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INVITED REVIEW

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Targeting carnitine palmitoyltransferase 1 isoforms in the hypothalamus: A promising strategy to regulate energy balance

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Abstract

Tackling the growing incidence and prevalence of obesity urgently requires uncovering new molecular pathways with therapeutic potential. The brain, and in particular the hypothalamus, is a major integrator of metabolic signals from peripheral tissues that regulate functions such as feeding behavior and energy expenditure. In obesity, hypothalamic capacity to sense nutritional status and regulate these functions is altered. An emerging line of research is that hypothalamic lipid metabolism plays a critical role in regulating energy balance. Here, we focus on the carnitine palmitoyltransferase 1 (CPT1) enzyme family responsible for long-chain fatty acid metabolism. The evidence suggests that two of its isoforms expressed in the brain, CPT1A and CPT1C, play a crucial role in hypothalamic lipid metabolism, and their promise as targets in food intake and bodyweight management is currently being intensively investigated. In this review we describe and discuss the metabolic actions and potential up- and downstream effectors of hypothalamic CPT1 isoforms, and posit the need to develop innovative nanomedicine platforms for selective targeting of CPT1 and related nutrient sensors in specific brain areas as potential next-generation therapy to treat obesity.

KEYWORDS
CPT1A, CPT1C, hypothalamus, lipid metabolism, obesity

1 | INTRODUCTION

Obesity, which implies an imbalance between food intake and energy expenditure, leads to adiposity and a myriad of metabolic and cardiovascular diseases and several forms of cancer.[1–3] In the last decades, the prevalence of obesity and related comorbidities has continued to increase worldwide, reaching pandemic proportions. In 2016, in fact, 39% of the global population was overweight and 13% obese, and predictive models suggest that the trend will increase to one in two adult by 2030.[4,5] Although lifestyle modifications (i.e., calorie restriction and exercise) are an integral part of obesity management, with limited clinical impact they are insufficient on their own. In terms of pharmacological strategies, the number of anti-obesity drugs reaching the market is very small, mainly for safety reasons and due to unsustainable long-term efficacy.[6] Obesity and related complications are, consequently, unmet medical needs that represent a major health and socioeconomic problem for society, yet more knowledge is required on obesity mechanisms and new therapeutic targets for drug discovery need to be identified.[4,5]

The central nervous system (CNS) is a major regulator of systemic metabolism and energy balance, with the hypothalamus, in particular, recognized as crucial to regulating the development and progression of obesity and related metabolic diseases.[7,8] Hypothalamic nuclei, which are sensitive to nutrients and hormones such as leptin and ghrelin, modify the expression, secretion, and activity of specific neuromodulators, resulting in changes in food intake, energy expenditure, and the functioning of key peripheral tissues such as liver and adipose tissues.[9,10] Lipid metabolism within the hypothalamus participates in this process and is a key molecular mechanism in controlling energy balance to counteract nutrient surplus.[9,11,12] There is strong evidence that a disturbance in hypothalamic lipid sensing may be partly responsible for a disrupted energy balance and the development of obesity and insulin resistance.[13,14] In fact, fatty acid (FA) sensing in hypothalamic neurons, via accumulation of long-chain FAs or FA intermediaries, acts as a satiety signal to decrease food intake and promote energy expenditure.[11,15,16] In the lipid sensing process, malonyl-CoA, a first intermediary in FA synthesis, restrains food intake as a primary step in the central nutrient-sensing pathway controlling energy homeostasis.[16,17] In the hypothalamus, malonyl-CoA levels are tightly regulated by nutrients, hormones, and the energy sensor AMP-activated protein kinase (AMPK), with malonyl-CoA acting as an upstream regulator of carnitine palmitoyltransferase 1 (CPT1).[18] Thus, in high-energy conditions, hypothalamic malonyl-CoA levels rise, modulating CPT1 activity, inhibiting FA oxidation (FAO), and leading to FA storage as triglycerides, food intake attenuation, and enhanced energy expenditure. In fasting conditions, in contrast, malonyl-CoA levels diminish triggering FAO reduction and feeding activation.[16,18]

The CPT1 proteins involved in long-chain FA metabolism are considered to be the main downstream effectors of the energy balance regulatory role of malonyl-CoA.[18,19] There are three different CPT1 isoforms: (i) CPT1A, the most ubiquitously expressed, is mainly found in the liver, kidney, and pancreas, but also in brain neurons and astrocytes; (ii) CPT1B is mainly expressed in muscle, heart, and adipose tissues; and (iii) CPT1C is almost exclusively expressed in neurons (Figure 1).[19]

