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Narrative Review

Burden of negative energy balance in anorexia nervosa: Role of circadian rhythm, mitochondrial dynamics, microbiota–gut–brain axis and their interactions

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SUMMARY

Anorexia nervosa (AN) is a chronic eating disorder that often requires prolonged hospitalisation for effective treatment. As a multifactorial disease, many environmental, psychiatric, and biological factors impede recovery, creating a vicious circle of anorexia, gastrointestinal disorders, and anxiety-depressive disorders. Individuals with AN often exhibit inappropriate physical activity, sleep disturbances, alterations in circadian hormonal profiles, disruption of the gut barrier, dysbiosis of the gut microbiota, oxidative stress, and alterations in brain function. The aim of this review is to provide a non-exhaustive overview of the biological factors involved to gain a deeper understanding of the pathophysiology of AN and to identify potential targets for clinical cure. We have chosen to describe the interconnected factors of gut microbiota, circadian rhythm, mitochondria, and brain alterations. Indeed, clinical and experimental data allow the establishment of relationships between these altered factors. Sleep disorders and brain changes have been linked to cognitive alterations, mood disorders, and disrupted feeding behaviour. Compulsive exercise behaviour has been associated with a negative energy balance, but adapted physical activity may confer protection against certain comorbidities. Circadian rhythm may be associated with mitochondrial dysfunction, sleep disorders, and physical activity. Mitochondrial dysfunction could lead to putative neuroinflammation, causing a reduction in grey matter volume. The gut microbiota, which exhibits circadian variations, interacts with both homeostatic and hedonic food

Abbreviations: 5-HT, serotonin; 26RFa, pyroglutamylated RFamide peptide (new symbol: QRFP); α -MSH, α -melanocyte-stimulating hormone; ABA, activity-based anorexia; AgRP, agouti-related protein; AMPK, AMP-activated protein kinase; AN, anorexia nervosa; anx, anorexia; ATP, adenosine triphosphate; BAX, BCL2 associated X, apoptosis regulator; BDNF, brain-derived neurotrophic factor; BMAL, basic helix-loop-helix ARNT-like protein 1; BMI, body mass index; BNIP3, BCL2/adenovirus E1B 19 kDa protein-interacting protein 3; CART, cocaine and amphetamine-related transcript; CCL2, chemokine ligand 2; CCNB1, G2/mitotic-specific cyclin-B1; Cidea, cell death inducing DFFA like effector a; CLOCK, circadian locomotor output cycles protein kaput; CLPB, caseinolytic peptidase B; CNS, central nervous system; CRY, cryptochrome circadian regulator; D receptor, dopamine receptor; DIA, dehydration-induced anorexia; Dio2, iodothyronine deiodinase 2; DMN, dorsomedial nucleus; DNM1L, dynamin-1-like protein; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; FAA, food anticipatory activity; FIS1, mitochondrial fission 1 protein; GABA, gamma-aminobutyric acid; GABRA5, gamma-aminobutyric acid A receptor alpha 5; GFAP, glial fibrillary acidic protein; GHSR, growth hormone secretagogue receptor; GI, gastrointestinal; GLP1, glucagon-like peptide-1; GWAS, genome-wide association study; HFD, high-fat diet; IgG, immunoglobulin G; IL, interleukin; KO, knock-out; LC3, microtubule-associated protein 1 A/1B-light chain 3; LHA, lateral hypothalamis area; LPS, lipopolysaccharide; MCR, melanocortin receptor; MFF, mitochondrial fission factor; MFN, mitofusin; NADH, nicotinamide adenine dinucleotide hydrogen; NDUFAF1, NADH ubiquinone oxidoreductase subunit A1; NLRP3, NOD-like receptor family, pyrin domain containing; NOD, nucleotide-binding oligomerization domain-containing protein; NPY, neuropeptide Y; Nr1d1, nuclear receptor subfamily 1 group D member 1; OPA1, dynamin-like GTPase 1; OXPHOS, oxidative phosphorylation; PER, Period circadian protein; PET, positron emission tomography; PKA, protein kinase A; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus; PYY, peptide YY; ROS, reactive oxygen species; SCFA, short-chain fatty acid; SCN, suprachiasmatic nucleus; SIRT1, NAD-dependent protein deacetylase sirtuin-1; TLR, toll-like receptor; TNF α , tumor necrosis factor α ; UCP, uncoupling protein; VMN, ventromedial nucleus; VTA, ventral tegmental area.

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intake regulation, and is associated with mitochondrial function and physical activity. Better understand all this relationship in anorectic conditions is an important issue to open new therapeutic strategies.

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1. Introduction

Anorexia is defined by a low food intake resulting in body weight loss. Several types of anorexia have been described: disease-associated anorexia (secondary anorexia or anorexia-cachexia syndrome), anorexia observed in the elderly and Anorexia Nervosa (AN). In this review, we focus on AN which is an eating disorder characterized by a low body mass index (BMI, $<18.5 \text{ kg m}^{-2}$), a disturbed perception of body shape image, and an intense fear of gaining weight [1], according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The prevalence of AN has increased in recent decades with a lifetime prevalence of 1.4 % in women and 0.2 % in men; and particularly affects adolescents (12–14 years) and young adults (18–20 years) [2]. AN is a multifactorial disease associated with numerous psychiatric and somatic dysfunctions [3] such as metabolic disorders, gastrointestinal (GI) disorders, cardiovascular abnormalities such as bradycardia and low bone mineral density [4]. AN is the mental disorder with the highest mortality rate reaching 5 % after 10 years of medical care [5]. To date, there are no specific recommended treatments for AN. The clinical goal is to refeed patients and to limit associated morbidities such as psychiatric and GI disorders. Although new therapeutic strategies are under evaluation (adapted physical activity, virtual reality or probiotics), the treatment of AN remains challenging [6].

This review aims to describe, in an integrative way, the biological dysfunctions that contribute to the negative energy balance, in particular the gut microbiota, the circadian rhythm, and the mitochondria. The links between these actors will also be addressed in an attempt to better understand the pathophysiology of AN.

