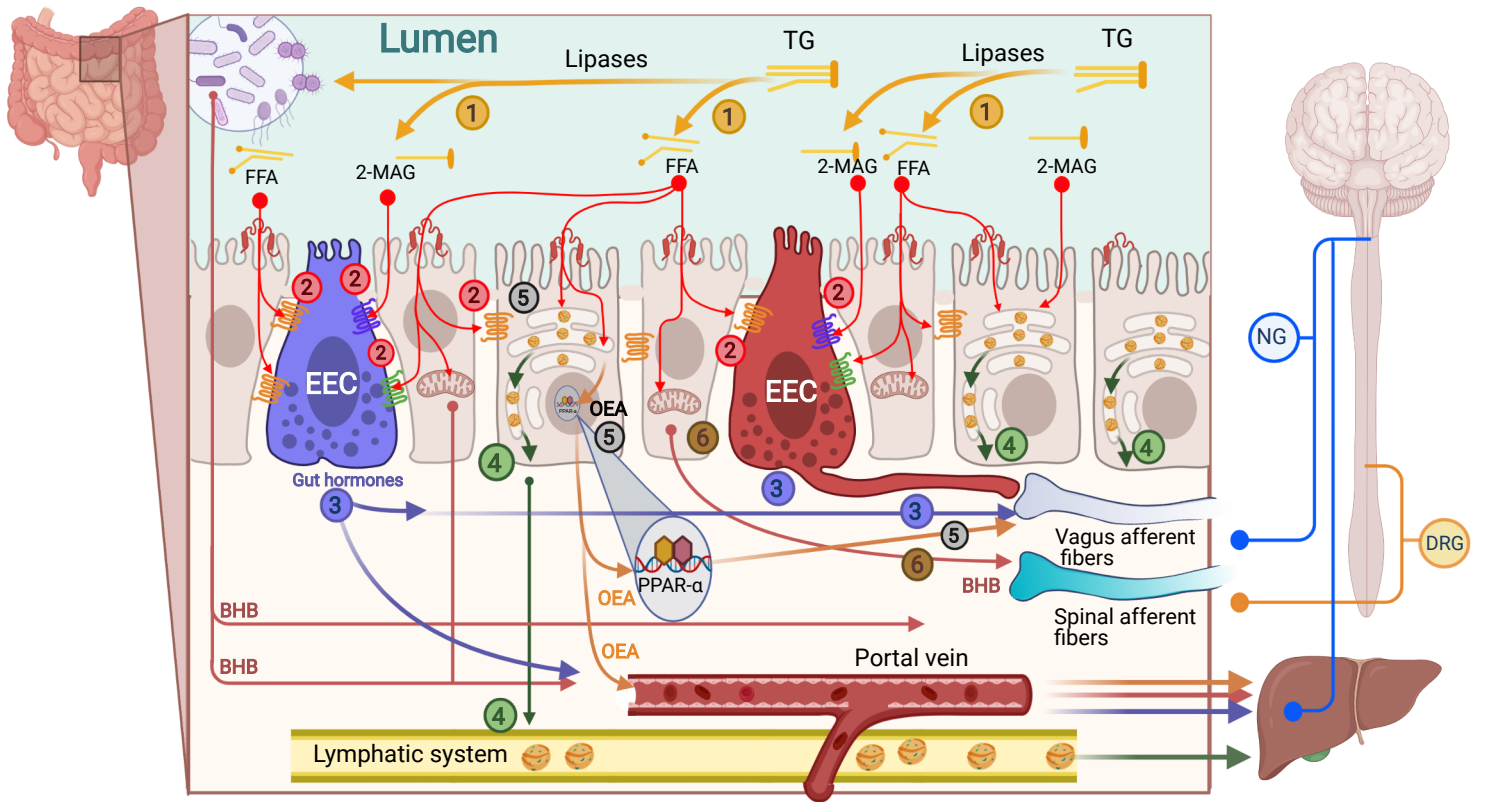
714 **Figure 4. Direct and indirect physiological routes of lipid sensing in the reward**  
 715 **system.**

716 (A) Dietary lipid sensing modulates dopamine (DA) release and signaling through  
 717 segregated direct and indirect physiological routes. Intestinal detection of lipids is  
 718 conveyed to the striatum via a vagus→nucleus tractus solitarius (NTS)→parabrachial  
 719 nucleus (PBN)→ 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  
 722 (LPL) in the brain microvasculature releases free fatty acids (FFA) from triglyceride (TG)-  
 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,  
727 TG/FFA-mediated signaling was shown to decrease firing activity. In the striatum,  
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, lipids-](#)  
731 [regulated circuits and neuronal responses concur in scaling reward-driven behaviors](#).  
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 \(DARPP-](#)  
735 [32\), glycogen synthase kinase 3 beta \(GSK-3b\)](#). This figure was created using  
736 BioRender.








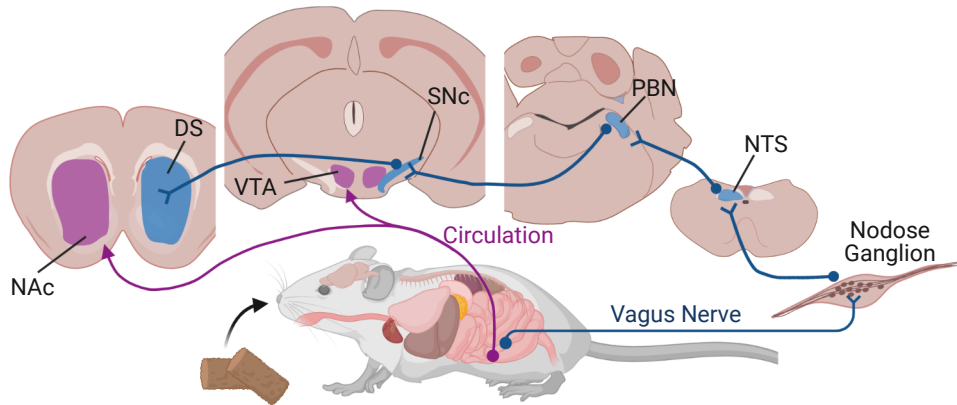
 GPR40/FFAR1:LCFAs, omega-3/6 PUFAs

 GPR120/FFAR4 :LCFAs

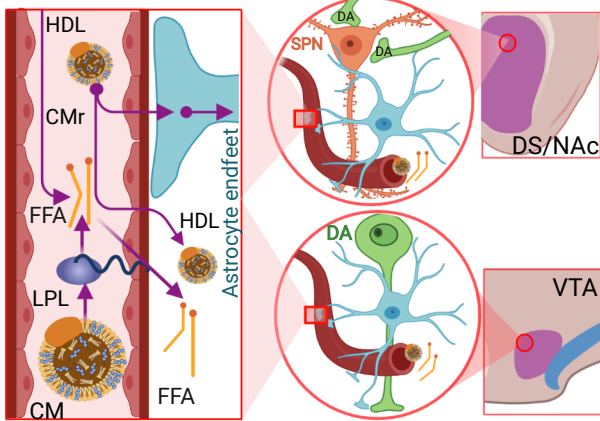
 GPR119:N-acylethanol-amines (OEA, PEA)

 CD36: LCFAs

A



B



C