The canonical isoforms, CPT1A and CPT1B, located in the outer mitochondrial membrane, are specific to long-chain fatty acyl-CoAs, generating the acyl-carnitine derivative that undergoes β-oxidation in the mitochondria. Malonyl-CoA regulates FAO by inhibiting CPT1A and CPT1B (Figure 1). Cloning experiments and sequencing have demonstrated that both isoforms show considerable sequence similarity.[20] Although no crystal structures are available, homology analysis with other members of the carnitine acyltransferase family have enabled development of in silico models of the CPT1A tertiary structure, revealing a small regulatory N-terminal domain and a large catalytic C-terminal domain, separated by two transmembrane domains and a short connecting loop; this tertiary structure is attributed to all three CPT1 isoforms.[19,21,22]

The neuron-specific CPT1C is the newest and most intriguing member of the CPT1 family, discovered in searches of expressed sequence tag results using the human CPT1A cDNA nucleotide of protein sequences.[23] CPT1C sequences were found to be restricted to neurons and are not detectable in glial or endothelial cells,[24,25] and CPT1C was also observed to be enriched in areas of the hypothalamus related to food intake and energy expenditure, as well as in the amygdala, hippocampus, and peripheral nervous system.[24,26] Unlike the canonical isoforms, CPT1C is located not in the mitochondria but in the endoplasmic reticulum, and since it has negligible catalytic activity, it is unable to facilitate FAO in cells[19,27] (Figure 1). Interestingly, CPT1C preserves all the structural motifs related to carnitine acyltransferase activity and the malonyl-CoA binding site, as it can bind malonyl-CoA at the physiological level and shows affinities similar to those of CPT1A (Figure 1). Those findings led our group and other researchers to propose CPT1C as a sensor of malonyl-CoA and lipid metabolism in neurons.[18,28,29]

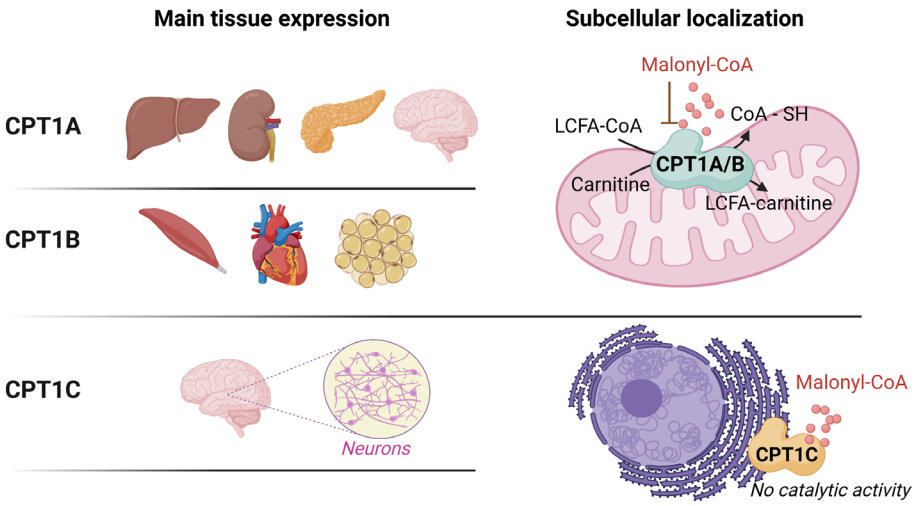

FIGURE 1 CPT1 isoforms: CPT1A, CPT1B, and CPT1C. CPT1A is the most ubiquitously expressed isoform, mainly found in the liver, kidney, and pancreas, but also in the brain, CPT1B is mainly expressed in muscle, heart, and adipose tissue, and CPT1C is almost exclusively expressed in neurons. The canonical isoforms, CPT1A and CPT1B, are located in the outer mitochondrial membrane and transport long-chain fatty acids (LCFA) into the mitochondria to undergo β-oxidation. By inhibiting CPT1A and CPT1B, malonyl-CoA, an intermediary in fatty acid synthesis (FAS), regulates fatty acid oxidation (FAO). CPT1C, located in the endoplasmic reticulum membrane and with minimal catalytic activity, acts as a sensor of malonyl-CoA in neurons.