1.1. Anorexia nervosa: a vicious circle

Anxiety disorder and depression are the two main psychiatric comorbidities observed in patients with AN. Antidepressants and anxiolytics are therefore one of the main lines of treatment along with refeeding and behavioural therapy, although they do not improve weight gain or anorexia symptoms [3]. 59.8 % of patients received at least one psychotropic medication before admission (32.9 % and 47.3 % for antidepressants and anxiolytics, respectively), and 67.6 % at discharge [7]. In addition, there is a positive correlation between the severity of these mood disorders and the severity of anorexia [7]. The causal relationship between anxiety and depressive symptoms and AN is still debated: these disorders could either occur after the onset of AN, or facilitate its development, or only constitute an associated comorbidity without a direct link [7].

GI symptoms are common in patients with AN [8]. One study estimated that GI symptoms affect 62 % of patients with AN and almost 50 % of them had already GI symptoms prior to clinical care [9]. Among these GI symptoms, patients mostly suffer from functional dyspepsia with delayed gastric emptying, irritable bowel syndrome, bloating and constipation [8,10–12]. These symptoms represent an obstacle to the nutritional management of patients [12–14].

Alteration of gut microbiota composition and/or function, named gut dysbiosis, has been reported in patients with AN that

may contribute to the pathophysiological mechanisms and to the perpetuation of AN [15,16]. The role of gut microbiota dysbiosis in AN remains to be elucidated but may contribute to GI symptoms, as well as to eating behaviour and mood disorders [17].

1.2. Animal models

There are many animal models that mimic the biological pathophysiology of AN to better understand the integrative pathophysiology involving inter-systemic hormonal, cellular and molecular dysfunctions, and in particular the neurobiological aspects. Here, we describe the main models used in the literature, considering that the most widely described model is the *activity-based anorexia* (ABA) rodent model.

1.2.1. Anx/anx model

The first model is a genetic model using *anx/anx* mice, which are characterized by a spontaneous mutation of the *Anx* (anorexia) gene located on the chromosome 2. This model leads to a reduced food intake and hyperactivity. Hypothalamic mitochondrial dysfunction, some neuroinflammatory signals and an altered melanocortin system have been reported in *anx/anx* mice [18,19]. However, the lifespan of *anx/anx* mice is rather short (3–5 weeks), which limits its use in AN studies [20]. GI disorders, a major component of AN symptoms, have not been evaluated in this model. Thus, this model is preferentially used to mimic anorexia-cachexia syndrome [21] due to neuroinflammation in the hypothalamus, which is also a feature of the anorexia-cachexia syndrome [22].

1.2.2. Dehydration-induced anorexia model

The dehydration-induced anorexia (DIA) model was introduced in rats by Watts in 1997. The drinking water of these animals is replaced with a 2.5 % NaCl solution for 4–14 days while maintaining *ad libitum* feeding. This hyperosmolar drink leads to reduced food intake and a 29 % weight loss compared to the control group [23]. The DIA group is often compared with a food-restricted group in which the quantity of food available to the animals is matched to the amount consumed by DIA rats, and clear water (pair-fed group), in addition to a control group with *ad libitum* food and clear water [24].

The DIA model shares some features with the ABA model such as changes in neuropeptides expression [25], stress response [26], or disrupted circadian rhythms of food intake [27]. Neuroinflammation is also observed in this model [23,28,29]. The main limitation of this model is the strong increase in osmolarity that is not always observed in patients with AN [21].

1.2.3. Activity-based anorexia model

The core principle of the ABA model is to expose animals to two challenges: food restriction, and free access to an activity wheel. The original model developed by Routtenberg in rats was based on time-restricted feeding, typically allowing 1 h of food access per day. Over time, a wide range of protocols have emerged, including in mice, ranging from 1 h to 6 h of daily food access, with some implementing a gradual reduction each day. Access to the running wheel is either blocked or with free access during food

consumption. Alternatively, food restriction can be quantitative, limiting intake to 30–60 % of basal food intake, preventing the weight gain often observed at the end of the protocol [24].

It leads to many of the symptoms and pathophysiological mechanisms observed in humans. Several publications have highlighted the relevance of this model [24,30]. For instance, neurobiological data on ABA appears to be relevant for the study of AN [31]. The ABA model also induces common peripheral complications of AN such as cardiometabolic, gonadal and GI dysfunctions [32]. Both sexes have been studied in the ABA model. A sexual dimorphism has been shown in patients, both at the biological level [33] and at the physiological level, such as the greater compulsive movements observed in males, especially with more intense and frequent events [34]. Furthermore, males are more severely affected than females [35,36]. This dimorphism has also been described in mice with the higher food anticipatory activity (FAA) in males than in females. FAA is a phenomenon that has been well observed in the literature. It corresponds to the development of physical activity before the fixed time of a meal in food-deprived animals. However, this activity is conditioned by a fixed meal time; if meal times are random, this phenomenon is no longer observed [35,37].

The ABA model shares many features with AN such as severe food restriction, acute weight loss, hyperactivity, activation of the hypothalamo–pituitary axis, delayed gastric emptying, anxiety-like disorders, amenorrhea and neurological changes. However, it does not take into account genetic predispositions and environmental factors such as social predisposition and childhood trauma.

1.3. Factors contributing to negative energy balance

1.3.1. Central regulation of energy balance

The hypothalamus is a very important and complex cerebral tissue with numerous nuclei involving in energy metabolism. AN patients present brain alterations, namely a global reduction of white matter and focal reduction of grey matter volumes, particularly in the hypothalamus [38] and the amygdala [38,39], an area important for emotional processing. Moreover, a thinning of cortical area on acute AN patients is described [40]. In patients, an atrophy of the cerebral cortex is also observed, certainly due to a reduction in the number of astrocytes, as observed in post-mortem samples of insular cortex [41], or in animal data [42]. A direct correlation between volume reduction and reduced density of astrocytes, but not neurons or oligodendrocytes, is found in chronic ABA rats [43,44]. This astrocyte specificity is further supported by similar findings in other brain regions, in both ABA and DIA models [28,29,45–47]. The loss of astrocytes has been explained by a reduction in neurogenesis in preclinical models [47,48], and by an increased apoptosis in human post-mortem samples (41). Nevertheless, these changes appear to be reversible after body weight recovery [46,47,49,50].

1.3.1.1. Homeostatic regulation. The hypothalamus is a key brain area involved in the regulation of food intake and energy expenditure. It integrates various metabolic and neuroendocrine signals that reflect the nutritional status of the body and is involved in producing a behavioural response that will satisfy the individual's nutritional needs. Several of its nuclei are involved.

