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Hypothalamic ceramide metabolism in obesity and dysregulation of glucose homeostasis

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Abstract
The central nervous system is a key regulator of energy and glucose homeostasis, integrating peripheral signals such as hormones and nutrients to maintain metabolic balance. Among its regions, the hypothalamus plays a central role in monitoring energy status and orchestrating physiological responses via neuronal and glial circuits. Recent research highlights the influence of de novo ceramide synthesis on central nervous system regulation of metabolism. Indeed, ceramides have emerged as critical signalling molecules linking fatty acid sensing to hypothalamic control of feeding, energy expenditure, and glucose regulation. This review details the mechanisms of de novo ceramide synthesis and explores how dysregulation of this pathway in the hypothalamus contributes to obesity and type 2 diabetes. Serine palmitoyl-transferase and specific ceramide synthase isoforms are shown to play roles in mediating neuronal responses to metabolic stress. The findings also emphasize that hypothalamic ceramide metabolism is modulated by both nutritional and hormonal cues and suggest that targeting this pathway may offer new strategies for treating metabolic disorders.

Keywords Ceramide · Hypothalamus · Obesity · Type 2 diabetes · Inflammation · Food intake · ER stress · CPT1c

1 Introduction

The nervous system plays a vital role in maintaining energy balance by continuously adjusting energy flow in response to the body's physiological demands [1]. This regulatory mechanism is crucial for supporting key metabolic functions, including blood glucose control and body weight regulation. Specific areas within the central nervous system (CNS) constantly monitor the body's energy status through afferent signals from the vagus nerve and through circulating cues such as hormones and nutrients [1].

Once these inputs are processed, the CNS coordinates responses that influence peripheral organs, such as the liver, skeletal muscles, adipose tissue, and the pancreatic islets, modulating both anabolic processes and catabolic pathways [2]. This delicate balance supports stable body weight and glucose levels across an individual's lifetime.

Several brain regions are implicated in this regulation. The hypothalamus is central to maintain metabolic equilibrium [3], while other areas, including the striatum, nucleus accumbens, and ventral tegmental area, contribute to reward-based eating and food preference [4]. These regions are populated by neurons capable of sensing nutritional states and responding to fluctuations in blood glucose, free fatty acids (FAs), and triglycerides [5]. Moreover, many of these neurons express leptin and insulin receptors, making them potentially vulnerable to resistance under conditions of metabolic imbalance [6]. Among the nutrients that influence these brain circuits, lipids play a key role by affecting the function of neurons, astrocytes, and microglia [6]. Research from the last decade suggests that impaired lipid sensing in the brain may contribute to disrupted energy regulation and the development of metabolic disorders, including obesity and insulin resistance.

Of particular interest is the role of de novo ceramide synthesis. Evidence is accumulating that ceramides in the brain is a crucial factor in the neural control of energy and glucose homeostasis. This review will explore the latest

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findings on how ceramide synthesis influences central regulation of energy balance and how its dysregulation may contribute to obesity and metabolic diseases such as type 2 diabetes (T2D).

1.1 Overview of de novo ceramide synthesis

Ceramide belongs to the sphingolipid (SL) family, a key group of lipids found in eukaryotic cells. Initially, ceramides were thought to function mainly as intermediates in lipid biosynthesis. However, they are now recognized for their crucial structural roles in cellular membranes and their ability to act as signalling molecules that influence processes such as cell death (apoptosis), proliferation, and inflammation [7]. Sphingolipids are characterized by a sphingoid base containing 18 carbon atoms, along with an amine and two hydroxyl groups [7]. This lipid class encompasses a wide variety of molecules with diverse structures and biological functions.

Ceramide biosynthesis via the de novo pathway begins on the cytosolic side of the endoplasmic reticulum (ER) membrane (Fig. 1). The process starts with the condensation of palmitate and serine, forming 3-keto-dihydrosphingosine, a reaction catalyzed by serine palmitoyltransferase (SPT) [7], which also serves as the rate-limiting step of the pathway. The SPT functions as a multi-component enzyme complex [8]. It

