Review

The return of malonyl-CoA to the brain: Cognition and other stories

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ARTICLE INFO

ABSTRACT

Nutrients, hormones and the energy sensor AMP-activated protein kinase (AMPK) tightly regulate the intracellular levels of the metabolic intermediary malonyl-CoA, which is a precursor of fatty acid synthesis and a negative regulator of fatty acid oxidation. In the brain, the involvement of malonyl-CoA in the control of food intake and energy homeostasis has been known for decades. However, recent data uncover a new role in cognition and brain development. The sensing of malonyl-CoA by carnitine palmitoyltransferase 1 (CPT1) proteins regulates a variety of functions, such as the fate of neuronal stem cell precursors, the motility of lysosomes in developing axons, the trafficking of glutamate receptors to the neuron surface (necessary for proper synaptic function) and the metabolic coupling between astrocytes and neurons. We discuss the relevance of those recent findings evidencing how nutrients and metabolic disorders impact cognition. We also enumerate all nutritional and hormonal conditions that are known to regulate malonyl-CoA levels in the brain, reflect on protein malonylation as a new post-translational modification, and give a reasoned vision of the opportunities and challenges that future research in the field could address.

1. Introduction: an historical perspective

Malonyl-CoA is the precursor of fatty acid (FA) synthesis and its levels fluctuate greatly in response to nutrients and hormones. However, malonyl-CoA is not only a metabolic intermediary, it is also an allosteric regulator of carnitine palmitoyltransferase 1 (CPT1) enzymes, as was first demonstrated in 1977 by McGarry and col. [1]. This crucial finding unveiled the mechanism by which the synthesis and degradation of FAs are perfectly coordinated in cells, with a special importance in tissues such as liver, muscle or adipose tissue. Years later, by experimental serendipity, the teams of Lane and Kuhjada evidenced that malonyl-CoA accumulation in the hypothalamus resulted in satiety and weight loss [2] suggesting a signaling role, in addition to controlling FA metabolism. Since then, a great deal of effort has been made to elucidate the role and targets of malonyl-CoA in different hypothalamic nuclei in the control of food intake and energy homeostasis.

However, other functions of malonyl-CoA beyond the regulation of energy homeostasis have recently emerged in the regulation of brain development, cognition abilities and motor function [3–5]. Moreover, it cannot be ruled out that malonylation of proteins, a new post-translational mechanism [6], may represent another way by which nutrients impact brain function. We will discuss how these recent findings contribute to the comprehension of the molecular mechanisms that drive nutrients' effects on cognition and neuron function, and we will give some guidance on future research in this field.

2. FA synthesis and oxidation pathways are perfectly coordinated by a unique lipid metabolite

Malonyl-CoA is synthesized by acetyl-CoA carboxylase (ACC) from acetyl-CoA, to subsequently generate long-chain FAs by fatty acid synthase (FASN) (see Fig 1), or be used to elongate preformed FAs by two-carbons units [7]. ACC is an enzyme that is very well regulated, both allosterically and by phosphorylation, since it catalyzes the first committed and rate-determining step in FA synthesis [8]. There are 2 different ACC enzymes: ACC1 in the cytosol and ACC2 associated to the
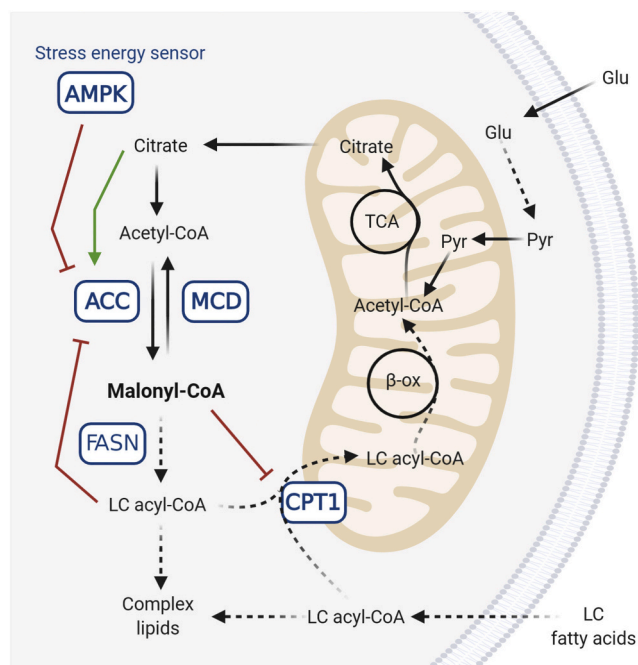
Fig. 1. Malonyl-CoA coordinates the synthesis and oxidation of fatty acids. Malonyl-CoA is the precursor of fatty acid synthesis in the cytosol, and behaves as a negative allosteric regulator of CPT1A and CPT1B enzymes, therefore regulating the mitochondrial oxidation of long-chain fatty acids. This means that the two metabolic pathways, fatty acid synthesis and oxidation, do not occur simultaneously. Malonyl-CoA is synthesized by acetyl-CoA carboxylase (ACC) from acetyl-CoA, while malonyl-CoA decarboxylase (MCD) catalyzes the conversion of malonyl-CoA back to acetyl-CoA. ACC activity is highly regulated: upon energy stress or in response to hormones, the energy sensor AMPK phosphorylates and inhibits ACC, causing a decrease in malonyl-CoA levels. Whereas, under glucose availability, citrate is shuttled out of the mitochondria to act as an allosteric activator of ACC, resulting in an increase of malonyl-CoA. On the other hand, long-chain acyl-CoAs, such as palmitoyl-CoA, are inhibitors of ACC.

outer mitochondrial membrane [9]. Malonyl-CoA is also generated in the lumen of the mitochondria by the acetyl-CoA synthetase ACSF3 from malonate. However, in this subcellular localization, malonyl-CoA synthesis is aimed to detoxify malonate but is not involved in FA synthesis [10].

One allosteric activator of ACC is citrate. In conditions of nutrient abundance, especially high glucose availability, accumulated citrate in the mitochondria is shuttled to the cytosol for conversion to acetyl-CoA. Cytosolic citrate highly activates ACC fostering the synthesis of FAs to store excess nutrients in form of fat [8]. By contrast, palmitoyl-CoA and other acyl-CoA behave as allosteric inhibitors. Interestingly, ACC polymerization into extensive filaments of different conformations stabilizes the catalytically competent or incompetent states of the protein [11]. Moreover, some proteins such as Mig12 and Spot14 modulate ACC polymerization, and in consequence, its activity [12,13].

