Yin-Yang control of energy balance by lipids in the hypothalamus: the endocannabinoids vs bile acids case

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Highlights

- Endocannabinoids and bile acids act as Yin-Yang regulators of the body energy needs

- Master lipid sensors in the brain could integrate the actions of multiple lipid signals

- Obesity might originate from dysregulation of master lipid sensors in the brain

Abstract

Obesity is a chronic and debilitating disorder that originates from alterations in energy-sensing brain circuits controlling body weight gain and food intake. The dysregulated syntheses and actions of lipid mediators in the hypothalamus induce weight gain and overfeeding, but the molecular and cellular underpinnings of these alterations remain elusive.

In response to changes in the nutritional status, different lipid sensing pathways in the hypothalamus direct body energy needs in a Yin-Yang model. Endocannabinoids orchestrate the crosstalk between hypothalamic circuits and the sympathetic nervous system to promote food intake and energy accumulation during fasting, whereas bile acids act on the same top-down axis to reduce energy intake and possibly storage after the meal. In obesity, the bioavailability and downstream cellular actions of endocannabinoids and bile acids are altered in hypothalamic neurons involved in body weight and metabolic control. Thus, the onset and progression of this disease might result from an imbalance in hypothalamic sensing of multiple lipid signals, which are possibly integrated by common molecular nodes.

In this viewpoint, we discuss **a possible model that explains how bile acids and endocannabinoids may exert their effects on energy balance regulation via interconnected mechanisms at the level of the hypothalamic neuronal circuits.** Therefore, we propose a new conceptual framework for understanding and treating central mechanisms of maladaptive lipid action in obesity.

Keywords

Obesity, endocannabinoids, bile acids, hypothalamus, lipid metabolism

Abbreviations

Central nervous system, CNS; arcuate nucleus, ARC; neuropeptide Y, NPY; agouti-related peptide, AgRP; amphetamine-regulated transcript, CART; proopiomelanocortin, POMC, blood-brain barrier, BBB; lipoprotein lipase, LPL; hormone-sensitive lipase, HSL; high-fat diet, HFD; mediobasal hypothalamus, MBH; sympathetic nervous system, SNS; Δ^9-tetrahydrocannabinol, THC; cannabinoid type 1 receptors, CB1; brown adipose tissue, BAT; 2-arachidonoylglycerol, 2-AG; single-minded 1, SIM1; steroidogenic factor 1, SF1; 2α/β-hydrolase domain containing 6, ABHD6; ventromedial hypothalamic nucleus, VMH; 2-arachidonoylglycerol, 2-AG; nucleus tractus solitarii, NTS, arachidonoylethanolamine, AEA; body mass index, BMI; farnesoid X receptor, FXR; G-protein coupled receptor G-protein bile acid-activated receptor, GPBAR-1/TGR5; glucagon-like peptide-1, GLP-1; cholic acid, CA; chenodeoxycholic acid, CDCA; diet-induced obese, DIO; tyrosine hydroxylase, TH; oleoylethanolamide, OEA; *N*-acylphosphatidylethanolamine-selective phospholipase D, NAPE-PLD; *N*-acylethanolamines, NAEs; small extracellular vesicles, sEV.

1) Introduction

Over million years of evolution in an environment characterised by cataclysms and often scarce energy sources, the mammalian brain has developed adaptive mechanisms that promote survival by manoeuvring the body energy state. Multiple studies have shed light on the neurobiology of these mechanisms, and this advancement provides a more precise framework for understanding and treating pathological conditions linked to altered energy balance regulation, such as obesity. Accordingly, we now know that obesity is primarily a brain disease since most of the genetic mutations underlying disease progression map in the central nervous system (CNS). These mutations affect molecular factors responsible for synaptic transmission and neuronal responses to hormones and energy substrates (1).