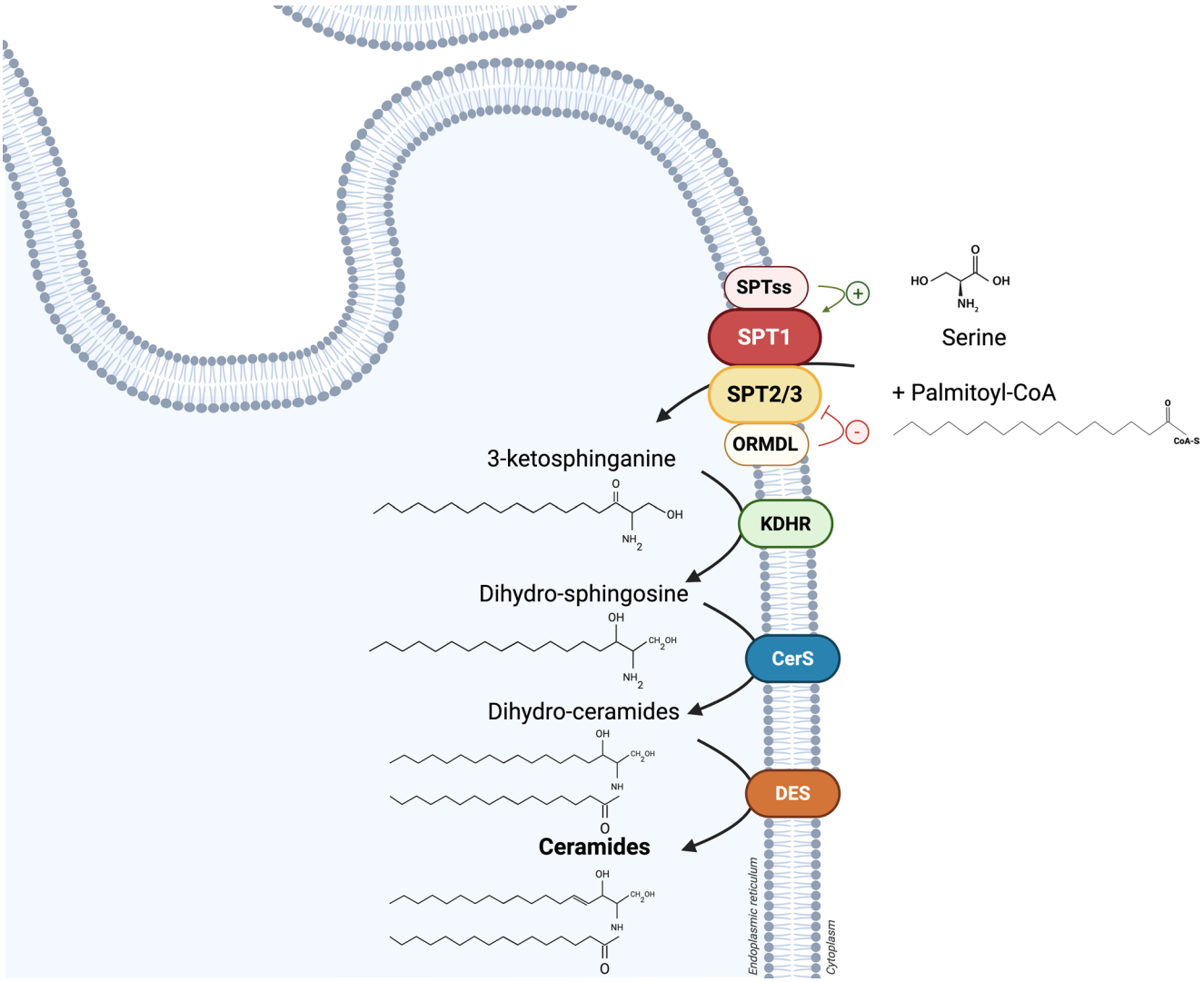

Fig. 1 : Overview of de novo ceramide synthesis De novo ceramide synthesis starts with the condensation of palmitate and serine to form 3-keto-sphinganine. This reaction is catalyzed by the serine palmitoyl transferase (SPT). The SPT complex is heterodimer formed with SPT1 and SPT2 or SPT3 associated with small subunit SPT (SPTss) and orosomucoid-like proteins (ORMDL). The accessory subunits SPTss are important for substrate specificity and increase of SPT activity. ORMDL negatively regulate SPT activity. 3-keto-sphinganine formed is reduced to dihydrosphingosine by the keto-sphinganine reductase (KDHR). Dihydrosphingosine will be acylated by ceramide synthases (CERS) to produce dihydroceramides. Finally, dihydroceramides will be desaturated by the dihydroceramide desaturase (DES) to give ceramides. Created with BioRender.com