The main kinase that regulates ACC activity is the energy sensor AMP-activated protein kinase (AMPK) [14]. ACC is one of the best-characterized canonical targets of AMPK. In conditions of energy stress (fasting, prolonged exercise, etc.) or in response to hormones (glucagon, ghrelin, etc.), AMPK is activated and phosphorylates and inactivates ACC, resulting in a decrease of malonyl-CoA levels and FA synthesis, leading to significant savings in cell energy expenditure. Interestingly, drugs and nutrients can also regulate AMPK and lead to changes in malonyl-CoA levels in cells. For instance, metformin (anti-diabetic drug) and resveratrol (a natural polyphenol found in grapes and red wine) inhibit ATP synthesis, therefore activating AMPK indirectly by increasing AMP levels [14].

The levels of malonyl-CoA can also be modulated by malonyl-CoA decarboxylase (MCD), the enzyme that catalyzes the conversion of malonyl-CoA back to acetyl-CoA (Fig. 1). MCD is mainly regulated by genetic expression in response to nutrients and hormonal changes [15].

In addition to being the first intermediate in FA biosynthesis, malonyl-CoA is the physiological inhibitor of carnitine palmitoyl-transferase 1 (CPT1) enzymes, which regulate the entry of long-chain FAs to the mitochondria for beta-oxidation [1]. In this way, only one metabolite, whose synthesis and degradation is highly regulated by nutritional and hormonal conditions, coordinates the synthesis and the oxidation of FAs, meaning that the two pathways are not active at the same time, but rather they are segregated in time. Moreover, taking into consideration that the glucose-derived metabolite citrate is the main allosteric activator of ACC, we can say that malonyl-CoA is at the crossroad between glucose and FA metabolic pathways (see Fig. 1), which explains the importance of this metabolite in the control of energy metabolism.

3. Malonyl-CoA sensing by CPT1 enzymes

CPT1 proteins are thought to be the main malonyl-CoA downstream effectors in the brain. There are three different CPT1 isoforms: CPT1A, with a ubiquitous distribution in the body but highly expressed in the liver, kidney and pancreas; CPT1B, mainly expressed in muscle, heart and adipose tissue; and CPT1C, exclusively expressed in the brain [16]. CPT1A and CPT1C coexist in the brain, though they are chiefly localized in different cell types: CPT1C in neurons and CPT1A in astrocytes [17,18]. CPT1A and B catalyze the transesterification of long-chain acyl-CoA into acyl-carnitines in order to facilitate their entry into the mitochondrial matrix, and their activity is negatively regulated by malonyl-CoA, in order to block FA oxidation (FAO) when FA synthesis is underway. CPT1C is the most intriguing isoform since, in contrast to the other canonical isoforms, it is an endoplasmic reticulum (ER)-resident protein, it has insignificant catalytic activity and it is unable to facilitate FAO in cells [19–21]. Interestingly, it maintains the ability to bind malonyl-CoA in the physiological range, which led our group and others to hypothesize that CPT1C could be a pseudoenzyme with the unique role of sensing malonyl-CoA in neurons [16,20,22]. Recently published articles have confirmed this hypothesis [3,5,23,24], and unveiled some downstream signaling mechanisms, which we will summarize and discuss later.

The crystal structure of CPT1 enzymes is yet to be achieved, but it is well known that the three isoforms have a short N-terminal cytosolic domain, two transmembrane domains with a short intraluminal loop between them, and a long C-terminal cytosolic region that includes the catalytic domain and the malonyl-CoA binding site [25] (see Fig. 2 for a 3D model of CPT1 proteins). Since the N-terminal region has negative or positive effects on malonyl-CoA sensitivity and carnitine affinity [26], it has been named the regulatory domain. Nuclear magnetic resonance (NMR) spectroscopy studies have elucidated the structure of the N-terminal regulatory domain of CPT1A and CPT1C. Interestingly, it can switch between two alternative conformations, which determines the binding of malonyl-CoA to the protein [27,28]. In CPT1C, one of the two conformation is destabilized, suggesting a different specific role for this isoform.

On the other hand, CPT1C has an additional 30 residues in the C-terminal region, not present in CPT1A or CPT1B (Fig 2), which are necessary for the binding to other proteins [3]. Since a high resolution proteomic analysis has revealed that CPT1C interacts with a different array of ER-resident proteins [29], it is to be expected that changes in CPT1C conformation by malonyl-CoA binding would trigger conformational changes to its interacting proteins and modulate their function. This points to the idea that malonyl-CoA plays a thus far undiscovered role in the brain in addition to the regulation of lipid metabolism.
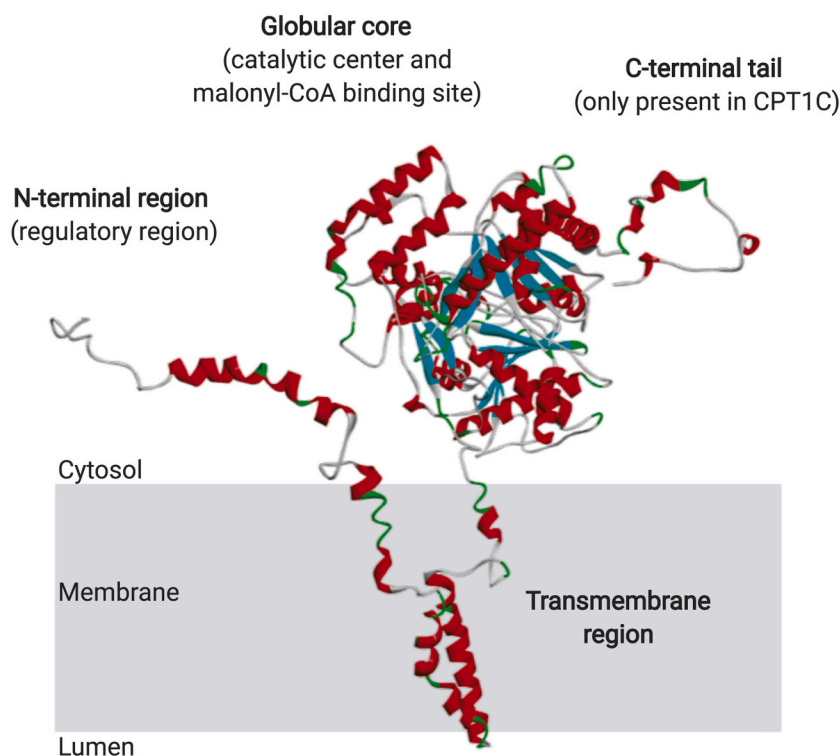
Fig. 2. Representation model of CPT1 proteins. CPT1 proteins show the following domains: a N-terminal regulatory domain, which switches between two different conformations depending on malonyl-CoA binding; two transmembrane domains that anchor the protein to the outer mitochondrial membrane (CPT1A and CPT1B) or to the endoplasmic reticulum (CPT1C); the protein is always facing the cytosol; the globular core that comprises the catalytic center and the malonyl-CoA binding site; and a C-terminal tail of about 30 residues, which is only present in CPT1C and is the region that binds the GluA1 subunit of AMPA receptors.