The outstanding ability of CNS neurons to monitor and maintain energy balance relies on its dynamic crosstalk with the peripheral organs. In the hypothalamic arcuate nucleus (ARC), the heterogeneous populations of neurons relay the peripheral signals by producing neurotransmitters

and neuropeptides that regulate feeding and metabolism (2-4). When energy reserves decline during fasting, neuropeptide Y (NPY) and agouti-related peptide (AgRP) co-expressing neurons are activated to promote food consumption and energy accumulation in peripheral organs (5). Conversely, when energy becomes available after dietary intake, neurons that co-express amphetamine-regulated transcript (CART) and proopiomelanocortin (POMC) are recruited to antagonise the actions of NPY/AgRP neurons to reduce food intake and stimulate whole-body energy expenditure (6). AgRP and POMC neurons compose a unique neural circuit known as the melanocortin system (6), which is modulated by the neighbouring non-neuronal cells, including microglia, astrocytes, tanycytes, and endothelial cells (7). Non-neuronal cells regulate the melanocortin system by two mechanisms, the secretion of signalling molecules that influence synaptic plasticity directly and the modulation of blood-brain barrier (BBB) permeability (7), which subsequently impacts the transport of metabolic messengers from the bloodstream to the brain. **As thoroughly reviewed, hypothalamic neuronal circuits integrate these peripheral metabolic signals into output autonomic responses that influence feeding behaviour and maintain the metabolic processes necessary for survival (8, 9).**

The intercellular signalling between hypothalamic cells is tightly controlled by lipid-derived messengers, either produced from cellular precursors in the brain or transported from the bloodstream. Free fatty acids, for instance, can cross the BBB (10-13). These lipids can also reach the hypothalamus as triglyceride-rich lipoproteins, which are then hydrolysed by enzymes, such as the lipoprotein lipase (LPL) in neurons and glia (14, 15). Genetic ablation of LPL in glial cells induces exaggerated body weight gain and glucose intolerance in mice exposed to a high-fat diet (HFD), possibly impacting the function of hypothalamic neuronal circuits (15, 16). Likewise, non-selective deletion of LPL in the mediobasal hypothalamus (MBH) by viral transfection induces weight gain and glucose intolerance in mice fed with a chow diet (17). **Additionally, hormone-sensitive lipase (HSL), which regulates intracellular lipolysis, is expressed in appetite-regulating hypothalamic neurons, and its activity in the MBH suppresses stress-induced food intake and HFD-induced obesity (18).**

Hence, the action of lipids in the hypothalamus is critical for body weight control and the maintenance of energy homeostasis, although the resulting neurophysiological adaptations can be either beneficial or detrimental to metabolic health. The chemical configuration of the lipid species, for instance, the double bonds in the fatty acids, can affect the metabolic outcome.

Accordingly, intracerebroventricular administration of the saturated palmitic acid enhances hepatic gluconeogenesis in mice, possibly due to central leptin resistance and inflammatory responses in the hypothalamus (19), whereas central administration of unsaturated oleic acid modulates the excitability of hypothalamic POMC neurons (20) and elicits beneficial metabolic responses, including inhibition of hepatic glucose production and food intake (21, 22).

Of note, certain lipid species, such as endocannabinoids (ECs), can act as retrograde neuromodulators regulating neural plasticity in the CNS, including the hypothalamus. ECs are endogenous ligands of cannabinoid receptors that favour food intake and energy accumulation when energy is scarce, for instance, during fasting (23). **These lipid mediators inform the body about low energy availability by acting on the hypothalamus-sympathetic nervous system (SNS) axis (23). In contrast, other periphery-derived lipids, such as bile acids (BAs), can convey information about energy accumulation in the body through the same top-down axis (24, 25). After being produced by the liver and released in the gastrointestinal tract following dietary intake, BAs are reabsorbed into the circulation and act on the hypothalamus to enhance SNS activity, promote energy dissipation, and inhibit appetite, thus eliciting opposite physiological effects to ECs (24, 25). Intriguingly, the bioavailability and downstream signalling cascades of both ECs and BAs are altered in the hypothalamus in obesity. These multiple lipid-mediated cascades might therefore converge to common molecular nodes that act as 'super lipid sensors' in regulating metabolism, while the onset and progression of metabolic diseases might result from the unbalanced regulations by these cascades.**

Here we will discuss the recent evidence on the roles of ECs and BAs in fine-tuning the hypothalamic circuits regulating energy balance. Moreover, we will interrogate the potential interconnection of BAs- and ECs-mediated signalling pathways along the hypothalamus-periphery axes implicated in body weight control. Finally, we will highlight how these investigations have led us to propose a novel framework for understanding and possibly treating maladaptive changes in hypothalamic lipid action in obesity.