is formed by two main catalytic subunits, SPTLC1 and either SPTLC2 or SPTLC3 alongside smaller, regulatory proteins [9]. The additional small subunits, SPTssa and SPTssb, enhance enzymatic function by facilitating the alignment of acyl-CoA and improving catalytic efficiency (Fig. 1). Moreover, these accessory proteins also influence acyl-CoA selectivity. SPTssa favors 16-carbon acyl-CoA substrates, whereas SPTssb exhibits specificity toward 18-carbon acyl-CoA [10]. While SPTLC1 is indispensable for enzyme activity [8], SPTLC2 and SPTLC3 serve partially redundant roles, differing mainly in their ability to generate various long-chain base lengths: SPTLC2 typically produces C18 to C20 bases, whereas SPTLC3 enables a broader range of products [9]. The activity of SPT is also tightly modulated by a group of three regulatory proteins called orosomucoid-like proteins (ORMDL) that bind to the enzyme complex and inhibit its function in response to sphingolipid levels [8](Fig. 1). Recent breakthroughs using cryo-electron microscopy have revealed how ORMDL3 integrates into the SPT complex [11] Structural evidence also suggests that ORMDLs are responsive to ceramide levels [12], elevated intracellular ceramide induces a conformational shift in the N-terminal region of ORMDLs, which in turn blocks the access channel for acyl-CoA, reducing sphingolipid synthesis and preventing lipid overload [8].

The 3-keto-dihydrosphingosine formed by the SPT complex is then reduced to dihydrosphingosine and subsequently acylated by ceramide synthases (CerS), resulting in dihydroceramide [7] (Fig. 1). There are six CerS isoforms in mammals, named CerS1 through CerS6 [13]. Although they catalyze the same reaction, each isoform prefers acyl-CoA substrates of specific chain lengths, contributing to the fatty acid diversity seen in ceramide molecules. The final step in ceramide production involves the enzyme dihydroceramide desaturase-1 (DES1), which introduces a double bond into the molecule [14] (Fig. 1).

1.2 Hypothalamic de novo ceramide synthesis: a strong link in lipid sensing

For a long time, fatty acids (FA) in circulation were considered to play a minimal role in neural regulation of energy balance, largely because they have limited permeability across the blood-brain barrier and are not utilized by neurons as a primary energy source [15]. Instead, glucose sensing by neurons was viewed as more central. However, evidence indicates that both neurons and astrocytes can detect circulating FAs, which in turn can influence energy balance by modulating insulin release, hepatic glucose output, and food intake, potentially through alterations in sympathetic and parasympathetic activity [16–18].

Recent findings also point to the involvement of hypothalamic ceramide production, specifically, the de novo ceramide synthesis, as a mechanism for FA sensing. One potential connection between circulating FAs and ceramide synthesis involves lipoprotein lipase (LPL), which hydrolyzes triglyceride-rich lipoproteins. LPL is expressed in brain regions such as the hypothalamus, hippocampus, and nucleus accumbens, where it supports local FA delivery to cells, thereby contributing to the regulation of energy homeostasis [19]. Mouse studies have shown that partial deletion of LPL in the ventromedial hypothalamus (VMH) results in obesity, not due to increased food consumption, but linked to lower energy expenditure and reduced thermogenic activity [20]. This LPL deletion also disrupts de novo ceramide synthesis [20]. When LPL is selectively removed from astrocytes, mice similarly develop obesity and show increased food intake alongside heightened ceramide levels in the hypothalamus [21]. Collectively, these observations suggest that targeted lipoprotein metabolism in hypothalamic neurons and astrocytes may contribute to energy balance, with LPL playing a protective, anti-obesity role, potentially through upregulation of ceramide biosynthesis.

Mitochondrial oxidation of FAs is another important component in energy homeostasis, involving enzymes like carnitine palmitoyl-transferase 1a and 1c (CPT-1a and CPT-1c). When levels of malonyl-CoA, an intermediate in FA metabolism, rise, CPT-1a is inhibited, blocking the mitochondrial entry of long-chain acyl-CoA [22]. Accumulated cytoplasmic acyl-CoAs then function as appetite-suppressing signals, leading to reduced expression of orexigenic peptides AgRP and NPY within the arcuate nucleus (ARC) of the hypothalamus [23–25]. This mechanism is modulated by leptin and ghrelin, which exert opposing effects on hypothalamic AMPK activity, and subsequently on malonyl-CoA levels [26] (Fig. 2).