The arcuate nucleus integrates the peripheral hunger and satiety signals. It contains two populations of neurons with antagonistic and complementary roles, described as first-order neurons: pro-opiomelanocortin (POMC) neurons, which express the anorectic peptides α -melanocyte-stimulating hormone (α -MSH) and cocaine and amphetamine-related transcript (CART), and neuropeptide Y (NPY) and agouti-related protein (AgRP)

orexigenic neurons [51,52]. These neurons carry the receptors for leptin (a satiety hormone) and ghrelin (a hormone that stimulates food intake), among others, and project to second-order neurons located in the paraventricular (PVN), ventromedial (VMN), dorsomedial (DMN) nuclei and lateral hypothalamic area (LHA). α -MSH, produced by POMC neurons, activates melanocortin family receptors (MC3 and MC4R), while AgRP is a competitive antagonist on these receptors. NPY exerts its orexigenic effect *via* the stimulation of Y1 and Y5 receptors. This neural network is called the melanocortin circuit and sends its afferents to extra-hypothalamic circuits such as the solitary tract nucleus or the reward system [51,53,54].

It seems then relevant to focus on the melanocortin circuit in the context of AN. POMC and related peptides were decreased in the cerebrospinal fluid of patients during malnutrition and were restored after weight recovery [55]. Furthermore, a polymorphism in the *AgRP* gene is observed in patients with AN [56], which leads to a change in the structure of the protein and consequently to a lower antagonistic activity on MC4R. Kas et al., found an over-expression of these MC4R in the VMN in the ABA model, resulting in a reduced hunger signal. The use of MC4R antagonists has been proposed as a treatment for AN [57], and may be beneficial against cachexia [58]. However, until now, these approaches have not been evaluated in AN patients. In addition, an increase in the mRNA expression of AgRP and NPY peptides is observed in the ABA model, in parallel with a decrease in the expression of CART and POMC mRNA, and this at early [59] and late [57,60] stages of the development of the pathology. POMC-immunoreactive cells in ARC are also reduced in the rat ABA model [61]. Even if these findings are not observed in all studies [62,63], it represents an adequate homeostatic response to the negative energy balance of ABA rodents, suggesting that the lack of increased food intake is caused by a downstream dysfunction of this circuit. However, some sex differences have been reported [64]. Indeed, in contrast to male ABA mice, female animals tend to regain normal food intake towards the end of the protocol, in line with hypothalamic *Npy* and *Pomc* expression [64].

In 2001, Otto et al. first demonstrated that blood levels of ghrelin, an orexigenic hormone, are elevated in patients with AN and return to physiological levels after partial weight recovery [65]. Plasma ghrelin can be found in des-acylated or acylated forms, which have low or high affinity for the ghrelin receptor, respectively [66–68]. Also, we may wonder whether this active form is also increased; in fact, the total isoform and des-acyl ghrelin were increased in patients with AN [69]. Accordingly, ghrelin resistance has been described in AN by many authors [65,70–72], and may be due to the poor ability of the hormone to be transported to targets in the hypothalamus [71]. Ghrelin is present in plasma in free form or complexed with immunoglobulin G (IgG), which protects it from degradation and promotes binding to the receptor, thereby enhancing the orexigenic signal [73–75]. However, in patients with AN, the levels of complexed ghrelin are lower than in controls, in addition to an increase in the rate of dissociation of the complex [75], which justifies the poor response to hunger signal. Administration of ghrelin coupled to IgG has been tested as a treatment in the ABA model, but no orexigenic effect has been demonstrated, maybe due to the limited food access model properties [76]. Moreover, nesfatin-1, described as an anorexigenic molecule activating the hypothalamic PVN [77], is retrieved in lower plasma levels in patients with restrictive AN compared to healthy controls [78]. In addition, in plasma, patients with AN did not present modification of anorexigenic peptides glucagon-like peptide 1 (GLP1) and peptide YY (PYY) compared to normal weight controls, but showed lower levels of leptin while the orexigenic 26RFa and ghrelin were both increased [79,80].

1.3.1.2. Hedonic regulation of feeding behaviour. Scores for depression, anxiety, obsessions and compulsions are higher in patients with AN than in controls and are partially but not fully reversed with weight restoration [81,82] highlighting the importance of studying the reward circuitry in the context of AN. As a primary motivated behaviour, eating behaviour is regulated by the reward system or mesolimbic dopaminergic system, which includes projections from ventral tegmental area (VTA) mainly to the nucleus accumbens but also to the amygdala, hippocampus, and prefrontal cortex [83]. The key neurotransmitter in this system is dopamine, which can bind to five specific receptors classified in two families depending on the G-protein to which they are coupled: the D1-like family (D1, D5), which induces depolarization of the postsynaptic neurons, and the D2-like family (D2, D3 and D4), which causes hyperpolarization. The D2-like receptors have a higher affinity for dopamine than the D1-like [84]. The reward system supports 3 aspects that lead to the repetition of behaviour: the “liking” which refers to the pleasure brought by the reward, the “wanting” which defines the motivation to obtain the reward, and the third cognitive component, the “learning”, which is responsible for the associative learning between a stimulus, in this case food, and the context in which it is found [85]. When this context is presented again, there is an anticipatory phenomenon encoded by an increase in dopamine release in the nucleus accumbens, which is at the origin of the motivated behaviour. The individual's positive (pleasure) or negative (displeasure) representation of the stimulus then induces a different orientated behaviour (consumption or avoidance of the stimulus, respectively) [86]. Besides, D2 receptor null mice have been shown to have reduced food intake and body weight compared to control mice, resulting to a lean phenotype [87]. These results would therefore reflect a lack of motivation for food intake. Food restriction in rats leads to an increase in the expression of D1 and D2 receptors by postsynaptic neurons [88], and to a greater release of dopamine in the nucleus accumbens in a reward-associated situation than in *ad libitum* fed animals [89]. Food restriction would therefore be at the origin of a neuroadaptation and, in particular, an increase in the sensitivity of the mesolimbic dopaminergic system [86]. Recently, Beeler and Burghardt have proposed a model of dopaminergic synthesis in two phases during AN. The first phase of food restriction would lead to an increase in dopamine levels in the midbrain, resulting in the associative learning described above and thus the development of the eating disorder. The repetition of these maladaptive behaviours would then lead to a drastic fall in dopamine levels, resulting in the mental inflexibility or rigidity characteristic of patients with AN. This study highlights the complexity of the neurobiology of AN and may explain the divergence of results found in the literature on this subject [90].