2) Hypothalamic sensing of endocannabinoids: from physiology to obesity development

For centuries, marijuana (*Cannabis sativa*) has been known to stimulate food intake, particularly for sweet and palatable food. However, the discovery of the biological mechanisms

underlying 'the munchies' started only in the 60s with the identification of Δ^9-tetrahydrocannabinol (THC), the main psychoactive component of *Cannabis sativa* (26). Almost 30 years later, specific cannabinoid receptors were identified as the downstream targets of THC (27, 28), which was followed by the characterisation of their endogenous lipid-derived ligands, ECs (29, 30) and the enzymatic machinery necessary for ECs syntheses and degradations (31). We now know that these molecular components form the endocannabinoid system, which mainly operates to maximise the introduction, accumulation, and storage of energy substrates in the body (32). These effects are achieved by tissue-specific changes in ECs syntheses and the subsequent activation of cannabinoid type 1 receptors (CB1) expressed in the brain and peripheral organs (23, 32, 33). **From a biochemical standpoint, certain ECs, such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are derived from the precursor arachidonic acid (AA) (33). Others, such as *N*-eicosapentaenoylethanolamide and *N*-docosahexaenoyl-ethanolamide, are synthetized from the n-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), respectively (33). PUFAs, including linoleic acid and linolenic acid, are essential fatty acids that must be obtained from the diet, and the amount and the types of PUFA from dietary intake can influence ECs biosyntheses. Hence, amongst the several factors influencing ECs production, the availability of lipid precursors directly obtained through the diet plays a crucial role.**

ECs are produced from several sources in the body, for example, the brain and peripheral tissues; their production is dependent on the global energy state of the organism. When body energy level drops during fasting, brain ECs levels are increased to achieve energy homeostasis by restoring the internal energy loss (23). ECs-mediated control of **neuronal** functions contributes to this adaptive response. In 2010, our group characterised a transgenic mouse model bearing selective CB1 deletion in the principal forebrain (including the hypothalamus) and sympathetic neurons (CB1-KO mice) and observed that these mutants are resistant to obesity with higher energy expenditure and enhanced brown adipose tissue (BAT) thermogenesis (35). Since the SNS controls adaptive thermogenesis and BAT function (36), we asked whether neuronal ECs actions modulate these peripheral metabolic outputs. Using chemical and surgical SNS denervation procedures, we have observed that the increased functional activity in the BAT of CB1-KO mice results from an upregulated SNS tone (35). Likewise, Piomelli and his team have studied the phenotype of a transgenic murine model

overexpressing the presynaptic hydrolase monoacylglycerol lipase (MGL), an enzyme that degrades 2-AG, in forebrain neurons. In this model, reduced 2-AG levels in the forebrain results in phenotypic changes that resemble those observed in the CB1-KO mice, including leanness, elevated energy cost of activity, resistance to diet-induced obesity, and increased expression of the thermogenic protein uncoupling protein 1 in the BAT (37). These two studies have set up a well-accepted model whereby ECs operate in a CB1-dependent manner in the brain to modulate whole-body energy homeostasis and thermogenesis via peripheral sympathetic neurotransmission.

Subsequent studies have then uncovered the role of the hypothalamic circuits in mediating this top-down axis. Mice presenting specific genetic deletion of CB1 in different populations of hypothalamic neurons, including single-minded 1 (SIM1)- or steroidogenic factor 1 (SF1)-expressing neurons, display increased energy expenditure and a modified sensitivity of the peripheral SNS to circulating hormones, such as leptin and dietary cues (38, 39). Besides, genetic deletion of the ECs-degrading enzyme 2α/β-hydrolase domain containing 6 (ABHD6) in the ventromedial hypothalamic nucleus (VMH), which promotes hypothalamic production of 2-AG, has been shown to provoke opposite metabolic effects compared with the prior CB1-KO model, including impairments in adaptive thermogenesis in response to cold exposure or high-fat feeding (40).

Peripheral organs, such as the adipose tissue, also express enzymes and receptors necessary for ECs syntheses and actions (34). To explore whether CB1 influences behavioural and metabolic responses in the adipose tissue, we have characterised a transgenic mouse model with adipose-tissue-specific CB1 deletion. Notably, we observed adaptive changes in peripheral SNS neurotransmission and protection from diet-induced obesity (41). Moreover, we have documented that the hypophagic action of the CB1 antagonist rimonabant inhibits feeding by activating visceral afferents and glutamatergic transmission in the brain stem nucleus tractus solitarii (NTS) in a periphery-to-brain manner (42).