Further studies implicate CPT-1c, located in the endoplasmic reticulum (ER), as a key mediator linking FA sensing and ceramide synthesis. According to Gao et al., CPT-1c may act downstream of malonyl-CoA during anorexigenic signaling by modulating ceramide production. Although CPT-1c has relatively low acyl-transferase activity compared to CPT-1a [27], it preferentially utilizes palmitoyl-CoA [28] a precursor in the ceramide synthesis pathway catalyzed by SPT [7, 29], Gao et al. also found that increasing CPT-1c expression in the ARC raised ceramide levels, while deleting it had the opposite effect [27]. Notably, this pathway appeared essential for leptin's ability to suppress food intake, and disruption of CPT-1c impaired this effect (Fig. 2). Meanwhile, ghrelin's orexigenic action seems to depend on AMPK activation and subsequent reduction of malonyl-CoA, which lifts inhibition on CPT-1c

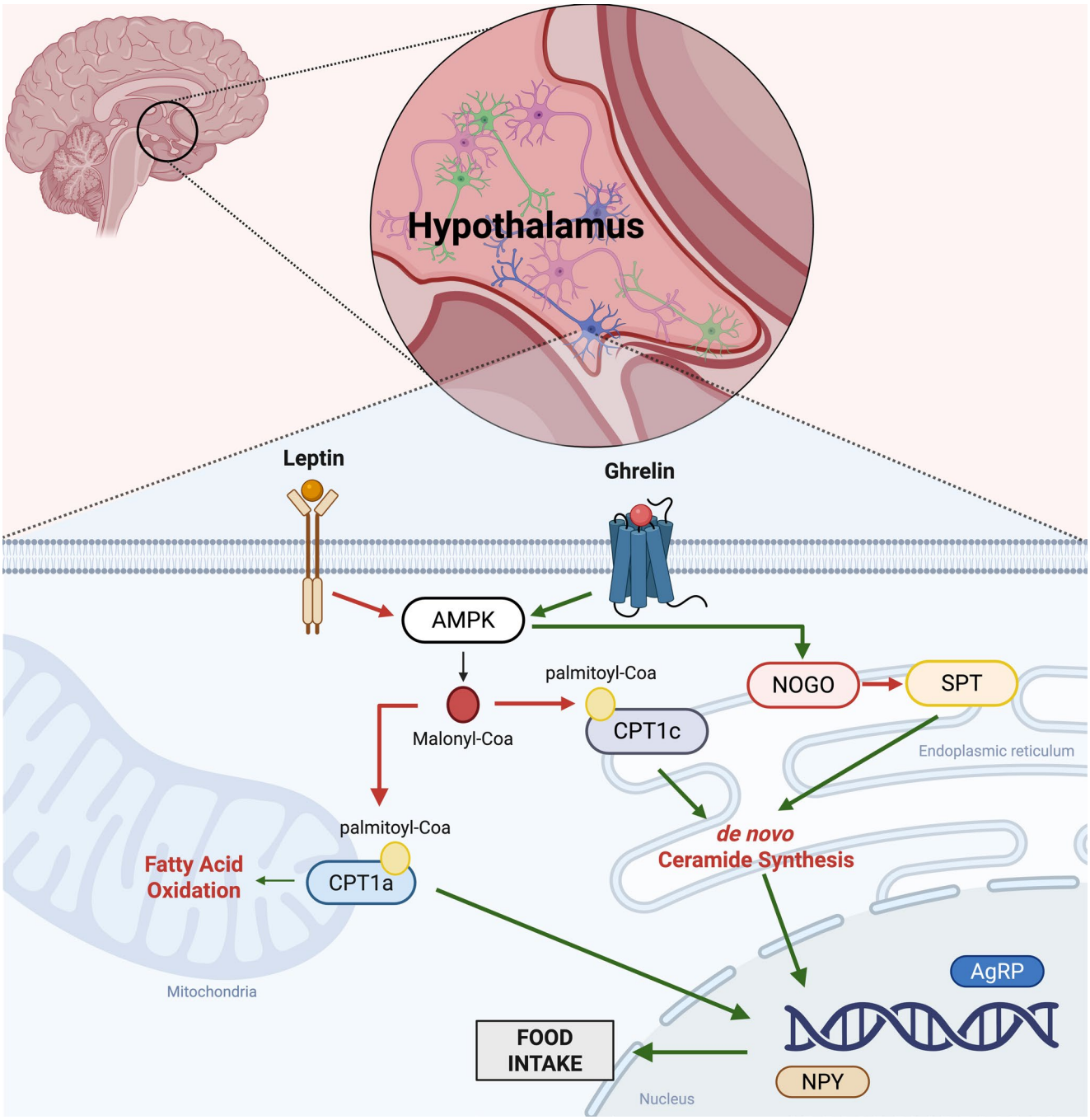

Fig. 2 : Role of hypothalamic de novo ceramide synthesis in the regulation of food intake When the AMPK pathway is inhibited by leptin, this will result in an increase of malonyl-CoA levels, which inhibits carnitine palmitoyl-transferase 1a (CPT1a) function and thereby decrease FA oxidation in mitochondria. This will be responsible for a decrease of expression of orexigenic neuropeptides AgRP and NPY in order to increase food intake in response to leptin. In opposite, when the AMPK pathway is activated by ghrelin, the resulting decrease of malonyl-CoA levels relieves its inhibitory action on CPT1a and therefore favours FA oxidation in mitochondria. Decrease of malonyl-CoA also favours the entry of FA through CPT1c in ER and their metabolism into ceramide through the de novo pathway. Ghrelin could also increase Nogo-A expression through an AMPK-dependent pathway in AgRP neurons. Nogo-A will, in turn, inhibits SPT and the de novo ceramide synthesis, favouring FA oxidation in mitochondria. Red arrow: inhibition; green arrow: stimulation. Created with BioRender.com

and promotes ceramide biosynthesis [30] (Fig. 2). This in turn stimulates AgRP and NPY gene expression, enhancing appetite. Interestingly, using myriocin, an inhibitor of SPT neutralized the opposing effects of leptin and ghrelin on orexigenic neuropeptides, underscoring the importance of hypothalamic ceramides in appetite regulation [27, 31].