It is important to note that the hedonic aspect of reward is strongly regulated by opioidergic signalling rather than by dopamine itself. The opioid peptide family includes enkephalins, dynorphins and β -endorphins, which bind to the G protein-coupled receptors μ , δ and κ respectively [83]. This system is widely expressed throughout the brain and is involved in the regulation of nociception, stress, but also mood and reward behaviours, such as feeding behaviour [83]. While dopamine is through to encode the anticipatory aspects of feeding, opioids may act through the modulation of the hedonic perception of food, i.e. palatability. The regions involved are the PVN, the central nucleus of the amygdala, the ventral striatum and the nucleus of the solitary tract [91]. Galusca et al., reported on the cerebral opioid activity in AN using PET imaging. They showed a reduced availability of opiate receptors in several areas such as the nucleus accumbens, amygdala or prefrontal cortex, suggesting an increased endogenous opioid neurotransmission in patients with AN, which was

confirmed by serum analysis. These results lead to the hypothesis of a behavioural addiction, in which self-restriction is perceived as pleasant due to the release of opioids, thus favouring the repetition of this behaviour [92]. The involvement of the opioid system in AN is also supported by a genomic study describing the opioid delta receptor as a candidate gene for the aetiology of AN [93].

The reward system is also known to be preferentially activated by palatable food. It has also been shown that when AgRP neurons are impaired, hedonic eating behaviour takes precedence over homeostatic needs, and mice exhibit a more pronounced sensitivity to stress-induced anorexia [94]. Similarly, at the cellular level, AgRP dysfunction is associated with a higher firing rate of VTA dopamine neurons [95]. Therefore, it seems interesting to study the reward system in the context of AN.

Serotonin (5-HT), a monoaminergic neurotransmitter, is also involved in the hedonic regulation of eating behaviour. It is synthesized by the raphe nuclei in the midbrain whose neurons project to several prosencephalic regions. 5-HT is thought to inhibit food intake *via* the action of leptin on the melanocortin circuit [52]. Changes in neurotransmitter levels, as well as alterations in the structure, activity, and connectivity of several regions of the reward system are observed in anorexic patients and in related animal models. Levels of 5-HT metabolites in the cerebrospinal fluid of patients with AN are higher than those found in healthy subjects, and imaging studies have shown increased binding of 5-HT to its receptors on [96]. Some 5-HT neurons in the dorsal raphe nucleus receive dopaminergic projections from the VTA, and consequently express D1 and D2 receptors. Dopamine levels and excitability of these 5-HT neurons have been shown to be higher in the ABA model. This could be explained by a D2 to D1 shift during the onset of restriction, leading to activation of 5-HT neurons in the dorsal raphe nucleus and consequently inhibition of food intake [96]. In control mice, physiological levels of dopamine preferentially stimulate D2 receptors, due to their higher affinity, which does not inhibit food intake. As the ABA protocol in this experiment lasted 5 days, it is likely that the mice were in the first phase of the development of the anorexic phenotype of Beeler and Burghardt described above, which would then be consistent with their hypothesis. Cai et al., also showed that modulation of D1 and D2 receptors can reduce or even prevent the establishment of the ABA phenotype. These studies support the results of the Genome Wide Association Study (GWAS) published in 2019 [97], which highlighted that dopamine and 5-HT neurons are among the cells most associated with AN [96].

Regarding the structure of the reward circuit, AN patients show a decrease in hippocampal [98], amygdalar [99], orbitofrontal and medial prefrontal cortex volumes [100]. A downregulation of brain-derived neurotrophic factor (BDNF) levels in the amygdala has been described in ABA rats [101]. Some of these brain regions have been targeted by neurostimulation (deep brain stimulation and transcranial magnetic stimulation) in preliminary clinical studies with effects ranging from improved body image ratings [102] to weight gain [103]. Further studies are needed to confirm the observed results, to define the most responsive brain regions and to understand the underlying mechanisms [104].

There is a loss of functional connectivity between several regions that are part of the reward circuit but also with the hypothalamus, reflecting an altered communication between energy needs and the pleasure of eating [105]. Interestingly, neuroimaging studies have shown that the response to hunger and satiety in anorexic patients is the same in reward and cognitive circuits. Energy balance is then not taken into account in the decision to eat [106]. The connection between the homeostatic and hedonic systems thus seems to be involved in the pathophysiology of AN. These two components are indeed in bidirectional

communication [52], for example *via* peptides such as leptin and ghrelin, which are also able to interact with the reward circuit [106].

1.3.2. Circadian rhythms

Eating behaviour is discontinuous and episodic, with an active phase including episodes of food intake, consumption and storage of nutrients, and a resting phase with fasting and consumption of reserves. This rhythmicity of feeding is controlled by a set of central and peripheral biological clocks, known as circadian clocks. Biological rhythms allow organisms to adapt to and anticipate changes in their environment, thus promoting the optimal and coordinated performance of essential functions [107]. The master clock, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, is mainly controlled by light and partly modulates and coordinates the secondary clocks, whose activity is synchronized by neuronal and humoral pathways and food intake. Secondary clocks are found at the central level, such as the arcuate nucleus or the amygdala, but also and in greater numbers at the peripheral level, such as liver, adipose tissue, adrenal gland and intestine [108,109]. It has been shown that the SCN is able to produce and maintain an oscillation of about 24 h in an autonomous manner [107]; the master clock is then referred as the circadian pacemaker. Its rhythmicity is adjusted by synchronizing signals, the most important of which is the day–night cycle. More specifically, photosensitive retinal ganglion cells project to the SCN to facilitate this but interestingly, these cells innervate also another area, lateral habenula, which also shows spontaneous circadian activity [110]. This spontaneous activity is enabled by a coordinated set of molecular actors, called clock genes that interact with each other and constitute a transcriptional and post-translational negative self-regulatory loop [111]. The main clock genes are *Per*, *Cry*, *Clock*, *Bmal1* and *Nr1d1* (mainly known as *Rev-erb α*), which are expressed in the SCN but also in secondary clocks [112] and are responsible for the rhythmic expression of mRNAs and proteins in tissues, as documented in CircaDB [113]. Many studies link feeding behaviour to the circadian system [114–121]. Indeed, the master clock is closely linked to the metabolic and hedonic pathways that control eating behaviour. Food intake is therefore controlled by a so-called circadian-metabolic-hedonic network, in which the SCN would impose a precise rhythmicity to optimize the metabolic-pleasure balance [114].