Altogether, these studies emphasise the existence of bidirectional brain-periphery signalling mechanisms, whereby ECs can act centrally and peripherally to modulate food intake **and energy use through the SNS. An additional peripheral route through the vagus nerve is possibly involved in mediating brain-periphery crosstalk (43, 44). Hence, how can we**

translate these empirical findings to delineate the neural basis of the onset and progression of obesity? One should mention that brain ECs levels, particularly in the hypothalamus, vary in response to diet-induced metabolic stress. ECs act as a signal that alerts the brain when energy reserves are low and need to be restored under physiological conditions. Paradoxically, their levels in the brain and peripheral organs remain elevated in obesity (23, 45), a condition of excess energy. Several studies have reported that plasma ECs are found at supraphysiological levels in obese individuals and positively correlate with body mass index (BMI) and several biomarkers of disease severity (23, 45). Dysregulated ECs syntheses and degradation by the enzymatic machinery may be responsible for impaired energy balance regulation and disease development. Accordingly, ECs syntheses are increased in association with reduced degradation in a tissue-dependent manner in obesity (46, 47), particularly in the adipose tissues (34). Besides, missense polymorphisms involving the fatty acid amide hydrolase (FAAH), a key enzyme controlling AEA degradation, are associated with a high BMI in humans. Interestingly, the elevated circulating levels of the ECs 2-AG and AEA in obese subjects after the exposure to rewarding food (23, 45) may augment their motivation to ingest the palatable food, which further exacerbates obesity.

Another example of how ECs are involved in the bidirectional brain-periphery crosstalk comes from a study investigating ECs levels during short-term exposure to HFD. Based on this study, the hypothalamic 2-AG and AEA levels are transiently elevated 7 days after HFD feeding in mice, followed by a subsequent decline, with levels lower than those in chow-fed mice (48). The initial transient elevation of the hypothalamic ECs levels is concomitant with the activation peak of BAT thermogenesis due to the caloric overload (48). To reconcile the initial ECs surge in the hypothalamus, the authors acutely administered CL316,243, a β3-adrenoceptor agonist that stimulates BAT thermogenesis mainly via its peripheral action (49). This treatment increased hypothalamic ECs levels substantially (48-50). These data not only reveal the existence of a feedback loop linking peripheral changes in BAT function to central hypothalamic ECs levels, but also suggest that the elevated hypothalamic ECs levels in obesity may represent a maladaptive counterregulatory mechanism that prevents excessive energy loss from the body in response to increased BAT thermogenesis.

Given that ECs signalling in the hypothalamus results in overfeeding and impaired SNS-mediated energy dissipation, this maladaptive adipose tissue-ECs crosstalk accelerates weight gain after prolonged exposure to an energy-rich diet. However, why are the levels of hypothalamic ECs reduced after several weeks of HFD feeding when diet-induced obesity is established (48)? This could be explained by the existence of protective mechanisms that aim at hindering the upregulated peripheral EC tone (50) and, therefore, disease progression, albeit without success, since the animal continues to gain weight.

In conclusion, the dysregulated hypothalamic ECs action may cause, or be caused by, the maladaptive brain-periphery crosstalk mediated by the SNS and likely the vagus nerve in obesity. These signalling pathways dynamically contribute to the establishment and the progression of weight gain and its associated metabolic perturbations.

3) Bile acids: A novel hypothalamic brake on energy excess

BAs are liver-derived products of cholesterol metabolism that exert a series of metabolic functions via mainly (but not only) their signalling through the nuclear transcription factor farnesoid X receptor (FXR) and the seven-transmembrane G-protein coupled receptor G-protein bile acid-activated receptor (GPBAR)-1, also known as TGR5 (51).

A rapid elevation of hepatic BAs syntheses is observed during the transition from fasting to the fed state, which aids the absorption of ingested lipids in the gastrointestinal system (for a specific review on this subject, see (52)). Besides, BAs act as endocrine signals in the liver, the intestine, and the pancreas to modulate multiple metabolic outputs, including lipid and glucose metabolism (53), hepatic gluconeogenesis (53, 54), insulin and glucagon-like peptide-1 (GLP-1) release (53, 55), as well as mitochondrial respiration and thermogenesis in white and brown adipocytes (56-58).