4. Hypothalamic malonyl-CoA as a mediator of feeding behavior and peripheral metabolism

The hypothalamus is a major player maintaining the balance between food intake and energy expenditure. In addition to the classical regulation of energy homeostasis by endocrine action, a novel hypothalamic regulatory mechanism was identified whereby malonyl-CoA acts as a modulator of satiety and energy expenditure. This mechanism was first evidenced based on the observation that pharmacological inhibitors of FASN (C75 and cerulenin) suppressed food intake and produced a substantial body weight loss and adiposity reduction after systemic or central administration to obese or lean mice, in a leptin-independent manner [2]. Importantly, central simultaneous administration of 5-tetradecyloxy-2-furoic acid (TOFA), an inhibitor of ACC, antagonized the satiating effect of C75. In line with these results, the authors proposed a model in which C75 causes an accumulation of hypothalamic malonyl-CoA, which in turn acts to downregulate neuropeptide Y (NPY) synthesis, thereby suppressing food intake.

The role of malonyl-CoA as a satiating signal was then supported by other studies using not only pharmacological strategies [30–34], but also nutritional situations and hormonal treatments known to regulate malonyl-CoA levels, such as fasting/feeding cycles [30], central glucose administration [35], or in response to leptin [35–37] or ghrelin [38,39] (Table 1) (Fig. 3). The fact that a decrease in hypothalamic malonyl-CoA was sufficient to induce appetite and body weight gain was further confirmed by studies overexpressing MCD in the mediobasal hypothalamus of rodents [40,41]. The importance of the malonyl-CoA pathway has also been proposed in relation to human satiety. Patients with a rare MCD deficiency show abnormal brain development [42] and some of them also have a low appetite, in agreement with the suggested role of malonyl-CoA as a satiating signal [43,44].

Malonyl-CoA in the hypothalamus has other functions beyond regulating feeding behavior. An increase in hypothalamic malonyl-CoA levels correlates with increases in peripheral energy expenditure. This finding was first described in longitudinal pair-feeding investigations, showing that C75-treated obese mice lost more body weight than their control counterparts [33]. Supporting this notion, Cha and col. [45,46] found that an increase in hypothalamic malonyl-CoA rapidly signals to skeletal muscles via the sympathetic nervous system, increasing FAO and therefore energy expenditure (Fig. 3). Later, Lopez and col. demonstrated that thyroid hormones, through the inhibition of AMPK in the ventromedial hypothalamus (VMH), increased hypothalamic malonyl-CoA levels, and through the sympathetic nervous system activated brown adipose tissue (BAT) thermogenesis [47] (Fig. 3).

When evaluating the intracellular signaling mechanisms of malonyl-CoA on energy homeostasis, it looks quite clear that the AMPK/ACC pathway plays an essential role as an upstream mediator [48,49]. The changes in hypothalamic malonyl-CoA led by nutritional or hormonal stimuli are tightly coupled with changes in the AMPK/ACC pathway [36,50], even in specific hypothalamic nuclei such as the VMH [47,51] (Fig. 3). But, what about the cellular target of malonyl-CoA and how is its signal transmitted? The group of Rossetti pointed CPT1A as a downstream target of malonyl-CoA, since inhibition of CPT1A in the hypothalamus of rodents resulted in diminished food intake and hepatic glucose production, and body weight attenuation [52–54] (Fig 3). In line with this evidence, CPT1A overexpression in the VMH of rats increased food intake and body weight [55,56]. However, the downstream mechanisms underlying the hypothalamic effect of CPT1A on food intake and glucose homeostasis are not well understood. The regulation of K_{ATP} channels by long chain fatty acyl-CoAs, and the activation of FAO leading to the production of reactive oxygen species (ROS) and the expression of uncoupling protein 2 (UCP2) have been pointed to as potential mechanisms [53,56–59]. The cell type in which CPT1A exerts those effects is not clear either. CPT1A expression is higher in astrocytes than in neurons [18], and astrocytes are an active component of the tripartite synapse and its metabolism is coupled with neuronal activity [60]. However, we cannot rule out that CPT1A-mediated regulation of FA metabolism in neurons play a signaling role. Selective deletion of CPT1A in specific neuronal populations or astrocytes of hypothalamic nuclei will shed light on the mechanisms by which CPT1A controls food intake and energy homeostasis.