These studies revealed, in addition to the CPT1a pathway, the existence of a parallel pathway involving CPT1C, which triggers a short-term increase in ceramide synthesis to mediate orexigenic effect of ghrelin (Fig. 2). However, the role of hypothalamic ceramide in ghrelin's effect has been recently challenged by Diano's group [30]. This group found that ghrelin increased expression of Nogo-A levels in AgRP neurons through an AMPK-dependent pathway. Nogo proteins have shown to be potent inhibitors of de novo ceramide synthesis [32]. The increase of Nogo-A inhibited SPT and the sphingolipid de novo biosynthesis, which allows FA to undergo fatty acid mitochondrial oxidation to favour food intake in response to ghrelin [30] (Fig. 2).

Structural analyses suggest that the active site of the SPT complex but also CerS is cytoplasm-facing [8, 33] raising questions about how palmitoyl-CoA delivered by CPT-1c into the ER lumen affects ceramide synthesis. Moreover, while the broader function of hypothalamic ceramide synthesis in energy homeostasis is established, the specific roles of individual ceramide species remain unknown up to now. It was recently shown that disruption of CerS6 expression in specific hypothalamic neurons influences feeding behavior and energy expenditure in obese mice [34], supporting the idea that CerS6-derived C16:0 ceramides in the hypothalamus could control the regulation of energy balance in obese mice. Whether other CerS-derived ceramide species could act as lipid sensor in the hypothalamus remain unknown. It will also be important to determine the role of regulatory proteins of the SPT complex in FA sensing (Fig. 1). Interestingly, whole-body ablation of ORMDL3 increase body weight gain in mice fed with an obesogenic diet [35]. ORMDL3 appears to have a lower expression in some area of the hypothalamus (Allen Brain Atlas Adult Human Brain Tissue Gene Expression Profiles; [36] which could favour ceramide synthesis and body weight gain in response to FA. A last question concerns the role of metabolism of ceramide in FA sensing. Knock-out mice for the glucosylceramide synthase (GCS) in POMC neurons fail to respond to peripheral energy signals such as leptin, resulting in obesity in these mice [37]. It has been shown that the deletion of GCS in hypothalamus neurons in mice, resulted in the accumulation *de novo* ceramides under HFD, which is sufficient to counteract leptin's action. These data support the notion that both ceramides and its metabolites produced by GCS, gangliosides, are potent regulators with antagonistic behavior on leptin signalling in the hypothalamus.