The brain, therefore, has two CPT1 isoforms: CPT1A and CPT1C. However, despite CPT1A and CPT1C similarities in terms of sequence homology, CNS presence, and malonyl-CoA binding capacity, notable differences in subcellular localization and activity suggest differing neuronal functions and mechanisms implicated in hypothalamic obesity regulation for each. Considering the potential for effective targeting of lipid metabolism via CPT1 regulation in the hypothalamus as a means of regulating energy balance, the aim of this review is to describe and discuss the metabolic activity and potential up- and downstream effectors of the hypothalamic CPT1 proteins, CPT1C and CPT1A, currently the focus of intensive research.

2 | HYPOTHALAMIC CPT1C AND THE AMPK-ACETYL-COA CARBOXYLASE (ACC) AXIS FOR ENERGY BALANCE REGULATION

There is strong evidence to suggest that CPT1C within specific areas of the hypothalamus plays a major role in regulating food intake and energy expenditure, mostly controlled by AMPK. The development of CPT1C knockout (KO) mice by our group and other researchers has shed light on the physiological role played by CPT1C in neuronal control of energy homeostasis. Research has focused on food intake control, since CPT1C is highly expressed in the appetite-regulating arcuate nucleus (ARC), paraventricular hypothalamus (PVH), and ventromedial hypothalamus (VMH) neurons.[24] Those studies have demonstrated that CPT1C is crucial for the ghrelin-induced feeding response and that it mediates the leptin anorectic signaling pathway in the ARC according to malonyl-CoA levels[29,30] (Figure 2). In particular, increased food intake and food-seeking behavior induced by intracerebroventricular (icv) injection of ghrelin in satiated mice is blunted in CPT1C-KO mice.[29] Moreover, expression of orexigenic neuropeptides remains unchanged by ghrelin in the ARC of mice lacking CPT1C.[29] Interestingly, a parallel downstream pathway involving CPT1C has also been identified that elicits rapidly increased synthesis of ceramides (a class of complex sphingolipids) after ghrelin treatment in the ARC-enriched area (mediobasal hypothalamus, MBH). This ceramide signal increases orexigenic neuropeptides and food intake, and so acts as an alternative pathway to mitochondrial CPT1A and FAO (as will be described in more detail below). This pathway is attenuated not only in CPT1C-KO mice but also in mice treated with an inhibitor of ceramide synthesis.[29] Exploration of the role of hypothalamic CPT1C in leptin's anorexigenic activity reveals that, in rats, leptin evokes satiating effects through decreased ceramide levels in the ARC, which in turn, mediated via AMPK-malonyl-CoA and CPT1C, downregulates expression of neuropeptide Y (NPY) and *Bsx*