Since the discovery of the neuron-specific CPT1 isoform in 2002

Table 1
Malonyl-CoA fluctuations in the brain

Stimulus		Species	Model	Effect on each brain region				Whole brain	Ref.
				HPT	CTX	HPC	CRB		
Nutrients	Glucose	Mouse	Acute IP injection of glucose (1 g/kg or 4 g/kg of body weight; 1 h) in food deprived mice	↑	-	-	-	-	[35]
	Fructose	Mouse	Acute IP injection of fructose (4 g/kg of body weight; 10 min) in food deprived mice	ns	-	-	-	-	[145]
Hormones	Leptin	Mouse	Acute ICV administration of leptin (200 ng; 2-3 h) in food deprived mice	↑	-	-	-	-	[35]
		Rat	Acute ICV administration of leptin (15 µg; 3 h)	↑ (ARC)					[36]
		Mouse	Chronic ICV administration of leptin (10 µg) daily for 7 days in DIO or control mice	ns	-	-	-	-	[37]
	Ghrelin	Rat	Acute ICV administration of ghrelin (3.2 nmoles; 2 h) in fed satiated rats	↓ (VMH)	-	-	-	-	[38]
		Rat	Acute ICV administration of ghrelin (5 µg; 2 h) in fed satiated rats	↓	-	-	-	-	[39]
	T4 thyroid hormone	Rat	Chronic SC administration for 21 d (100 µg/d)	↑	-	-	-	-	[47]
Diets	Fasting	Mouse	Fasting for 16 h (vs refed 2 h)	↓	-	-	-	-	[30]
		Rat	Fasting (male and female) for 16 h (vs SD)	↓	↓	↓	↓	-	[104]
		Rat	Fasting for 24 hours (vs SD)	↓	-	-	-	-	[146]
	High fat diet	Rat	HFD (62.2 %) for 4 weeks + 16 h fasting (vs HCD, 63.5 %)	↑	ns	ns	ns		[147]
		Rat	HFD (60 %) for 9 weeks (vs 10 % FD)	ns	-	-	-	-	[37]
	High protein diet	Rat	HPD (56.5 %) for 4 weeks + 16 h fasting (vs HCD, 63.3 %)	↑	ns	ns	ns	-	[147]
	Calorie restricted diet	Rat	50 % CR for 4 weeks (vs SD)	↑	-	-	-	-	[146])
		Rat	9-18 % CR for 5 weeks (vs SD)	↓	-	-	-	-	[148]
	Ketogenic diet	Rat	30 % of total calories from ketone bodies	-	-	-	-	↑	[113]
Drugs	C75	Mouse	Acute ICV administration of C75 (10 µg; 2.5 h) in fasting mice	↑	-	-	-	-	[30]
	Tamoxifen	Rat	Chronic SC administration of tamoxifen (0.5 mg/kg/day) for 5 days	↑	-	-	-	-	[34]
	AICAR	Mouse	Acute ICV administration of AICAR (6 µg; 2h)	↓	-	-	-	-	[41]
	Compound C (AMPK inhibitor)	Rat	Acute ICV administration of Compound C (10 µg) in fasting rats	↑	-	-	-	-	[39]
Genetic-based approaches	AMPKα dominant negative	Rat	Injection of AMPKα-DN adenoviruses into the VMH	↑ (VMH)	-	-	-	-	[47]
	Leptin R mutation	Rat	Zucker-diabetic fatty (vs Zucker)	↓	ns	ns	↑	-	[118]
	Leptin R mutation	Rat	Zucker-fatty (vs Zucker-lean)	ns	↓	↓	ns	-	
Behavior	Stress	Rat	Social defeat procedure daily for 5 weeks, which results in anorexia	↑	-	-	-	-	[125]
Hypermetabolic state	Pregnancy	Rat	Female pregnant at day 16-17 of gestation	↑	-	-	-	-	[126]

ARC: arcuate; CBR: cerebellum; CR: caloric restriction; CTX: cortex; DIO: diet-induced obesity; DN: dominant negative; h: hours; HCD: high-carbohydrate diet; HFD: high-fat diet; HPD: high-protein diet; HPT: hypothalamus; HPC: hippocampus; ICV: intracerebroventricular; IP: intraperitoneal; ns: not significant; R: receptor; SD: standard diet; SC: subcutaneous; VMH: ventromedial hypothalamus; vs: versus. A dash (-) means no data available.

[20], many research groups have proposed and demonstrated that CPT1C is a downstream target of malonyl-CoA in the regulation of food intake and peripheral energy expenditure. Knock-out (KO) mice of CPT1C show a disruption of leptin and ghrelin signaling on feeding behavior [61–63], and impaired diet- and leptin-induced brown fat thermogenesis, making them more susceptible to become obese under high fat feeding [64–67]. Moreover, hypothalamic CPT1C is responsible for food preference [23] and fuel selection under fasting conditions [68]. The role of CPT1C as a downstream target of malonyl-CoA in the hypothalamus was evidenced by the use of a mutated CPT1C isoform unable to bind malonyl-CoA [24]. Moreover, BAT thermogenesis was not triggered by acute AMPK silencing in the VMH of CPT1C KO mice [24]. Altogether, CPT1C is revealed as a downstream mediator of the AMPK/ACC axis in the regulation of energy homeostasis. However, the hypothalamic downstream effectors of CPT1C are still unknown. In cortical neurons, CPT1C regulates the trafficking of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors to the neuron surface depending on malonyl-CoA levels [3]. AMPA receptors (AMPARs) mediate fast excitatory neurotransmission in the central nervous system and are the main determinants of synaptic plasticity. Recent findings demonstrate that AMPARs are mediating hypothalamic responses to nutritional challenges and to endocrine stimuli, such as high fat diet, fasting/refeeding, leptin or the endogenous glucagon-like peptide-1 (GLP-1) [69–72]. Since all these nutritional and

hormonal conditions are associated with fluctuations in hypothalamic malonyl-CoA levels (Table 1), it would not be unreasonable to think that CPT1C is converting the "malonyl-CoA signal" into changes in excitatory neurotransmission through the regulation of AMPAR abundance at the synapse.

Altogether, strong evidence suggests both CPT1A and CPT1C as major effectors of malonyl-CoA regulation of food intake and energy homeostasis, although the downstream molecular mechanisms are not well understood.

5. The sensing of malonyl-CoA in cognition and brain development

Despite the extensive role of malonyl-CoA in the control of energy homeostasis in the hypothalamus, recent data indicate that malonyl-CoA sensing in other brain regions could contribute to the regulation of neuronal development and cognitive function by nutrients. A description of the physiological processes and molecular mechanisms involved is detailed below.