1.3 De novo ceramide biosynthesis plays a role in hypothalamic lipotoxicity-induced obesity and dysregulation of glucose homeostasis

In insulin sensitive tissues, the build-up of ceramides is a known contributor to insulin resistance, which is a precursor to T2D [38]. This lipotoxic effect typically involves inflammatory responses and endoplasmic reticulum (ER) stress. In the hypothalamus, ER stress is implicated in both insulin and leptin resistance, potentially leading to weight gain [39, 40]. Under lipotoxic conditions, ceramide accumulation in the brain has been implicated in energy balance disruption [41]. Early evidence from studies in genetically obese rats (e.g., Zucker rats) demonstrated increased hypothalamic ceramide content [41, 42] (Fig. 3). Further, both endogenous and exogenously administered ceramides were shown to induce hypothalamic dysfunction, ER stress, and reduced sympathetic output, which in turn decreased thermogenesis and led to weight gain without increased food consumption [41] (Fig. 3). Beyond ER stress, ceramides also impair insulin signalling directly [43]. In neuronal GT1-7 cells, ceramide synthesis led to insulin resistance via activation of PKCζ [42] (Fig. 3). In muscle cells, PKCζ has been shown to interact with and phosphorylate the pleckstrin homology domain of Akt, leading to its sequestration and subsequent inability to be activated by insulin [43, 44]. Ceramide metabolism may also influence neuroinflammation [45] (Fig. 3), which is central to brain insulin resistance. Inhibiting SPT with L-cycloserine reduced palmitate-driven ceramide accumulation and downregulated proinflammatory cytokines IL-6 and TNFα in hypothalamic cell lines [45]. However, more in vivo studies are needed to fully understand this relationship.

Disruptions in energy balance, often associated with obesity, are known to impair glucose regulation and contribute to the onset of T2D. Lopez's research team demonstrated that enhancing the expression of the chaperone protein GRP78 in the VMH of rats could mitigate the harmful effects of ceramide, leading to better glucose regulation [41]. This intervention also reversed insulin resistance in obese Zucker rats [41]. On the other hand, directly inhibiting ceramide production in the brain using the SPT inhibitor myriocin did result in improved glucose tolerance in these animals [42]. In obese rats, glucose intolerance is not just tied to insulin resistance, but also to impaired insulin secretion [42] (Fig. 3). Lowering ceramide levels in the hypothalamus helped restore the pancreas's ability to release insulin in response to glucose, thereby enhancing glucose metabolism [42]. Glucose influences insulin secretion in part by modulating the parasympathetic nervous system [46, 47] (Fig. 3). In obese rats, basal parasympathetic activity is heightened, but it does not increase further in response to glucose, indicating