Dietary supplementation of specific BAs, such as cholic acid (CA) and chenodeoxycholic acid (CDCA), prevents body weight gain and promotes weight loss significantly in diet-induced obese (DIO) mice through TGR5-mediated signalling (56, 59). These metabolic benefits are likely the result of increased thermogenesis and energy expenditure (56, 59). Indeed, circulating BAs levels correlate with energy expenditure in healthy human subjects (60) and with changes in energy substrate metabolism in obese subjects subjected to Roux-en-Y gastric bypass surgery

(61). Hence, beyond their actions on nutrient absorption and glucose homeostasis, the observed systemic elevation of BAs after dietary intake may signify positive energy balance and prompt adaptive responses towards energy dissipation to restore energy homeostasis.

But can the brain be a possible target of BAs action? BAs are detected in several brain areas, including the hypothalamus (25, 62). Under cholestasis, when the bile constituents are accumulated in the blood due to the obstruction of bile ducts or excretory failure of hepatocytes, the hypothalamic BAs level is augmented, promoting the synthesis of the hypothalamic hormone vasopressin to protect the liver from BAs-induced hepatotoxicity (63). Indirectly, BAs can stimulate FGF15 release from the intestine, which enters the brain and activates FGF receptors in the hypothalamic AGRP/NPY neurons (64). The BAs-mediated gut-brain axis leads to improvements in glucose tolerance that are likely mediated by changes in the peripheral autonomic nervous system (64).

Our group has also observed that the hypothalamic BAs levels in mice change according to the nutritional state based on a fasting-refeeding paradigm experiment (25). We have inquired whether activating TGR5 in the brain affects food intake and body weight in C57BL6 mice fed with a regular chow diet. After acute infusion of a BAs mix into the brain, we have observed a significant reduction in food intake and the syntheses of the orexigenic peptides AgRP and NPY from the hypothalamus (25). To investigate whether hypothalamic TGR5 signalling mediates long-term effects on body weight control, we have chronically infused a TGR5-specific, semi-synthetic BAs analogue into the cerebral ventricles. Coherently, food intake is transiently reduced, but the prolonged activation of central BAs signalling does not lead to changes in food intake or body weight (25). Hence, BA-TGR5 signalling in the hypothalamus coordinates satiety during the fasting-refeeding transition but is not involved in long-term body weight maintenance under physiological conditions.

As previously discussed, lipid-mediated homeostatic responses in the hypothalamus can be compromised in obesity. In an additional study, we have explored whether the brain BA-TGR5 axis might have a more dominant role in regulating energy balance in obesity. Using pharmacological and genetic approaches, we have observed that activating brain TGR5 signalling counteracts diet-induced obesity (DIO) progression in mice by reducing food intake and increasing energy expenditure through increased SNS activity. On the other hand, genetic down-regulation of hypothalamic TGR5 actions accelerates obesity development and progression (24).

Thus, the role of the hypothalamic BA-TGR5 pathway in the top-down control of body weight seems more prominent in obesity. This also implies that hypothalamic BAs sensing may be impaired in obesity, which is supported by the observation that levels of BAs species acting as TGR5 agonists in the hypothalamus are reduced in DIO mice (24).

Due to their heterogeneous structure and target specificity, BAs may confer different metabolic effects through different downstream receptors. Brain infusion of the FXR agonist GW4064 reduces the expression of tyrosine hydroxylase (TH), the rate-limiting enzyme in catecholamine synthesis, and subsequently, the sympathetic tone (65). The reduction in the sympathetic tone might involve changes in hypothalamic neuronal activity, given that hypothalamic TH expression is reduced following brain GW4064 infusion (65). Conversely, in agreement with our observations (24), brain infusion of tauro-lithocholic acid, a TGR5 agonist, promotes lipid metabolism and enhances the SNS tone (66). Hence, the membrane receptor TGR5 and the nuclear receptor FXR might have opposing functions on energy balance regulation in the hypothalamus in response to changes in BAs species.