Many players in the regulation of feeding behaviour, such as leptin or the neuropeptides NPY and α -MSH, have been shown to follow a circadian secretory rhythm, and these dynamics are altered in patients with AN [115–117]. Other circadian activities are also affected in patients with AN, such as sleep [122,123,123–127]. Interestingly, the body temperature of patients with AN is impaired and differs in a circadian manner [128] which could be explained by a lower thermogenesis [129]. A shift of physical activity to the resting phase and some alterations of amplitude, acrophase and mean activity have been reported in ABA mice [46,130,131]. AN is therefore associated with variability in these rhythms [132], again highlighting the circadian component in the regulation of eating behaviour.

At the molecular level, dysfunction of the clock genes is at the origin of behavioural and physiological alterations. Notably, some clock proteins are transcription factors and bind to the promoters of hormones involved in the regulation of feeding behaviour [108,114,133]. For example, mutation in *Per2* gene leads to sleep and food intake disturbances [133]. In the SCN, gamma-aminobutyric acid-A (GABA_A) receptor-mediated neurotransmission is important for the SCN neuronal network. Indeed, SCN neurons receive a tonic GABA-A receptor-mediated current that varies in amplitude and frequency throughout the day, with a peak

in the middle of the inactivity phase of rats [134]. In fact, CLOCK and BMAL1 appear to interact with the GABA_A receptor γ 2 subunit in the paraventricular hypothalamus, essentially for the diurnal rhythmicity of metabolism. [135]. Alteration of this receptor may be involved in the development of AN [136]. It has only recently been described that the expression of these clock genes is altered in ABA mice, as *Cry1*, in a tissue- and sex-dependent manner [46,137], and seems to be reversed by refeeding [46].

More specifically, acyl coenzyme A binding protein, also known as diazepam binding inhibitor, is reduced in AN inversely of patients with obesity; this mediates an orexigenic effect that has been shown to be mediated through γ 2 containing GABA_A receptor in mice [136]. This receptor is also associated with anxiety-like behaviour in GABA_A receptor γ 2 subunit knockdown mice [138]. In addition, nutritional state, such as fasting and refeeding, influences neuronal activity and this is dependent on a functional circadian rhythm [135].

There is a bidirectional relationship between circadian clocks and feeding behaviour [118]. According to Challet et al., 2009, Damiola et al., 2000 and Wehrens et al., 2017, mealtime is a powerful synchronizer of peripheral clocks but it has a limited effect on the master clock which is mainly influenced by fluctuations in ambient light [107,119,120,139]. Paradoxically, a chronic hypocaloric diet enhances the circadian rhythm of the SCN by higher light sensitivity, in contrary to a chronic hypercaloric diet [107]. In addition, fasting is thought to reset some of these clocks [107,140]. The role of food intake as a synchronizer has also been shown in the ABA model; irregular access to food accelerates the ABA phenomenon and its development, in particular due to anarchic FAA [141]. Moreover, this physical activity is associated with the disruption of circadian rhythm observed by activity in resting ABA mice [142]. Furthermore, mice with a knockout of the receptor that is activated by ghrelin (Growth Hormone Secretagogue Receptor, GHSR) exhibit an enhancement in their circadian activity profile, characterised by a rise in nocturnal activity and a decline in diurnal activity [131]. All these points highlight the need for food intake to follow a strict circadian rhythm to ensure homeostasis.

1.3.3. The two sides of physical activity in patients

31 %–80 % of patients with AN have an inappropriate level of physical activity relative to energy intake, named physical hyperactivity [143,144]. There is a positive correlation between physical activity and genetic factors of AN [145]. The discrepancy in the percentage of patients with AN who are hyperactive may be explained by the different criteria used to define obsessive activity in clinical studies. For example, one study reported compulsive activity as more than 4 h of physical activity per week [146], whereas other studies described compulsive activity as at least 1 h per day [147,148]. Excessive exercise is associated with higher severity of AN, resulting in an average hospital stay of 3 weeks longer [149]. In support of this, in a preclinical model, some ABA C57Bl/6 mice (mainly males) ran more than twice the average distance, i.e. more than 10 km per day [137]. Paradoxically, while male ABA mice showed a daily physical activity disruption with running wheel activity during the inactivity phase, females adapted their activity to adopt a more normal activity profile [35]. In addition, the wheel access protect male ABA mice from colonic hyperpermeability [150].

Strikingly, although hyperactivity is described as detrimental to patients historically [143], recent studies support that adapted physical activity could be beneficial for both physical and mental aspects of AN [151,152]. Adapted physical activity is defined as personalized and regular physical activity supervised by health professionals. Indeed, patients with adapted physical activity

showed improvements in bone mineral density and anxiety levels [151]. Interestingly, a higher BMI is observed in hyperactive patients compared to dieting or fasting subjects [153]. These observations were later confirmed with adapted physical activity, which seems to be beneficial for patients with AN [152,154].

The reasons for patient's hyperactivity are still not fully understood. It could be a pathological behaviour in response to the fear of gaining weight, but there are other explanations for this characteristic, such as an addiction to exercise and the need to keep warm. In fact, a network of metabolic dysfunctions would support this last point, combining alterations in the regulation of eating behaviour and mitochondrial dysfunctions involved in thermogenesis. In some patients with AN, this brown adipose tissue thermogenesis seemed to be impaired [129] but the underlying mechanisms remain unknown. On human, "brownable" adipose tissue in healthy lean subjects at the cervical, supraclavicular, axillary, mediastinal, paraspinal and abdominal levels [155]. In addition, previous studies showed activation of adipose tissue when subjects are exposed to cold temperatures [156]. Interestingly, extremely emaciated female patients had a lower core body temperature up to -2°C compared to healthy controls, these patients reported feeling cold, particularly in their hands which may induce compensatory physical activity [157]. In addition, the inappropriate physical activity observed in patients appears to be related, at least in part, to an addiction to exercise [158]. A depressive disposition may have initially led to the engagement in intense physical activity as a means of stimulating the production of neuroactive substances with antidepressant effects [159], which in turn may have triggered an addictive pattern of behaviour that later interferes with refeeding during the acute phase of AN. It has also been shown that ghrelin, which is elevated in patients with AN [69], is necessary for the adaptation to a low-energy state by lowering body temperature, and thus by preventing energy wastage. As a matter of fact, increased ghrelin levels associated with decreased body temperature are observed during dietary restriction in mice, possibly related to the mitochondrial uncoupling protein 1 (UCP1). UCP1 dissipates the proton gradient across the mitochondrial inner membrane to produce heat rather than ATP. Ghrelin-deficient mice failed to downregulate *Ucp1* expression and body temperature downregulation normally induced by fasting [160]. Low UCP1 protein levels in the brown adipose tissue of ABA rat models is associated with hypothermia [161]. UCP1 is mainly expressed in brown adipose tissue, where it regulates thermogenic respiration [162]. These findings suggest a link between ghrelin levels and UCP1 that warrants further investigation.