5.1. Metabolic plasticity in astrocytes

Astrocytes express mainly the CPT1A isoform even though its expression is low compared to other peripheral tissues [18]. In
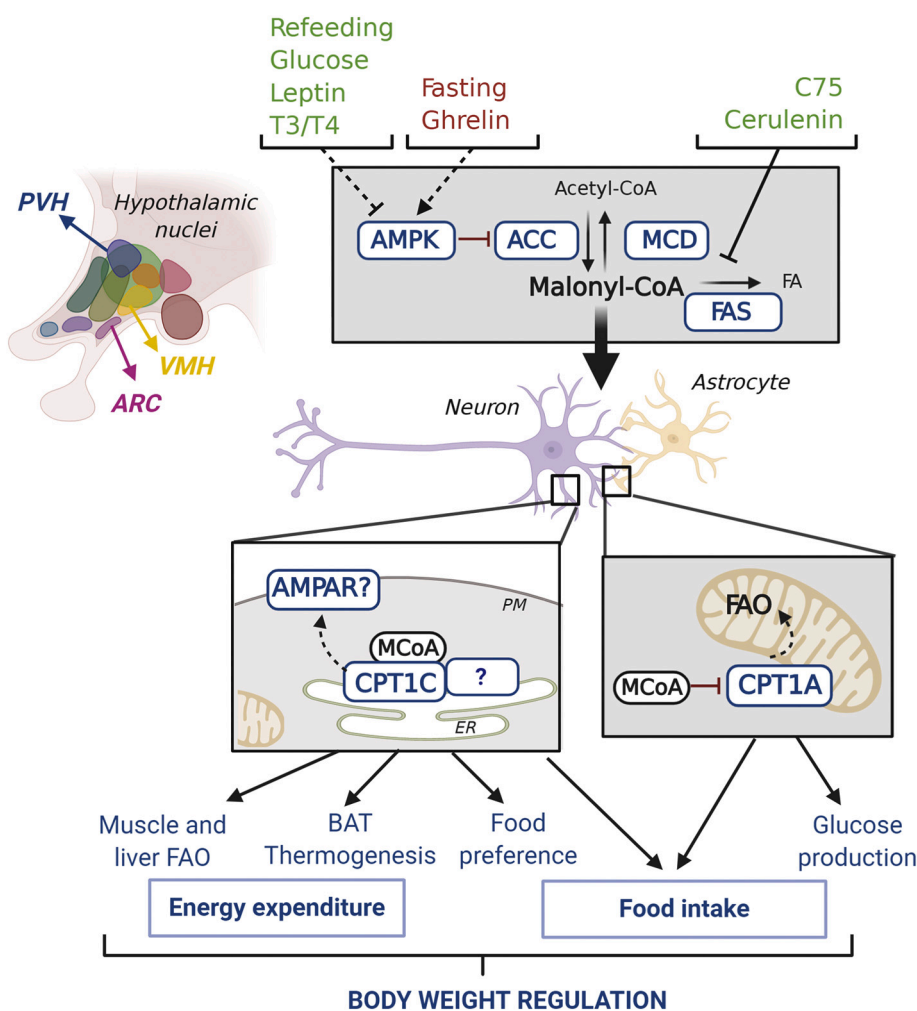
Fig. 3. Hypothalamic malonyl-CoA as a mediator of food intake and energy expenditure. In the hypothalamus, malonyl-CoA levels fluctuate in response to physiological (e.g., fasting/refeeding and glucose), hormonal (e.g., leptin/ghrelin, thyroid hormones T3/T4) or pharmacological (e.g., C75 or cerulenin) stimuli. Green and red lettering indicate the induction of malonyl-CoA levels increase and decrease, respectively. Hypothalamic malonyl-CoA rises induce activation of a satiety signal and energy expenditure leading to attenuation of body weight, whereas a reduction in malonyl-CoA concentration blunted these effects on feeding and energy expenditure leading to an increase in body weight. These malonyl-CoA fluctuations can be mediated via FAS inhibition or instead via AMPK/ACC depending on the stimulus, in hypothalamic areas such as the arcuate (ARC), the ventromedial hypothalamus (VMH) and the paraventricular hypothalamus (PVH). Cellular targets downstream malonyl-CoA in the hypothalamus are CPT1C and CPT1A. CPT1C regulates satiety at the mediobasal hypothalamus (a region that integrates ARC and VMH), food preference at the PVH, brown adipose tissue (BAT) thermogenesis at the VMH, and liver and muscle fatty acid oxidation (FAO) at the VMH. CPT1C is located in the ER of neurons and does not act as an enzyme, but instead interacts and regulates the activity of other neuronal proteins (e.g. AMPAR) involved in synaptic neurotransmission. CPT1A is the most ubiquitous CPT1 in the body, which is expressed in peripheral tissues and the brain, particularly in astrocytes. CPT1A in the hypothalamus regulates food intake and hepatic glucose production through the regulation of FAO.

astrocytes, CPT1A enhances FAO upon energy stress [73,74] or under high neuron activity [75], when the AMPK pathway is activated [76]. FAO is aimed at destroying peroxidised FAs delivered by adjoining neurons [75], and producing ketone bodies to fuel back neurons [77–79]. Although glucose and lactate are the primary energetic substrates for the brain, FAO plays a critical role in astrocyte metabolism, supporting neuron function and synapse maintenance in the case of glucose and lactate depletion, or during neuron hyperactivity. The metabolic coupling between neurons and astrocytes is essential for the health of the brain.

5.2. The regulation of cell fate in neural stem/progenitor cells (NSPC)

In addition to astrocytes, CPT1A is also highly expressed in NSPCs [4,18,80]. NSPCs are abundant in the developing brain but are also found in the subventricular zone and hippocampal dentate gyrus of the mammalian adult brain [81]. It has been recently described that the equilibrium between FASN-dependent de novo lipogenesis and CPT1A-mediated FAO determines the proliferative or quiescent stage of these cells [4,82]. FAO is linked to the maintenance of cell quiescence, while the switch to a proliferating state requires the inhibition of FAO and the activation of the novo lipogenesis, which will generate complex lipids for the formation of new membranes. Therefore, the addition of malonyl-CoA to NSPCs, which is both an inhibitor of CPT1A and the substrate of the novo lipogenesis, is enough to induce exit from quiescence and to enhance NSPC proliferation [4]. We can say that malonyl-CoA acts as a bioenergetic rheostat of stem cell fate [83].

Interestingly, malonyl-CoA regulation of CPT1A in NSPCs is necessary for proper neurogenesis both during development and in the adulthood [4]. Inborn errors of FAO, which are clinically linked to developmental brain disorders, promote NSPC differentiating divisions leading to reduced embryonic NSPC pool [84]. Adult neurogenesis is involved in cognition and its impairment has been associated with psychiatric disorders [81], therefore it cannot be ruled out that defects of the malonyl-CoA/CPT1A axis in NSPCs in the adulthood are at the base of some neurodegenerative disorders or psychiatric illnesses. Interestingly, the administration of an agonist of PPARbeta/delta (a transcription factor that upregulates CPT1A in a model of Alzheimer's disease (APP/PS1 mice), ameliorates memory deficits through increased FAO in astrocytes and the enhancing of brain neurogenesis [85]. The regulation of CPT1A by malonyl-CoA emerges as a key factor for both astrocyte and NSPC metabolism.

It is worth mentioning that even though CPT1A expression in neurons is negligible, there is one article demonstrating that CPT1A mediates the effects of ghrelin on GABA release in cortical neurons [86]. Further studies are necessary to confirm the signaling role of CPT1A in neurons.