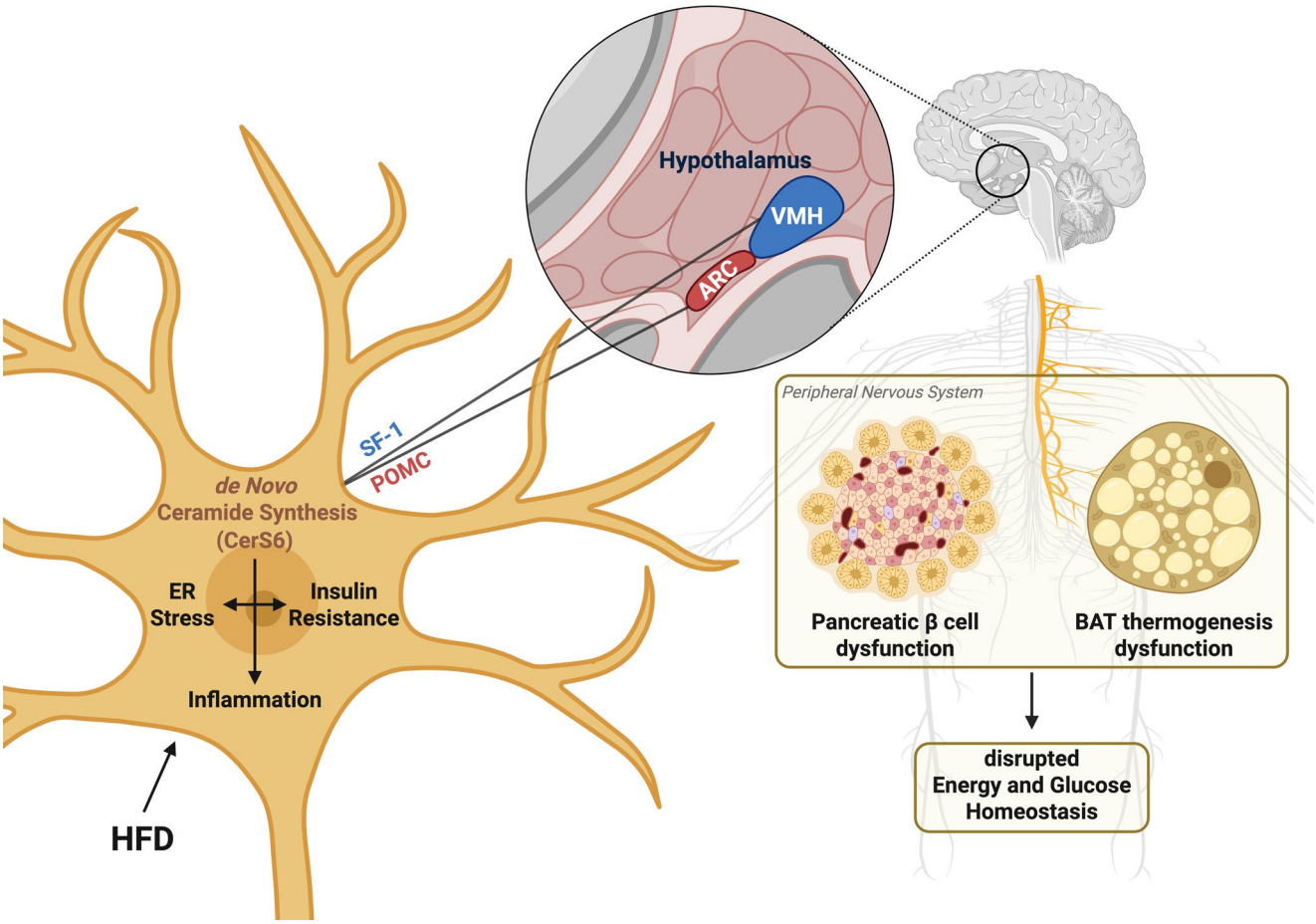

Fig. 3 : Dysregulation of energy and glucose homeostasis by hypothalamic *de novo* ceramide synthesis When ceramide levels are increased by *de novo* ceramide synthesis in the hypothalamus by high fat diet (HFD), the resulting ER stress, central insulin resistance and inflammation, will impair energy and glucose homeostasis. Hypothalamic ceramides reduce brown adipose tissue (BAT) sympathetic nerve activity which decreases thermogenesis and therefore favours body weight gain. Hypothalamic ceramides also decrease parasympathetic activity, which results in pancreatic β cell dysfunction and therefore favours hyperglycemia. The ceramide synthase 6 (CerS6) expressed in neurons expressing pro-opiomelanocortin (POMC) or steroidogenic factor 1 (SF-1) in the arcuate nucleus (ARC) and the ventromedial hypothalamus (VMH) mediate the effect of HFD on feeding behaviors and glucose homeostasis. Altogether, deregulation of body weight gain and glycemia by hypothalamic ceramide would be the premise to develop obesity and type 2 diabetes. Created with BioRender.com

a dysfunction in hypothalamic glucose sensing. This defect was traced back to ceramide synthesis, as treatment with myriocin restored glucose-induced parasympathetic activation [42]. Since the parasympathetic system also influences pancreatic β-cell proliferation [46], blocking ceramide production in the hypothalamus led to an increase in β-cell area and a greater number of small islets [42].

The biological effects of ceramides may vary depending on their fatty acid chain length which relies on CerS activity [13]. At the periphery, CerS6-derived C16:0 ceramides, a ceramide species that is also produced by CerS5, inhibit insulin signaling in liver and brown adipose tissue, while in skeletal muscle CerS1-derived C18:0 ceramides impair glucose homeostasis associated with obesity [48]. Importantly, both CerS1- and CerS6-deficient mice are protected from diet-induced obesity and glucose intolerance [44]. Interestingly, total CerS6-knock-out mice were protected from diet-induced obesity [49] suggesting a potential role of this CerS at the hypothalamic levels. Brüning and colleagues recently provided evidence for the role of hypothalamic CerS6 in the induction of obesity and glucose intolerance [34] (Fig. 3). By targeting CerS6 in subpopulations of hypothalamic neurons, they identified a specific role of CerS6-dependent ceramide synthesis in SF-1 neurons of the VMH and POMC neurons but not in AgRP neurons of the ARC in order to dysregulate glucose homeostasis (Fig. 3). In the N43/5 hypothalamic neuronal cells, selective inhibition of CerS6 prevents palmitate-induced ER stress [34], supporting the connexion between ceramide production in the VMH and hypothalamic ER stress in obese mice [41].