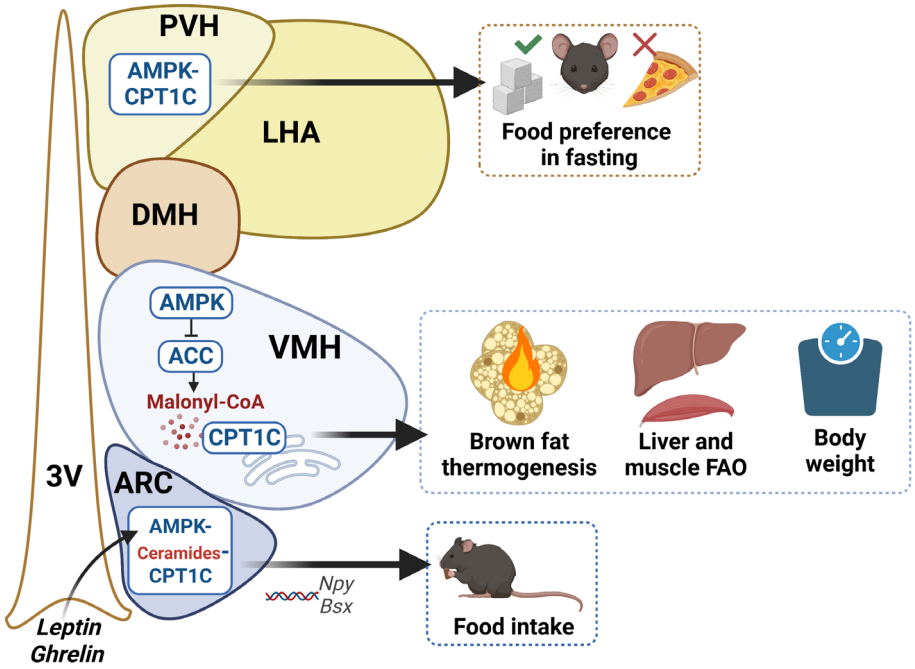

FIGURE 2 Neuron-specific CPT1C in different hypothalamic nuclei regulates food intake, bodyweight, and peripheral metabolism under AMP-activated protein kinase (AMPK) control. In the arcuate nucleus (ARC), CPT1C is crucial in the ghrelin feeding response and in the leptin anorectic signaling pathway depending on AMPK/malonyl-CoA and ceramide levels. In the ventromedial hypothalamus (VMH), CPT1C is necessary for the metabolic switch of fuel substrate in liver and muscle under fasting or high-fat diet (HFD) conditions and for protection against diet-induced obesity. CPT1C in the VMH is also needed for brown adipose tissue (BAT) thermogenesis activation in response to a HFD under the canonical pathway AMPK(VMH)-acetyl CoA carboxylase (ACC)-sympathetic nervous system (SNS)-BAT axis. In the paraventricular hypothalamus (PVH), the AMPK-CPT1C signal is the intracellular mechanism that mediates corticotropin-releasing hormone (CRH) release by PVH neurons in response to food deprivation, thereby ensuring appropriate fuel selection of a high-carbohydrate diet over a high-fat diet during refeeding. DMH, dorsomedial hypothalamus; FAO, fatty acid oxidation.

(a transcription factor of NPY)[30] (Figure 2). Overexpression of CPT1C in the ARC and icv ceramide infusion both blocked the leptin-induced downregulation of NPY and *Bsx* and the anorectic action of leptin.[30] Those findings show that leptin impacts on ceramide metabolism via malonyl-CoA and CPT1C, and that ceramide de novo biosynthesis acts downstream of both malonyl-CoA and CPT1C in regulating food intake and neuropeptide expression. Subsequent studies have also confirmed that dysregulation of hypothalamic de novo ceramide synthesis is a key starting point for central insulin resistance, endoplasmic reticulum stress, inflammation, and, ultimately, obesity.[14,31]

Hypothalamic CPT1C has also been demonstrated to play a critical role in metabolic adaptation of the peripheral tissues to the body's needs in response to a nutritional challenge. During food deprivation, CPT1C is necessary for sensing a negative energy balance and regulating fuel partitioning in liver and muscle.[32,33] CPT1C-KO mice fasted for 24 h have been demonstrated to show a continuous fed-like energy sensor status in the MBH, as observed in expression levels of phosphorylated AMPK, phosphorylated mammalian target of rapamycin (p-mTOR), and mitochondrial uncoupling protein (UCP) 2, decreased plasma catecholamine levels, and disrupted liver and muscle fuel partitioning.[32] CPT1C-deficient mice have been shown to be unable to activate liver and muscle FAO in response to fasting, and to exhibit increased hepatic gluconeogenesis and triglyceride levels, but normal fasting glycaemia. The importance of CPT1C in sensing nutrient deprivation specifically in the MBH is further confirmed by lentiviral-driven overexpression of CPT1C sufficient to reverse the metabolic phenotype of CPT1C-KO mice in the liver and muscle in response to fasting.[32] The role described for CPT1C in fuel selection is also in line with the mouse study by Okamoto et al.,[34] who showed that AMPK-CPT1C is the intracellular mechanism mediating corticotropin-releasing hormone (CRH) release by PVH neurons in response to food deprivation. This neuronal activation is necessary and sufficient for appropriate fuel selection of a high-carbohydrate diet over a high-fat diet (HFD) during refeeding after fasting (Figure 2).

In addition to its role in fasting, CPT1C in hypothalamic neurons has been demonstrated to play a key role in adapting energy balance in response to fat-rich diets. Wolfgang et al.[33] reported that both male and female CPT1C-KO mice gained 40%–50% more bodyweight than control mice when fed a HFD, with the obesogenic phenotype particularly notable from week 5 of diet administration, despite no difference in food intake compared to wild-type (WT) mice. CPT1C-KO mice fed a HFD have also been demonstrated to show a concomitant elevation of plasma phospholipids and a trend toward insulin resistance after 14 weeks of diet administration, in agreement with greater adiposity after long-term HFD feeding.[33] Those findings have been confirmed, using an adenoviral vector, by CPT1C overexpression in the ventral hypothalamus protecting mice fed a 24-day HFD from bodyweight gain.[24] Further demonstrating the potential effects of CPT1C in controlling bodyweight is the lower rate of bodyweight gain compared to control mice in response to a HFD in a brain-specific mouse model with exogenous CPT1C expression.[35] A CPT1C-KO mouse (with deletion in exon 3 rather than in exons 1 and 2 as in previous studies) with no differences between genotypes in bodyweight in response to a HFD, has been demonstrated to show greater susceptibility to HFD-induced insulin resistance and glucose intolerance compared to WT mice.[36] The fact that impaired glucose tolerance is associated with increased liver gluconeogenesis and decreased glucose uptake in the skeletal muscle of mice lacking CPT1C concurs with both lower FAO and elevated triglyceride content in liver and muscle tissues. Those findings suggest that CPT1C in the ventral hypothalamus is important for hypothalamus-peripheral tissue crosstalk to regulate liver and muscle FAO in response to HFD feeding (Figure 2).