5.3. Synaptic strength in neurons

CPT1C is highly expressed in neurons throughout the adult brain. CPT1C expression is low after birth but rapidly increases in cortex, hippocampus and cerebellum [87,88]. In the last few months, new published data have proved that the sensing of malonyl-CoA by CPT1C

regulates the vesicular transport of AMPAR and therefore synaptic function [3].

AMPARs mediate fast excitatory neurotransmission and play a critical role in synaptic strength and plasticity; key features encoding many brain functions such as learning and memory [89]. In the adult brain, AMPARs are homo- or hetero-tetramers of usually GluA1 and/or GluA2 subunits. The presence or absence of a given subunit within the receptor is determinant of its synaptic properties (such as permeability to Ca^{2+} ions). A noticeable array of interacting proteins finely regulates the subunit ensemble at the ER, the trafficking to the plasma membrane (PM), and the synaptic function of AMPARs. CPT1C is one such interacting protein [90] and is needed for proper AMPAR subunit synthesis [88] and multimerization into functional tetramers [91]. Moreover, CPT1C regulates the trafficking of GluA1- but not GluA2-containing AMPARs from the trans-Golgi network (TGN) to the PM depending on malonyl-CoA sensing [3]. Interestingly, this effect is exerted at the ER-TGN contact sites and through the phosphatidyl-inositol-4-phosphate (PI(4)P) phosphatase SAC1, another auxiliary protein of the AMPAR complex that also interacts with CPT1C. Under basal conditions, CPT1C inhibits SAC1 catalytic activity, allowing PI(4)P accumulation at the TGN, a signal necessary for efficient GluA1 vesicular trafficking. However, under low malonyl-CoA induced by glucose depletion, CPT1C

releases its inhibition over SAC1 resulting in the temporary retention of AMPARs at the TGN (Fig. 4). On the other hand, leptin, a hormone that increases the synthesis of malonyl-CoA [3,35,36], enhances AMPAR trafficking through the malonyl-CoA/CPT1C pathway [3]. These data coincide with the cognitive enhancing effects of leptin [92], and the fact that leptin resistance (usually found in obese patients) is a predisposition factor of cognitive decline [93,94].

In summary, CPT1C-sensing of malonyl-CoA determines the abundance and composition of AMPARs at the synapse in response to glucose and leptin. It remains to be explored whether other nutrients and hormones that regulate malonyl-CoA levels, such as ghrelin, GLP-1 and thyroid hormones (see table 1), affect synaptic AMPARs and cognitive functions through the malonyl-CoA/CPT1C axis. In line with these results, CPT1C KO mice show diminished AMPAR-mediated neurotransmission, impaired dendritic spinogenesis, and learning deficits [17,88]. By contrast, CPT1C overexpression in neurons results in increased seizures [95], likely due to excessive excitatory transmission.

5.4. Axon growth

The sensing of malonyl-CoA by CPT1C plays another key role in neurons, during brain development, through the regulation of another
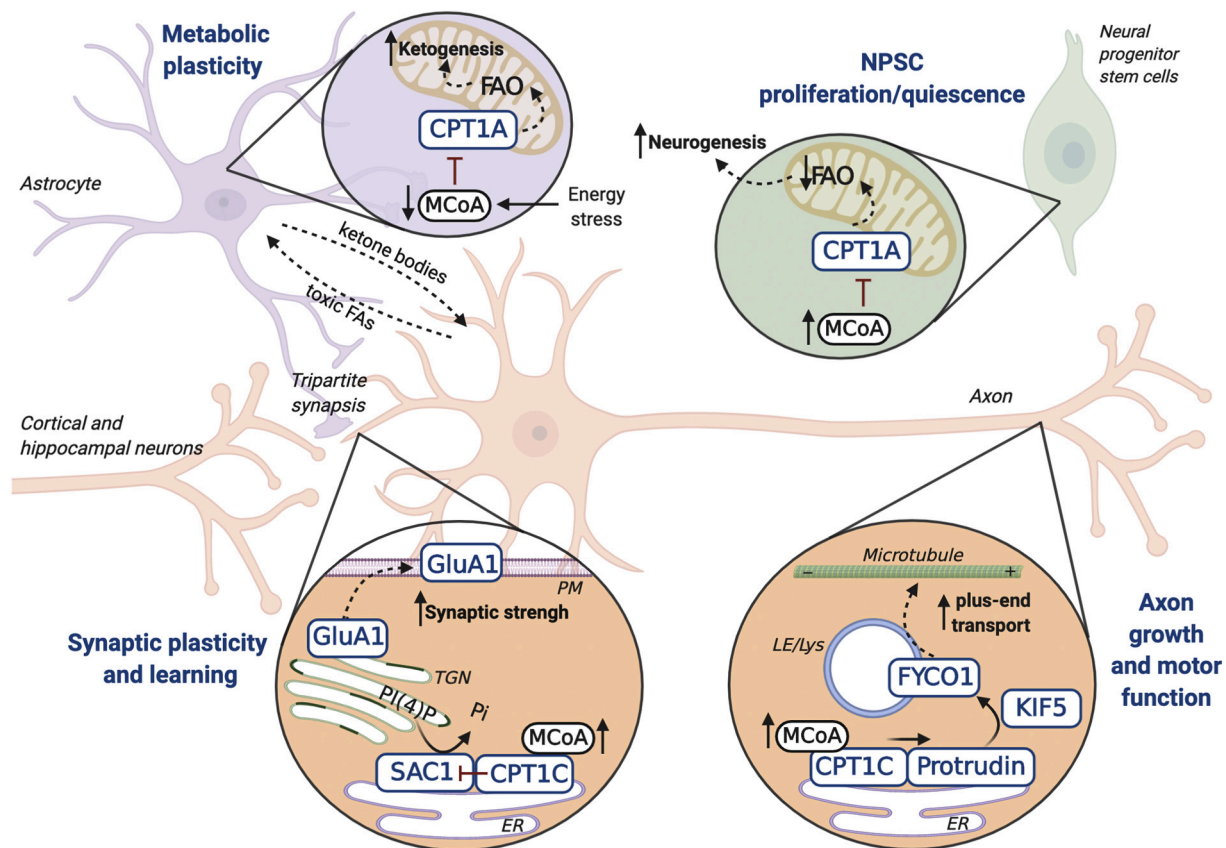