In summary, the hypothalamic BA-TGR5 pathway affects a top-down neurophysiological mechanism that leads to satiety and enhanced energy dissipation by changing peripheral SNS activity. This pathway may operate via the same hypothalamic circuits sensitive to ECs action, but with an opposite physiological goal: to counteract pathological conditions of energy excess, such as obesity.

4) Concluding remarks and perspectives

Under physiological conditions, the levels of BAs and ECs are regulated in an opposite manner in the hypothalamus in response to the nutritional state. The Yin-Yang regulation allows plastic changes in peripheral SNS neurotransmission and may affect metabolic flexibility between the fast-and-fed transition (Figure 1). ECs and BAs-mediated actions in the hypothalamus may act on common intracellular lipid sensors that integrate neuronal CB1 and TGR5 signalling to regulate food intake and the autonomic nervous system (Figure 1). The identities of these molecular underpinnings and the neuronal circuits involved are far from being elucidated. However, addressing this knowledge gap may provide progress towards understanding the aetiology of metabolic disorders, such as obesity.

Figure 1

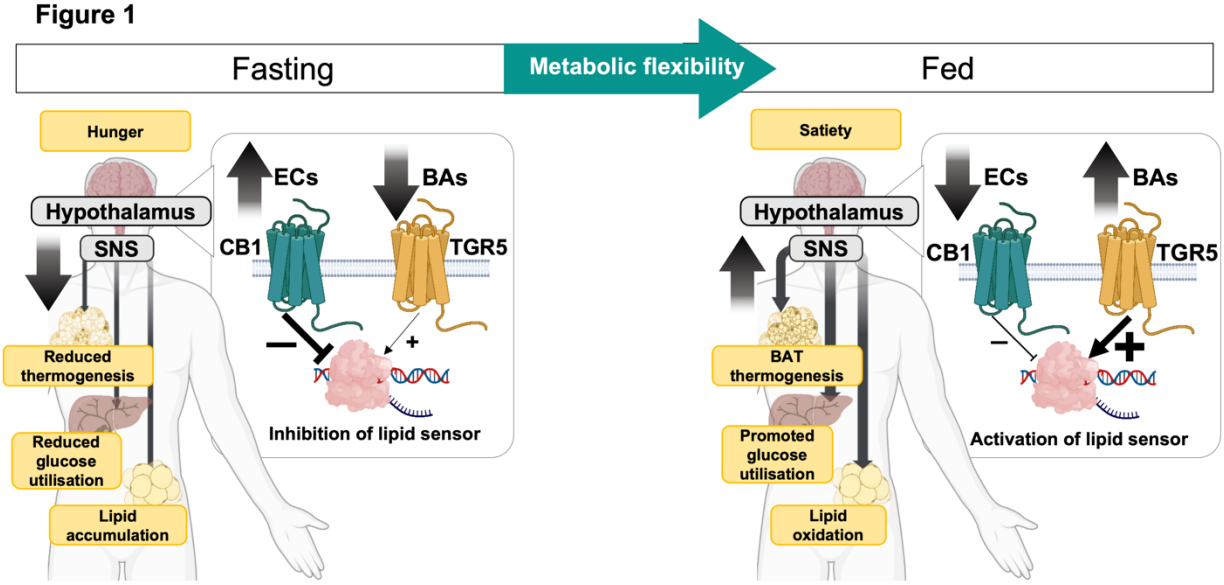

Figure 1. Graphical representation of a possible yin-yang mechanism of energy balance regulation by CB1 and TGR5 in the hypothalamus under physiological conditions. Endocannabinoids (ECs) and bile acids (BAs) might regulate whole-body metabolic flexibility in the hypothalamus through CB1 and TGR5 receptors, respectively. During fasting (left), the hypothalamic levels of ECs are increased, whereas BAs signalling is suppressed. This imbalance results in hunger and possibly in modification of the sympathetic nervous system (SNS) tone to impede energy storage. An opposite situation is observed after a meal (right), as hypothalamic ECs levels are reduced, whereas central BAs signalling is stimulated. This leads to satiety and dissipation of excess energy by thermogenesis via upregulated SNS activity. The 'super lipid sensor' might integrate the inhibitory CB1 signalling and the activatory TGR5 signalling in the hypothalamus to facilitate energy balance regulation and metabolic flexibility.