However, the mentioned research has not specified the precise molecular mechanisms through which CPT1C in neurons regulates peripheral metabolism and glucose homeostasis. The evidence indicates that hypothalamic AMPK/malonyl-CoA play a significant role in regulating FA metabolism in peripheral tissues,[37–39] and we suggest that CPT1C, in sensing malonyl-CoA levels in the hypothalamus, is the main downstream factor.

The obese phenotype and metabolic inflexibility that characterize CPT1C-KO mice has recently been linked, in a study by our group, to impaired activation of brown adipose tissue (BAT) thermogenesis following HFD exposure.[40] While white adipose tissue is responsible for energy storage and endocrine function, BAT is a specialized tissue, critical for nonshivering thermogenesis to produce heat via UCP1. In triggering thermogenic activation, and hence, anti-obesity potential, the BAT function is implicated in metabolic adaptation in response to cold exposure or a positive energy balance and diet.[41] There is strong evidence to suggest that diet-induced BAT thermogenesis is precisely regulated by specific hypothalamus pathways and neuronal populations (i.e., from the VMH and PVH).[42,43] In particular, an intact hypothalamus function is necessary for BAT thermogenesis activation, through acute HFD intake or leptin, to compensate for excessive weight gain.[42,44–46] It has been demonstrated that, after 7 days of HFD feeding, the robust activation peak of BAT thermogenesis observed in WT mice is blunted in CPT1C-KO mice, and the same response is also observed after icv injection of leptin.[40] In agreement with this result, lentiviral expression of CPT1C in VMH neurons is enough to restore the phenotype of HFD-induced activation of thermogenesis in KO mice. Hence, CPT1C in the VMH neurons is needed for functional BAT activation in response to nutritional challenges related to hypothalamic increases in malonyl-CoA levels, sensed, in turn, by CPT1C, which acts as a signal of metabolic adaptation that counteracts the progression of obesity. The fact that selective inactivation of AMPK within the VMH increases ventral hypothalamic malonyl-CoA levels and BAT activity and, in turn, promotes feeding-independent weight loss,[12,47] points to CPT1C involvement in the canonical AMPK-sympathetic nervous system (SNS)-BAT pathway.[40] In particular, BAT thermogenesis activation and bodyweight loss led by genetic inactivation of AMPK(VMH) is blunted in mice lacking CPT1C, which points to CPT1C in the VMH as a key downstream hypothalamic AMPK/malonyl-CoA pathway factor in modulating BAT thermogenesis (Figure 2). The involvement of AMPK as a key mediator of hypothalamic activity in peripheral hormones (i.e., estradiol,

thyroid hormones and BMP8B) that regulate functions such as BAT thermogenesis[8,12] suggests a possible role for CPT1C as a downstream effector of those hormones and so worth exploring.

Despite the apparent regulation by the AMPK/malonyl-CoA axis, the hypothalamic downstream effector of CPT1C in neuronal regulation of metabolic diseases continues to be intensively investigated. Our group and other researchers have recently reported that the neurometabolic actions of CPT1C are mediated throughout direct interaction with other proteins such as ABHD6 and SAC1, both involved in energy homeostasis[48–51] (Figure 3). In neuronal cells and brain tissues, CPT1C is the first physiological negative regulator of hydrolase activity by ABHD6,[49] the newest member of the endocannabinoid (eCB) system of importance in the degradation of 2-arachidonoylglycerol and other complex phospholipids,[52] and also implicated in endolysosomal function[53] and metabolic flexibility in the VMH.[54] The interaction and regulatory role of the CPT1C-ABHD6 axis is controlled by malonyl-CoA levels in the hypothalamus to adapt to the nutritional status of the brain.[49] As for SAC1, a PI4P phosphatase of importance in vesicular transport and lipid traffic between organelles,[55] CPT1C regulates its activity in a malonyl-CoA-dependent manner by controlling AMPA-type glutamate receptors trafficking to the cell surface in neurons[48] (Figure 3).