Fig. 4. Malonyl-CoA sensing in neuronal development and cognition. In astrocytes, AMPK activation by energy stress or enhanced neuronal activity induces a CPT1A-mediated enhancement of FAO and ketogenesis in order to supply fuel to neurons (top left circle). At the same time, neurons release toxic fatty acids (FAs) in lipid particles that will be internalized by astrocytes for their oxidation. In neural stem progenitor cells (NSPCs), under high malonyl-CoA (MCoA) levels CPT1A-dependent fatty acid oxidation (FAO) is downregulated and proliferation is enhanced, while under low malonyl-CoA content, FAO is activated and cells switch to a quiescent state (top right circle). In neurons, CPT1C sensing of malonyl-CoA controls synaptic strength and axon growth in response to metabolic challenges, by the modulation of SAC1 activity and protrudin function, respectively. On the one hand (bottom left circle), under basal malonyl-CoA levels, CPT1C downregulates SAC1 catalytic activity, allowing efficient trafficking of the GluA1-containing AMPA receptors to the plasma membrane (PM), and consequently the enhancement of synaptic function. However, under energy stress (low malonyl-CoA levels), CPT1C-dependent inhibition of SAC1 is lifted, causing a decrease in PI(4)P levels at the trans-Golgi network (TGN). This results in the retention of AMPAR at the TGN and a temporary decrease in the synaptic strength. On the other hand (bottom right circle), in normal energy conditions, CPT1C is bound to malonyl-CoA and enhances the transfer of kinesisn-1 (KIF5) from protrudin to FYCO1, a protein located at the surface of late endosomes/lysosomes (LE/Lys). This fact promotes the plus-end transport of LE/Lys, allowing proper axon growth. However, upon energy stress, a decrease in malonyl-CoA leads CPT1C to inhibit protrudin function and the blocking of axon growth.

interacting protein, protrudin [5]. Protrudin is an ER-resident protein mainly present in contact sites between the ER and late endosomes/lysosomes (LE/Lys) [96]. Its function is to recruit the motor protein kinesin-1 and transfer it to LE/Lys in order to favor the anterograde transport of these vesicles along the axon, and their posterior fusion to the axon tip, facilitating rapid axon growth (Fig. 4). In fact, protrudin overexpression in neurons promotes neurite outgrowth and its deletion results in the loss of neuron polarization [97]. Under normal conditions, CPT1C enhances protrudin function, but under low malonyl-CoA levels, CPT1C inhibits it, temporarily pausing axon growth. Interestingly, in this model, exogenous malonyl-CoA addition partially rescues the effects of glucose depletion or AMPK activation, demonstrating that malonyl-CoA is a "nutritional signal" that regulates the transport of LE/Lys. The role of amino acids and cholesterol in the regulation of LE/Lys transport was well known [98–100], but with these latest data, we now have a comprehensive view of how nutrients affect LE/Lys motility, which may be relevant to other cellular functions beyond axon growth.

Corticospinal motor neurons have the longest axon of any in the body; hence, it is not surprising that impaired axon growth can lead to movement disorders. Accordingly, CPT1C KO mice show motor deficits such as ataxia, incoordination, and muscle weakness [87]. Moreover, the only two heterozygous mutations of CPT1C described in humans are associated with hereditary spastic paraplegia [101,102], a neurological disorder that affects corticospinal motor neurons and occurs with ataxia, spasticity, leg weakness and other neurological symptoms [103].

In summary, we can say that malonyl-CoA is a metabolic signal that regulates brain development, synaptic function and cognition in response to nutrients and hormones. The sensing of malonyl-CoA by CPT1A at the mitochondria regulates neurogenesis and the metabolic plasticity of astrocytes. By contrast, CPT1C at the contact sites between the ER and other organelles (LE/Lys and TGN) is able to transfer the malonyl-CoA signal to other proteins involved in the vesicular transport in neurons, therefore regulating axon growth and AMPAR-mediated synaptic plasticity. Therefore, it is of high relevance to better understand which nutritional challenges, hormones, or even behaviors regulate malonyl-CoA levels in different brain regions and how.

6. Malonyl-CoA fluctuations in different brain regions

In addition to the well-documented changes in malonyl-CoA levels in the hypothalamus in response to nutrients and hormones, other brain regions classically involved in cognition also suffer malonyl-CoA fluctuations, though data are scarce (table 1). In the cerebral cortex, hippocampus and cerebellum of rats, malonyl-CoA levels greatly decrease in response to prolonged fasting (16-24 h), as observed in the hypothalamus [104]. We hypothesize that a permanent decrease in brain malonyl-CoA can contribute, even in a small part, to the cognitive deficits associated with severe undernutrition or exhaustive exercise [105,106]. In line with this, pharmacological activation of AMPK in rodents leads to impairment in synaptic plasticity and memory formation [107–109] and it is associated with neurodegenerative disorders such as Alzheimer's disease [110,111]. By contrast, caloric restriction and intermittent fasting have been associated with the amelioration of cognitive decline in aging and neurodegenerative diseases [112]. Malonyl-CoA levels in those conditions have not been measured but some of the healthy effects of dietary restriction have been attributed to the increase in circulating ketone bodies [112]. Interestingly, a ketone diet (30 % of the calories from a ketone ester supplementation) for 14 days increases whole brain malonyl-CoA levels in rats and improves cognitive performance [113,114].

On the other hand, it is well known that high-energy diets and obesity also impair cognitive function [115] and predispose people to memory loss with age [116,117]. Interestingly, cortical and hippocampal malonyl-CoA pools in Zucker-fatty rats are lower compared to lean animals [118], suggesting of some kind of association between malonyl-CoA levels on those brain regions and cognitive abilities. It would be

relevant to study malonyl-CoA levels in different brain regions in response to other high-caloric diets (Western diets, saturated HFD), and in different models of leptin resistance or glucose intolerance, which have been said to produce synaptic dysfunction and cognitive decline [93,119–121]. Moreover, it is not known whether conditions such as hypo- or hyperthyroidism, anorexia, stress, or pregnancy, which effectively modify malonyl-CoA levels in the hypothalamus and are associated with cognition alterations [47,122–127], do show malonyl-CoA fluctuations in the cortex and hippocampus.