Obesity is a disease characterized by the maladaptive upregulation of the ECs tone and the concomitant downregulation of central BAs actions. Of note, the hypothalamic expression of BAs transporters exhibits plastic changes during the transition from fasting to refeeding in control lean mice but not in DIO mice (24). Thus, dysregulated hypothalamic BAs and ECs availability and sensing in the brain might contribute to obesity development, possibly causing impaired hypothalamus-SNS communication and metabolic inflexibility (Figure 2).

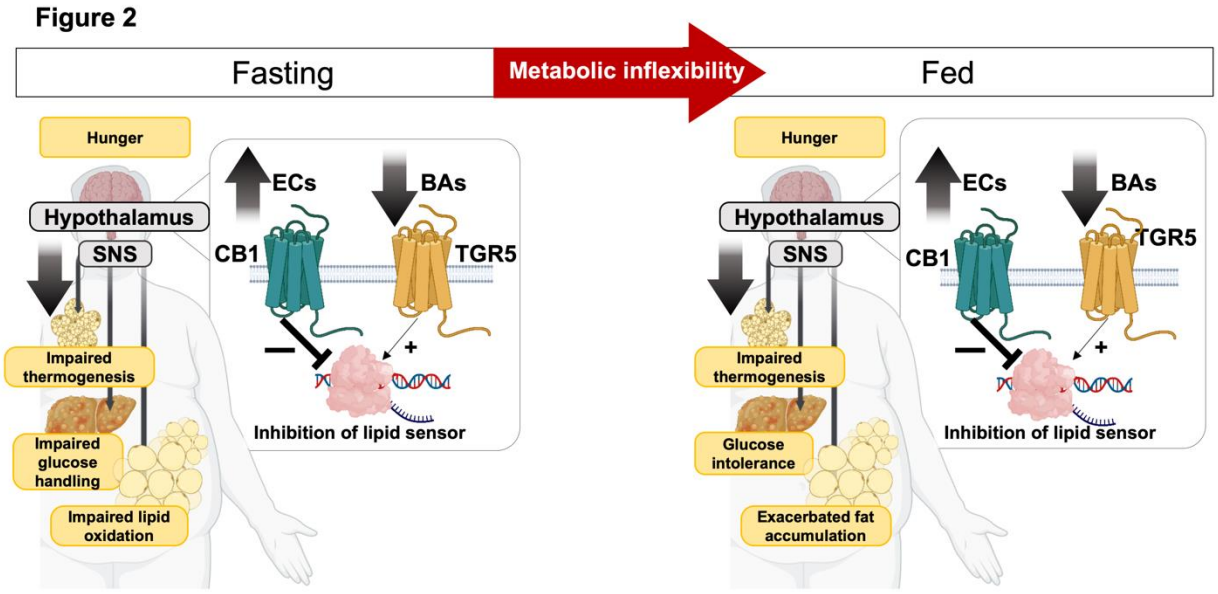

Figure 2. Graphical representation of a possible mechanism underlying maladaptive hypothalamic CB1 and TGR5 signallings in obese pathophysiology. In obesity, ECs levels in the hypothalamus are increased, while BAs levels are reduced in both the fasted and the fed state. As a result, the peripheral SNS does not cope with changes in energy availability during the transition from fasting to the fed state. The transition might lead to a constant feeling of hunger and a maladaptive drive towards excessive energy accumulation. An intracellular lipid sensor might mediate alterations in this top-down axis in hypothalamic neurons. The 'super lipid sensor' might be controlled in an opposite manner by ECs and BAs-mediated signalling via CB1 and TGR5, respectively.

Based on these proposed models, we envision that ECs and BAs-mediated actions on energy balance may be interconnected. Accordingly, peripheral administration of 2-AG promotes hepatic BAs syntheses (67), suggesting that the increased levels of certain ECs during a negative energy state during fasting may elicit BAs syntheses, perhaps to prepare the body for BAs release during the upcoming meal. On the other hand, BAs availability may influence ECs production in response to changes in the body energy needs. This latter hypothesis is supported by the observation that certain BAs, such as deoxycholic acid, can target specific binding sites of *N*-acylphosphatidylethanolamine-selective phospholipase D

(NAPE-PLD) (68), the enzyme required for the syntheses of ECs-like lipid species known as *N*-acylethanolamines (NAEs) (69).