While both these neuronal CPT1C-related axes are novel and promising pathways for regulating lipid metabolism in neurons, they need further research in the specific context of obesity development and progression.

3 | HYPOTHALAMIC CPT1A AND CONTROL OF FOOD INTAKE AND BODYWEIGHT

FAO and CPT1 mRNA and protein levels are downregulated in obese and diabetic patients.[56–58] In mitochondrial FAO, therefore, the regulatory role of the canonical CPT1 isoform CPT1A is an interesting target for controlling lipid metabolism and counteracting obesity, as previously demonstrated for peripheral tissues (i.e., white adipocytes and macrophages,[59] brown adipocytes,[60] liver,[61–63] pancreas,[64,65] and muscle[66]). In the hypothalamus, CPT1A has been revealed as a key enzyme responsible for sensing long chain-FAs and regulating food

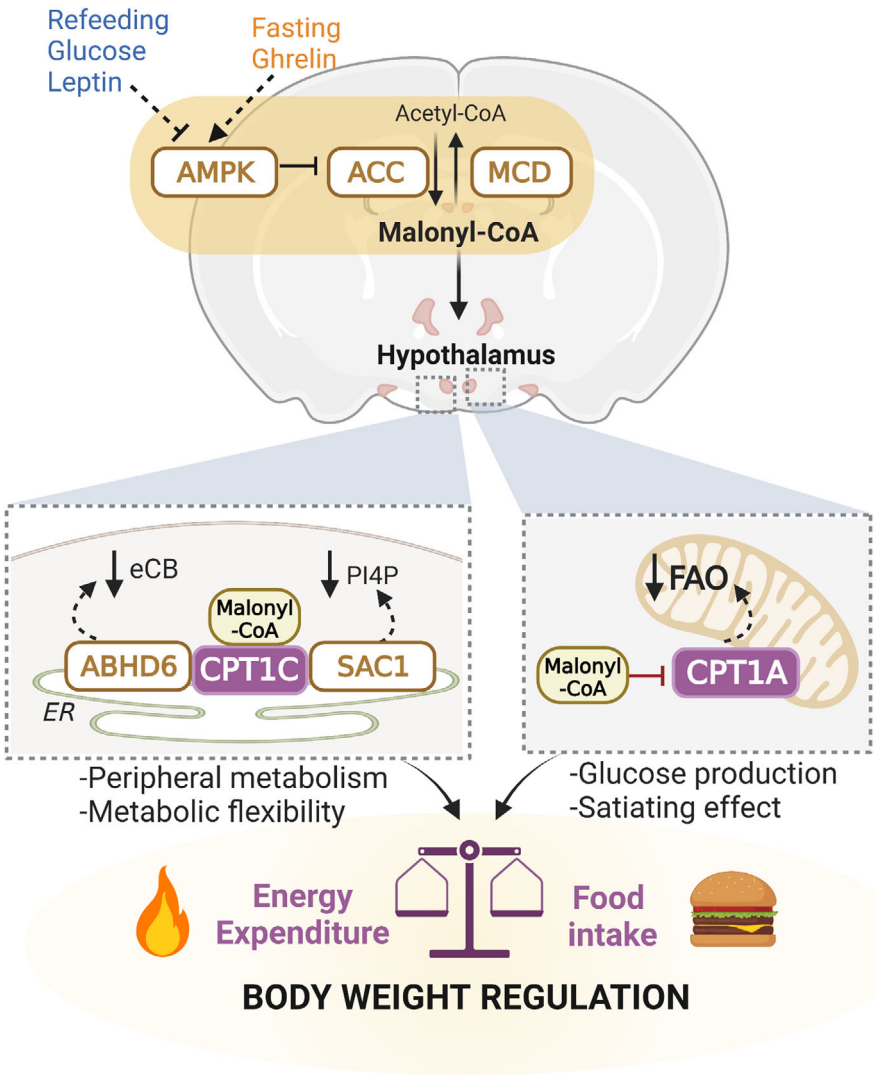

FIGURE 3 Up- and downstream effectors of brain CPT1 isoforms for bodyweight control. CPT1A and CPT1C functions are tightly regulated by AMP-activated protein kinase (AMPK)/malonyl-CoA axis. In the hypothalamus, malonyl-CoA levels are attenuated by fasting or ghrelin, and are raised in response to refeeding, glucose, or leptin. Changes in malonyl-CoA levels are sensed by CPT1C, which, in turn, regulates the activity in neurons of other effectors such as ABHD6, an endocannabinoid (eCB) and SAC1, a PI4P phosphatase, to modulate peripheral metabolism and metabolic flexibility. Increased malonyl-CoA levels inhibit CPT1A catalytic activity to attenuate fatty acid oxidation (FAO), leading to long-chain fatty acid (LCFA) accumulation in the hypothalamus, resulting in a satiety signal that controls liver glucose production. MCD, malonyl-CoA descarboxylase.