1.3.4. Mitochondria

Mitochondrial function has been studied in various species, including birds, dogs, and mice. These animals have different lifespans, energy expenditure, and circadian rhythms, with mitochondria playing a central role in these aspects through respiration and ATP production but also through the production of reactive oxygen species (ROS) [163]. Given the ubiquity of mitochondria and their critical role in cellular functions, such as food intake, circadian rhythms, and activity regulation, alterations in mitochondrial function have numerous consequences for cellular and physiological metabolism. Both physiological and molecular energy metabolism are affected in AN [41]. Mitochondria, being the primary organelles responsible for energy production, have been shown to be functionally altered in patients with AN. Regarding oxidative stress, leukocytes from patients with AN show impaired mitochondrial function and increased oxidative stress compared to controls [164]. Furthermore, a meta-analysis of seven longitudinal studies involving patients with AN ($n = 104$) revealed a

benefit of weight gain in this regard. Weight gain improves oxidative stress with higher levels of serum apolipoprotein B and antioxidant albumin [165]. A deficiency of antioxidant molecules has also been described in patients with AN [166]. In parallel to the clinic, ABA female rats displayed elevated plasma oxidative stress markers, which were restored after refeeding [167].

In addition to the hypothesis that high plasma ghrelin levels, induced by ghrelin resistance, inhibits *Ucp1* gene expression and then thermogenesis [168,169], another hypothesis links an area of the hypothalamus involved in food intake and energy balance to brown adipose tissue thermogenesis. Briefly, astrocytes, especially reactive ones, act on a neuronal population thanks to the release of GABA to inhibit thermogenesis in brown adipose tissue [170]. We can therefore wonder how this communication might be altered in patients with AN (Fig. 1). Few studies show an increase in diet-induced thermogenesis, assessed using metabolic chambers during refeeding in patients with AN compared to healthy controls [171,172], even if patients with AN exhibit a lower absolute value of resting energy expenditure [173] but not of the normalized value on body surface area [174].

Maintaining mitochondrial function is critical for brain homeostasis due to the extensive morphology and high energy demands of the cells [176]. Neuronal axons and the branched morphology of glial cells require different energy supplies within the same cell, requiring a balance between interconnected mitochondrial networks and isolated mitochondria, known as mitochondrial dynamics. Mitochondrial fission primarily involves DNM1L (formerly DRP1), MFF, FIS1, and phosphatases that activate DNM1L, such as G2/mitotic-specific cyclin-B1 (gene *CCNB1*) and the associated kinase cyclin-dependent kinase 1. Mitochondrial fission has multiple functions, including mitochondrial DNA turnover during mitosis, mitophagy, and apoptosis [177]. In contrast, fusion, which is known to induce higher ATP production, involves other GTPases such as OPA1 and MFN 1 and 2 to fuse two mitochondria, the former for the inner membranes and MFN for the outer membranes [177]. Regarding the hypothalamus and food intake, fission is often associated with disease due to ROS production, increased risk of mitophagy and lower ATP production, whereas fusion is associated with higher ATP production and good metabolic status [178].

First, in cell culture, starvation induces a stress and promotes fusion: stress stimulates the protein kinase A (PKA) which mediates the phosphorylation of DNM1L on serine 637 and then leads to blunt fission [179]. Conversely, hyperglycaemia induces fission and ROS production [180]. In a complex organism, the mitochondrial dynamic response to nutritional stress is cell type- and tissue-dependent. Most studies in rodents have been performed in the context of obesity or fasting about mitochondrial functions in the hypothalamus [178,179], but few in chronic undernutrition and anorexia. Fission is stimulated by fasting in both AgRP and POMC neurons [178]. The link between NPY and mitochondrial dynamics depends of the nutritional state, which may or not activate NPY neurons [181]. Furthermore, Nasrallah and Horvath showed an increase in mitochondrial fission and low ROS levels in activated AgRP neurons during fasting or caloric restriction [54]. Fasting induces mitophagy in AgRP neurons releasing intrinsic fatty acids that stimulate AgRP peptide expression and food intake [182], highlighting the importance of mitophagy in AgRP neurons to adequately respond to food restriction. The use of fatty acids for β -oxidation is followed by an increase in the number of mitochondria in NPY/AgRP neurons and in UCP2 levels and activity. UCP2 is a mitochondrial protein involved in the mitochondrial respiration and stimulates fission [54]. In addition, mitochondrial dynamics and mROS production are interconnected. For example, inhibition of DNM1L in the mediobasal hypothalamus blocks