Mitochondrial function also plays a role in glucose sensing by POMC neurons. Recent research indicates that

mitochondrial rigidity in these neurons impairs glucose detection, leading to inadequate insulin secretion [50]. Similarly, SF-1 neurons in the VMH depend on regulated mitochondrial dynamics for regulation of glucose homeostasis [51]. CerS6 is a potent regulator of Gdf15 and Fgf21 in N43/5 hypothalamic neuronal cells, which as both signal for mitochondrial dysfunction [34]. Importantly, Brüning and colleagues found that CerS6 promotes mitochondrial fragmentation in POMC neurons upon HFD-feeding mice [34]. ORMDL3 has been identified as an obesity-related gene [52]. The deletion of ORMDL3, which could localized to mitochondria-associated membranes [53] increases insulin resistance in mice fed with an obesogenic diet [35]. Whether ORMDL3 plays a role in hypothalamic lipotoxicity remains to be explored.

Interestingly, glucose is known to activate POMC neurons in the ARC, which in turn affect parasympathetic output [54]. Glucokinase is an enzyme essential for glucose sensing, which is expressed abundantly in the ARC [55] and its activity is crucial for maintaining glucose tolerance and insulin secretion. In conditions where POMC neurons lose their ability to detect glucose, such as under a high-fat diet, glucose tolerance suffers [56]. The recent evidence of a role of CerS6 in POMC neurons to control glucose homeostasis, will prompt to investigate the role of C16:0-ceramide in the control of glucose-induced parasympathetic activation.

Previous studies have shown that C18-ceramide accumulates in the hypothalamus of obese rats [41]. However, selective deletion of CerS1 in hypothalamic neurons was unable to alter glucose metabolism in obese mice [34]. Therefore, it will remain to explore the role of others CerS-derived C18:0 ceramide in the hypothalamic control of energy and glucose homeostasis.

1.4 Conclusions and Perspectives

Over the past decade, numerous studies have highlighted the importance of de novo ceramide synthesis in specific hypothalamic regions as a key mechanism regulating energy balance, particularly through the action of neuropeptides. Notably, when ceramide levels are excessively elevated due to increased de novo ceramide synthesis under lipotoxic conditions, this imbalance can disrupt energy homeostasis, contributing to abnormal eating behaviors, obesity, and impaired glucose regulation. Continued research identified part of the specific neural cell types involved in ceramide production and action with the selective role of CerS-derived ceramide species.

Recent research also highlights hormonal regulation of hypothalamic ceramide synthesis. Thyroid hormone T3, for instance, reduces ceramide-induced stress in the hypothalamus and promotes thermogenesis through an AMPK-dependent mechanism in VMH neurons [57]. Similarly, estradiol regulates ceramide metabolism [58]. Reduced estrogen, as seen during menopause, elevates SPT expression and ceramide levels, while estradiol replacement reverses these effects, improving metabolism and promoting BAT thermogenesis [58]. Moreover, ceramide synthesis in the hypothalamus may influence the timing of puberty [59]. Childhood obesity has been linked to elevated SPTLC1 expression in the hypothalamus, accelerating ovarian development and advancing puberty onset. These findings collectively suggest that hypothalamic ceramide metabolism is responsive to hormonal and dietary cues and could be a target for obesity treatments. This is supported by the action of telmisartan, an angiotensin II receptor blocker, which prevents ceramide accumulation in the hypothalamus and has anti-obesity effects [60].

To conclude, hypothalamic de novo ceramide synthesis emerges as both a physiological regulator and a potential pathological driver of energy and glucose homeostasis. Enhancing our understanding, especially in the role of the SPT complex, including the SPTLC3 isoform which is increased during obesity [61] but also the negative regulators ORMDL, in this area could pave the way for earlier diagnosis and more effective treatments for obesity and its associated metabolic complications.

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Author contributions HLS and CM: conceived the idea. HLS, CM and PV wrote the manuscript and approved the final manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Clinical trial number not applicable.

Competing interests The authors declare no competing interests.

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