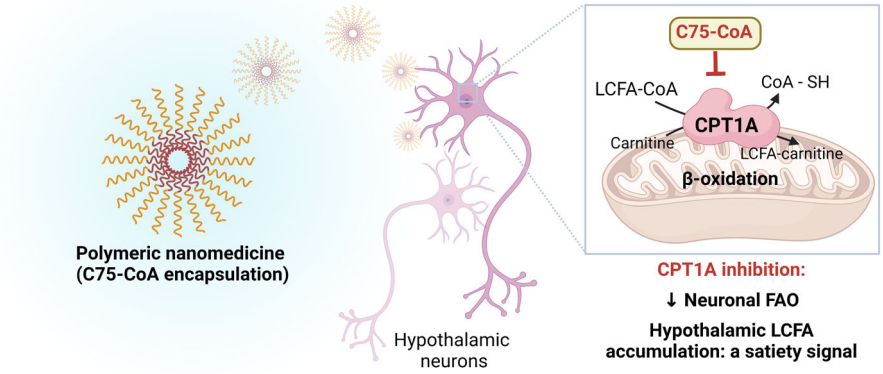

FIGURE 4 Nanomedicine potential to target neuronal CPT1 for hypothalamic regulation of energy balance. Development of polymeric micelles that encapsulate the CPT1A inhibitor C75-CoA for successful uptake by hypothalamic neurons to attenuate neuronal lipid metabolism. Long-chain fatty acids (LCFA) accumulation after CPT1A inhibition acts as a satiety signal that contributes to controlling bodyweight.

intake and glucose production[67] (Figure 3). In particular, inhibition of CPT1A activity in the MBH by icv injection of a specific riboprobe results in food intake suppression, downregulation of hypothalamic orexigenic neuropeptides (AgRP and NPY), and reduced hepatic gluconeogenesis.[67,68] This satiation activity is accompanied by an increase in long-chain FAs in the hypothalamus, and, in fact, inhibition of hypothalamic CPT1A activity itself has been shown to reproduce the effects of icv injection with oleic acid on food intake and glucose production.[11] It is therefore likely that long-chain FA accumulation rather than FA influx into the mitochondria is a major component in hypothalamic lipid sensing and satiety signaling. Mera et al.[69] have demonstrated that centrally administered C75—a synthetic FA synthase (FAS) inhibitor—is converted in the hypothalamus to C75-CoA, the active form of the drug acting on CPT1A, reducing catalytic activity and, in turn, food intake.[69,70] Conversely, the orexigenic action of ghrelin is reported to be mediated by AMPK activation, leading to malonyl-CoA reduction and a consequent increase in CPT1A activity and FAO activation.[71,72] CPT1A overexpression by a viral vector in the ventral hypothalamus has also been shown to trigger hyperphagia.[73] In rats, long-term overexpression of a permanently active form of CPT1A in the VMH is related to substantial changes in lipid profile (i.e., increased ceramides and sphingolipids, and decreased phospholipids) and in expression levels of glutamate and gamma-aminobutyric acid (GABA) transporters in the MBH.[74] It is suggested that, in the VMH, adeno-associated virus (AAV)-mediated overexpression of CPT1A increases FAO and modulates both reactive oxygen species (ROS) production and the cellular profile of sphingolipids and phospholipids, leading to mitochondrial UCP2 and FAS upregulation and an enhanced response to NPY and ghrelin. The alteration in glutamate and GABA transporters may support evidence for the orexigenic signal.[74]