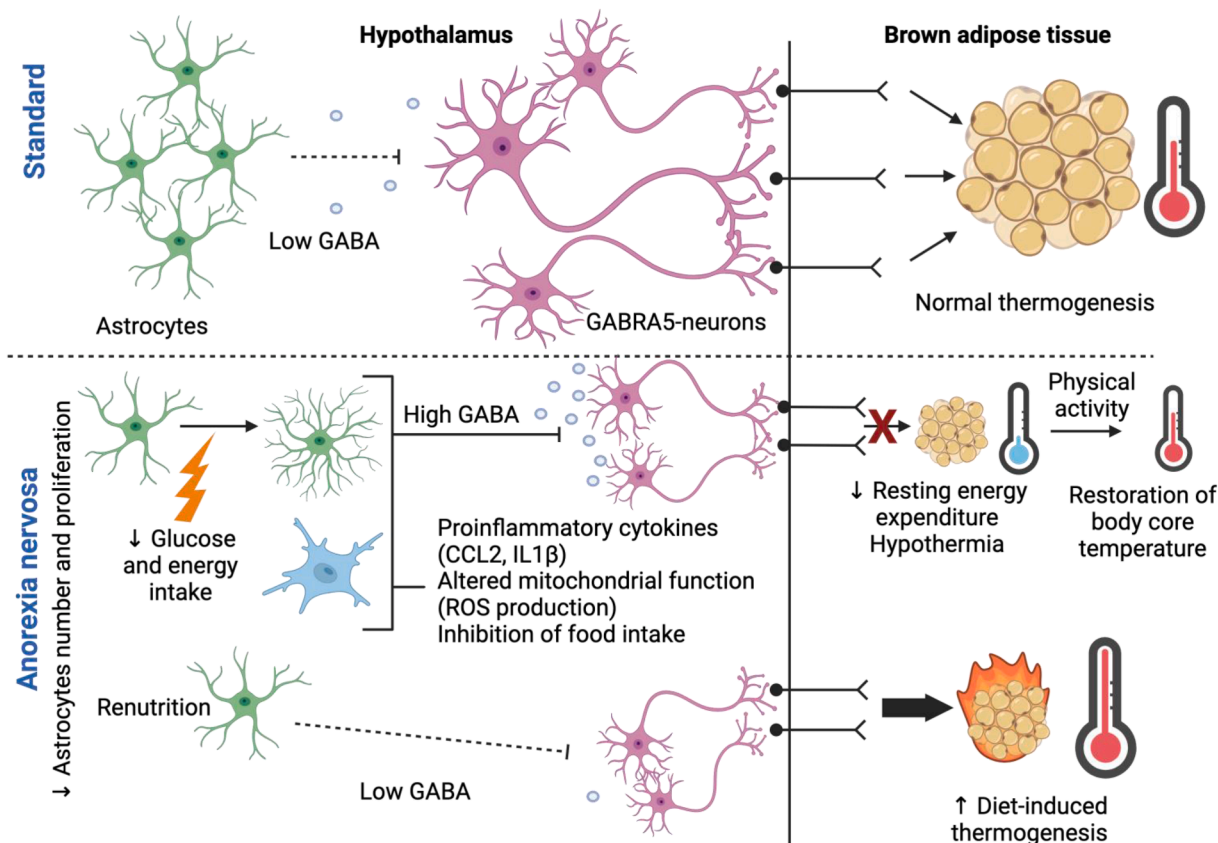


Fig. 1. Putative mechanism of an alteration of astrocytes regulation of brown adipose tissue thermogenesis in anorexia nervosa.

In the LHA of the hypothalamus, astrocytes act on GABRA5 neurons via GABA releasing to regulate thermogenesis in brown adipose tissue.

In anorexia nervosa, as astrocytes are known to be activated under glucose restriction *in vitro* [175], an increase of GABA synthesis and release could occur, leading to an inhibition of thermogenesis stimulation by GABRA5 neurons, and consequently leading to hypothermia that could be restored by physical activity, a compensatory mechanism retrieved in anorexia nervosa patients.

In case of refeeding, astrocytes would then return to basal secretion of GABA and thus increasing pacemaker firing of GABRA5 neurons. This could explain the rise of diet-induced thermogenesis observed during refeeding on anorexia nervosa patients.

GABA, gamma-aminobutyric acid; GABRA5, gamma-aminobutyric acid A receptor alpha 5; LHA, lateral hypothalamic area.

mROS production in response to intracarotid glucose injection and consequently inhibits insulin secretion [183,184]. Interestingly, mROS production and dynamics were also particularly important in the hypothalamus to regulate the activation of AgRP neurons [178,185].

We may wonder how mitochondria might be involved in the brain alterations observed in patients with AN. Thanks to AN rodent models, some altered mitochondrial functions have been uncovered, including changes in ROS production [19], mitochondrial dynamics [32,167,186] and mitophagy [32], particularly in the hypothalamus. More specifically, in the anx/anx anorexia model, a 50 % downregulation of *Ndufa1*, a gene involved in NADH dehydrogenase function, was observed in the hypothalamus and this downregulation was confirmed at the protein level. These findings indicate a dysfunction in mitochondrial respiratory complex 1, which is involved in cellular ATP production [19]. Indeed, oxidative phosphorylation (OXPHOS) complex 1 showed reduced efficiency, which was associated with an increase of hypothalamic oxidative stress and ROS production: together, these results suggest that mitochondrial dysfunction may partly explain the hypothalamic neurodegeneration in this anorexia model [187] (Fig. 2). Changes in mitochondrial dynamics were also observed for the first time in the ABA model through 2D electrophoresis of hypothalamic proteome [32]. Interestingly, DNM1L, which is involved in vesicles

trafficking was also increased at the end of the procedure. The LC3II/LC3I ratio suggested an increase in autophagy [32] and the fusion markers (OPA1, MFN1 and 2) remained unchanged. During the acute anorexic phase (5 days of starvation), total DNM1L levels increased in the hypothalamus of female ABA mice, but not at the end of the protocol (12 days of starvation). Nevertheless, the ratio of active form P616 to total DNM1L, an indicator of mitochondrial fission, increased in ABA mice only at the end of the protocol. The mitophagy marker BNIP3 also increased, suggesting a fission-induced mitophagy mechanism in the hypothalamus [32]. In female ABA rats, the same DNM1L ratio was increased in the medial prefrontal cortex, hypothalamus and hippocampus and was restored after refeeding. However, BNIP3 decreased in the medial prefrontal cortex, hypothalamus and amygdala, but was also restored after refeeding [167,186]. In the hypothalamus, the fusion was also altered with a decrease in the expression of MFN1 and 2, the latter remaining reduced after recovery [186]. Interestingly, in the amygdala, although no change in mitochondrial dynamics was observed initially, the mitochondrial dynamics was in favour of fission due after recovery to the increased DNM1L ratio and the decreased MFN2 [186]. Taken together, these findings emphasize the importance of time in the context of mitochondrial dynamics changes, which depend on nutritional status and tissue and cell type (Fig. 2).