The phenotypes observed in deficiencies of proteins that synthesize or metabolize malonyl-CoA also support the idea that fluctuations of this metabolite have an impact on neuronal development and cognition. Only a single case with ACC deficiency has been reported so far [128]. This patient showed symptoms of myopathy, growth restriction and severe brain damage, probably due to the absence of malonyl-CoA necessary for FA biosynthesis and the regulation of CPT1 proteins. By contrast, several cases of human MCD mutations have been published. These patients suffer malonyl aciduria, hypoglycemia and/or cardiomyopathy, and show some neurological signs and symptoms, like cortical abnormalities, mental retardation, epileptic seizures, psychomotor delay and/or spasticity [42–44,129,130]. This suggests that excessive malonyl-CoA has a detrimental effect on the development of the central nervous system and impairs neurotransmission. Further studies are needed to properly demonstrate this. Perhaps, time and tissue specific conditional transgenic mouse models of ACC and MCD would expand our knowledge in this sense.

In summary, metabolic stress, such as severe fasting, AMPK hyperactivation, obesity, or leptin resistance, result in a decrease in malonyl-CoA levels in different brain regions (hippocampus, cortex and cerebellum), and these changes are associated with cognitive alterations and memory loss with age. Genetic diseases causing the accumulation of malonyl-CoA, such as MCD deficiency, also lead to cognitive alterations, suggesting that both a long-time depletion or a permanent excess of malonyl-CoA can have harmful effects.

7. Malonylation, a new posttranslational modification of proteins

In recent years, it has been revealed that malonyl-CoA is not only the precursor of FA synthesis and the allosteric regulator of CPT1 enzymes; it is also the substrate for protein malonylation.

Protein malonylation is a new posttranslational modification that some proteins can undergo in lysine residues when malonyl-CoA levels increase [131]. Since malonyl moiety is negatively charged, malonylation triggers a significant conformational change in proteins with distinct functional outcomes, usually making them inactive. High throughput studies [6,132–134] have detected more than 1800 malonylated proteins in human cells. Interestingly, malonylated grade is dynamic and has been shown to be increased in MCD$^{-/-}$ human cells, the liver of *Sirt5*$^{-/-}$ mice (SIRT5 is the main enzyme that catalyzes protein demalonylation) [133,134], and genetic models of diabetes and obesity [135]. Notably, the majority of the malonylated proteins are cytosolic or mitochondrial and involved in metabolism [133,134], such as glyceraldehyde-3-phosphate dehydrogenase (GAPDH) [136] or mammalian target of rapamycin (mTOR) [137].

It is still not clear whether malonylation is a physiological way to regulate the function of proteins, or if it is just a toxicity issue that occurs when malonyl-CoA levels increase to excess, such as in drug treatments or genetic diseases. Up to now, little is known about the pathophysiological role of malonylation in the brain. In fact, brain malonyl-CoA levels are low compared to those of peripheral tissues [104]. Future research will elucidate whether malonylation of brain proteins can contribute to cognitive decline or neurodegenerative disorders.

8. Future perspectives

The regulation of cognitive functions by malonyl-CoA is an incipient field that will likely be developed in the near future. Below are some research suggestions that in our opinion would be worth pursuing.

- Current methods used to measure malonyl-CoA levels are based on liquid chromatography-mass spectrometry [138], or the biochemical cycling method [104], both of which require a high amount of tissue and cannot be performed on live cells. Development of cell-specific methods will help to dissect malonyl-CoA fluxes in a certain type of neurons or astrocytes. Genetic biosensors, in which the intensity of a fluorescent or a luminescent reporter protein fluctuates in response to malonyl-CoA changes, arise as promising approaches since they can be used in live mammalian cells [139,140]. These biosensors take advantage of the malonyl-CoA binding properties of the transcription factor FapR from *Bacillus subtillis* [141]. The future development of animal models carrying those biosensors integrated in specific neurons or astrocytes will elucidate how different stimuli affect malonyl-CoA levels in individual cells.

- In addition to AMPAR, SAC1 and protrudin, other CPT1C interactors have been proposed by high-resolution proteomic analysis [29]. The alpha beta hydrolase domain 6 (ABHD6), which catalyzes the conversion of 2-arachidonoylglycerol (2-AG) to arachidonic acid and glycerol, could be especially relevant. In turn, 2-AG is the endogenous ligand of the CB_1 and CB_2 cannabinoid receptors, and ABHD6 controls some of the endocannabinoid-dependent neuronal functions, like long-term synaptic plasticity [142]. It would be relevant to know if CPT1C modulates ABHD6 activity in the brain in a malonyl-CoA-dependent manner, as it does with SAC1 or protrudin.

- Taking into account that CPT1A and CPT1C are cellular targets of the malonyl-CoA satiating signal, the development of malonyl-CoA analogs could be a compelling approach for the treatment of obesity. On the other hand, since CPT1C is involved in the regulation of excitatory neurotransmission, specific CPT1C inhibitors could be postulated for the treatment of epileptic seizures, as previously suggested for the AMPK activator metformin or the AMPAR antagonists [143,144].

9. Conclusions

Malonyl-CoA, a metabolite that is in the crossroad of glucose and FA metabolism, has been revealed to regulate not only food intake and energy homeostasis but also other brain functions such as neurogenesis, axon growth and synaptic function. Malonyl-CoA levels fluctuate in response to nutrients, hormones and are tightly controlled by the master energy sensor AMPK [14]. CPT1A and CPT1C are end-targets of malonyl-CoA with a different array of ensuing outputs. Upon energy stress or high neuronal activity, malonyl-CoA sensing by CPT1A in astrocytes triggers FAO activation to provide neurons with an alternative energetic fuel [77] and to detoxify peroxided FAs [75], allowing the normal function of the synapse. In NSPC, the regulation of CPT1A activity by malonyl-CoA modulates the switch between proliferation and quiescence and, in consequence, the neurogenesis in both the embryo and the adult brain [4]. By contrast, in neurons, malonyl-CoA sensing is mainly performed by CPT1C, which transfers the nutritional and hormonal signals to its interacting proteins to regulate both the motility of LE/Lys and the vesicular transport of AMPARs, thus impacting axon growth and synaptic plasticity [3,5]. In conditions of prolonged fasting, anorexia, obesity, and some neurodegenerative diseases, malonyl-CoA levels in different brain areas are chronically depleted, which can contribute to the cognitive deficits observed in those situations. By contrast, malonyl-CoA accumulation, such as in MCD deficiency, also results in impaired brain development and cognition.

In summary, the malonyl-CoA signal is key not only in the hypothalamus, but throughout the brain. This highlights the importance of nutrients, hormones and energy metabolic challenges on brain development and cognition. A better understanding of the mechanisms

downstream of malonyl-CoA can give insight into the treatment of the cognitive alterations associated with metabolic disorders.

Declaration of Competing Interest

None declared

Acknowledgements

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