Since CPT1A is highly expressed in central and peripheral tissues, its anti-obesity potential is based on two different interventions. In peripheral tissues (i.e., liver and adipose tissues), CPT1A overexpression and FAO induction ameliorate insulin resistance and prevent obesity,[62,75] whereas in the hypothalamus, as described above, CPT1A inhibition reduces food intake and bodyweight. Hence, selective CPT1A inhibition in the hypothalamus, not in peripheral tissues, seems to be a promising strategy for obesity management. C75-CoA is a well-known CPT1A inhibitor,[69] originally identified as a FAS inhibitor with an anorectic effect via malonyl-CoA accumulation.[76–78] Nevertheless, enantioselective synthesis of C75 reveals that the active form inhibiting CPT1A is (+)-C75 or the racemic form with the CoA adduct, while FAS is exclusively inhibited by the (−)-C75 form without the CoA adduct.[69,70] Hence, to inhibit CPT1A and regulate food intake, while minimizing off-target effects on FAS and undesired actions in the periphery, it is crucial to deliver C75-CoA directly into the hypothalamus. A major challenge of C75-CoA as cargo is that it is a small, polar, and negatively-charged molecule, with low permeability across the cellular membrane.[79] Our group has used this particular property to design a polymeric-based nanomedicine that specifically allows direct cellular transport of C75-CoA[80] (Figure 4). This nanomedicine, which efficiently inhibits CPT1A-dependent lipid metabolism in cellular models of neurons and glioma cells,[80] has promising potential to regulate food intake and bodyweight in vivo.

Altogether, the above-described findings point towards a key role for CPT1A in affecting long-chain FA levels in hypothalamic ARC and VMH neurons and so in regulating food intake and glucose production. However, several questions remain: whether CPT1A in ARC and VMH neurons regulates peripheral metabolism beyond glucose production, what the exact molecular mechanisms involved are, and whether CPT1A in other neurons and non-neuronal cells is responsible for this regulatory effect. Considering the latest advances in nanotechnology, promising although poorly explored field of research, is the development of nanoplatforms for selective targeting of proteins in hypothalamic neurons to control energy balance.[81–83] Our preliminary studies with a new drug delivery system targeting CPT1A, which have proved challenging, have successfully modified lipid metabolism in neurons.[80]

4 | CONCLUDING REMARKS

Promising targets for food intake and weight management are CPT1A and CPT1C, CPT1 isoforms found in the CNS that play a clear role in

hypothalamic lipid metabolism. However, CPT1A and CPT1C differ substantially in tissue expression profiles, subcellular localization, and catalytic activity, suggesting that the corresponding molecular mechanisms underlying energy balance and neuronal functions are different, although they may occasionally complement each other.

An important hypothalamic target for food intake control is CPT1A, since its activity in the hypothalamus is under control of malonyl-CoA levels and AMPK, and when its catalytic activity is blocked in response to overfeeding, FAO is reduced and long-chain FA accumulation acts as a satiety signal. However, a matter for further research is whether the CPT1A function in the hypothalamus goes beyond this anorexigenic pathway to involve hypothalamic BAT thermogenesis regulation, some specific neuronal function (e.g., spinogenesis), or non-neuronal cells. CPT1C is also an AMPK downstream effector in the AMPK/ACC-malonyl-CoA pathway, but differs from CPT1A in its feeding-regulatory action in that it involves additional neuronal functions and mechanisms that are independent of CPT1 catalytic activity. Mice lacking CPT1C in neurons have been shown to exhibit blunted central ghrelin or leptin activity in food intake control, associated with altered ceramide metabolism in the ARC. The ceramide/CPT1C signal is necessary but not sufficient to induce food intake, and so may be a concomitant pathway to the CPT1A-dependent signal.

Despite their disparities, CPT1A and CPT1C may play a synergistic role in hypothalamic control of food intake. As a downstream player in the canonical AMPK-SNS-BAT axis, CPT1C in the VMH has also been revealed as a necessary protein for thermogenesis activation and adaptation to short-term HFD administration. The downstream effectors of CPT1C in this function, still poorly understood, may be related to CPT1C capacity to regulate the activity of proteins resident and nonresident in the endoplasmic reticulum, such as ABHD6 and SAC1, and the resulting potential impact on vesicular transport, axonal growth, synaptic activity, and intracellular lipid metabolism in neurons with an impact on obesity and neurodegeneration.

Altogether, findings point to both CPT1A and CPT1C as key effectors of nutritional status in brain cells and regulators of food intake and energy homeostasis. Although the downstream molecular mechanisms are not fully understood, these targets in the hypothalamus offer promise for the treatment of obesity and related complications. To develop a next-generation therapy to treat obesity, the challenge remains to develop new nanomedicine platforms for selective targeting of CPT1 and related nutrient sensors in specific brain areas.

AUTHOR CONTRIBUTIONS

Rosalía Rodríguez-Rodríguez: Conceptualization; writing – original draft. **Anna Fosch:** Writing – review and editing. **Jesus Garcia-Chica:** Writing – review and editing. **Sebastian Zagmutt:** Writing – review and editing. **Nuria Casals:** Writing – review and editing.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this review because no new data were created or analyzed.

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