If confirmed, these peripheral mechanisms of communication between BAs and ECs may impact the hypothalamic circuits via different routes. First, BAs (63) and ECs (70) can cross the blood-brain barrier. Also, CB1- and TGR5-expressing hypothalamic neurons in the ARC are ideally positioned in close contact with the fenestrated capillaries to sense systemic changes in ECs and BAs levels. Thus, hypothalamic neurons may be capable of responding to changes in the peripheral bioavailability of these lipid mediators. Additionally, although several peripheral organs are potential sources of ECs release in the bloodstream (71), the enzymatic machinery necessary for ECs syntheses and degradations is also expressed in the brain (31, 72). Therefore, it is tempting to speculate that the ECs syntheses in the hypothalamic neurons may be adjusted in response to changes in BAs levels and actions. Given that ECs are modulators of synaptic plasticity (31), modulating ECs productions may fine-tune synaptic functions to orchestrate whole body changes in energy needs.

It is noteworthy that EC-like species can be highly heterogeneous in their molecular functions and physiological effects. Oleoylethanolamide (OEA), for instance, is a shorter monounsaturated analogue of the endocannabinoid AEA. Unlike AEA, OEA acts independently of the CB1 signalling pathway and can suppress appetite (33), possibly via regulation of the nuclear peroxisome proliferator-activated receptor-alpha receptor (PPARα) and the G protein-coupled receptor GPR119 (33, 73). OEA can also modulate BAs syntheses, conjugation, and transport via PPARα-mediated activation (74). Moreover, the OEA receptor GPR119 mediates some of the effects of BAs on gastric emptying and satiation (74). Thus, the complexity may go beyond our proposed conceptual framework (Figure 1) because certain canonical ECs-like molecules may operate via CB1-dependent signalling in an opposite manner to BAs. In contrast, others, such as OEA, may resemble BAs-elicited physiological responses, such as satiety, through modulaiton of common hypothalamic downstream receptors.

Overall, this evidence suggests the existence of intracellular 'super lipid sensors' that integrate the extracellular actions of multiple lipid species in the hypothalamus. Uncovering the identity of these master regulators of neuronal lipid action might have therapeutic

implications, for instance, the development of novel anti-obesity pharmacological paradigms that target specific molecular pathways in specific neuronal populations. Several advancements have recently been made in this direction. For instance, small extracellular vesicles (sEVs) have been used to shuttle a pharmacological inhibitor of the energy sensor AMPK in hypothalamic SF1-expressing neurons in the obese murine models (75), and this approach lowers the body weight of obese mice by sympathetic activation of BAT function (75).

In the past few years, we have contributed to the generation and functional validation of novel unimolecular conjugates that combine GLP-1 analogues with synthetic activators of metabolic transcription factors, such as the glucocorticoid receptor or PPARs (76, 77). The GLP-1 moiety of these conjugates is designed to internalise the nuclear ligand in GLP-1R-expressing cells to target organs such as the hypothalamus, where GLP-1R expression is abundant. However, organs with negligible or low GLP-1R expression are spared from these conjugates, which can overcome the potentially toxic and off-target effects of glucocorticoids or PPARs (76, 77). Chronic treatments of obese mice with a conjugate that co-activates PPARα and PPARγ in GLP-1R positive cells elicit clear-cut anti-obesity and anti-diabetic effects partly through their actions on the hypothalamus (77). Notably, this cell-specific targeting approach does not induce cardiovascular and kidney dysfunctions associated with non-specific PPAR agonism (77). Thus, this chemical conjugation strategy combining GLP-1R agonists and nuclear-acting metabolic hormones offers a novel therapeutic option for ameliorating obesity and its co-morbidities in a safe and cell-specific manner.

To tackle the growing obesity epidemic and its negative impact on health (78), there is an urgent need to decipher the neural mechanisms leading to the dysregulation of energy homeostasis. Unidentified molecular pathways might integrate the action of multiple lipids-sensing mechanisms in the hypothalamus, thus contributing to disease development. Uncovering these pathways will expand our understanding of the aetiology and treatment of obesity. Towards this goal, exploring the functional interaction of ECs and BAs in the brain warrants further investigation.

Author contributions

T.H.L. and C.Q. co-wrote the manuscript, D.C. contributed to writing and editing.

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