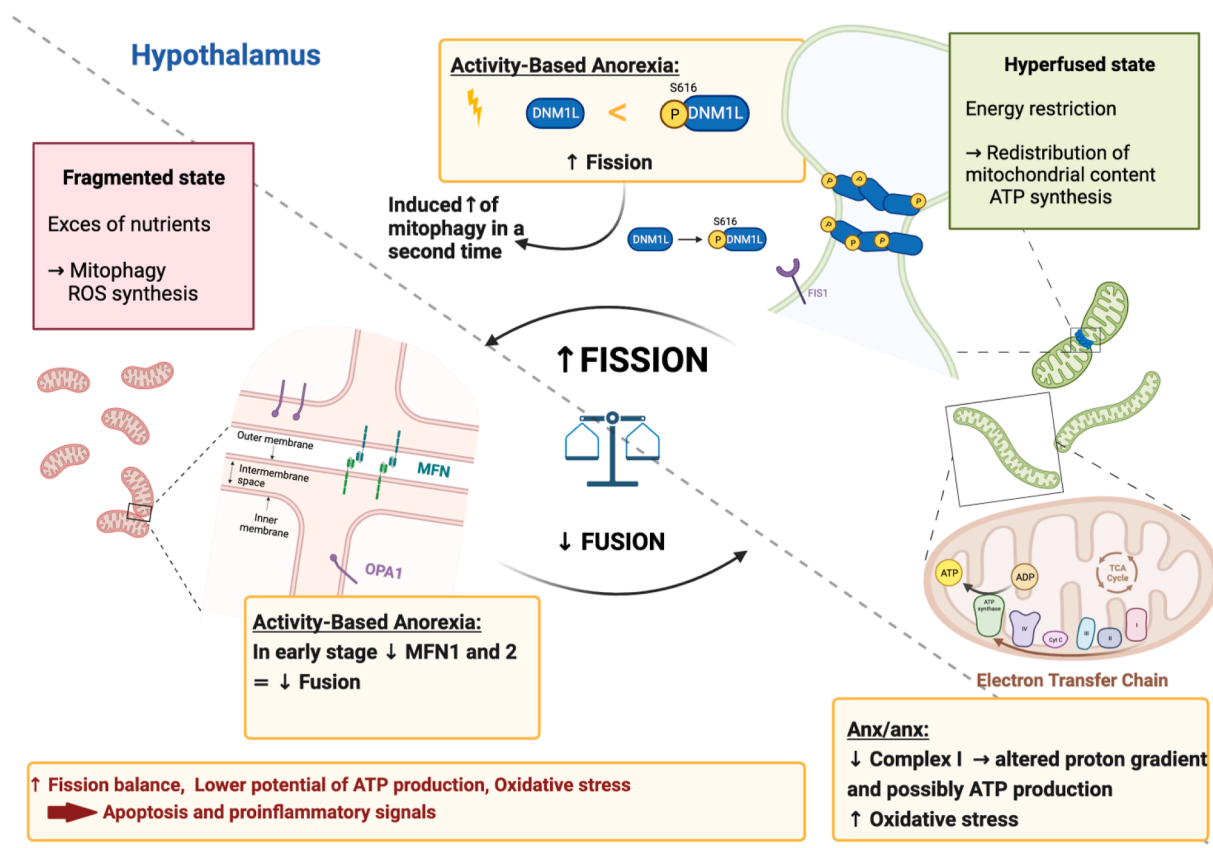


Fig. 2. Mitochondrial dynamics in anorexia nervosa models.

Fusion leads to the formation of large, elongated mitochondria, resulting in redistribution of mitochondrial content and optimisation of ATP synthesis. This process is regulated by the MFN and OPA1 GTPases, which allow fusion of the outer and inner membranes respectively. This phenomenon occurs in situations of energy restriction.

Fission leads to the formation of small fragmented mitochondria, which are responsible for significant ROS (reactive oxygen species) synthesis and the triggering of mitophagy mechanisms. The main player in this fission is the DNM1L protein, activated by phosphorylation of its serine 616, which binds to the Fis1 receptor, allowing the mitochondria to fragment in two. This phenomenon is triggered by an excess of nutrients. The fission-fusion balance supports healthy mitochondrial and homeostatic function.

In the ABA (activity-based anorexia) model, the ratio of DNM1L is altered centrally, in favour of an increase in its phosphorylated form, and a subsequent increase in mitophagy is observed. A decrease in mitofusins is also shown at early stages of the model. Furthermore, in anx/anx mice, complex I of the respiratory chain is less efficient, associated with an increase in oxidative stress.

Taken together, these data point to an alteration in mitochondrial dynamics, with increased fission leading to lower ATP production, oxidative stress and, consequently, apoptosis signaling pathways and the release of pro-inflammatory factors.

These results highlight the importance of studying mitochondrial dynamics in AN, where brain alterations, oxidative stress, and low-grade inflammation are observed.

1.3.5. Gut microbiota

It has been well described that numerous microbial metabolites interact with the brain to modulate feeding behaviour [188–191]. For example, caseinolytic peptidase B (CLPB) is a protein secreted by several gut microbiota bacteria and inhibits food intake thanks to its α -MSH mimetic structure [192,193]. Gut microbiota is involved in both the homeostatic and hedonic regulation of food intake through the modulation of humoral or nervous signals [189]. In particular, germ-free rodents show disturbances in dopamine turnover [189]. Interestingly, gut microbes can modulate the expression of enterohormones involved in homeostatic feeding behaviour as well as neurotransmitters involved in the reward system [189]. Numerous studies have attempted to discover new therapeutics that target or use gut microbiota to modulate the central nervous system [194].

Gut microbiota dysbiosis is observed in mouse models and in patients with AN and is involved in the dysfunction of the gut–brain axis [15,16,195–204]. To determine the causal relationship between dysbiosis and AN, Xia et al., performed Mendelian

randomization analysis [205]. Their method is a new method that excludes the interference of confounding factors to evaluate causal effects. In particular, they analysed GWAS database. As a result, after Bonferroni correction, only the class *Actinobacteria* was considered as a risk factor for AN. Interestingly, before this statistical correction, the *Lactobacillus* genus was also associated with a higher risk [205]. Mack and collaborators tried to decipher whether the observed gut dysbiosis is due to fasting, as in hibernating mammals, or specific to AN; they show a complex gut microbiota–host interaction which remains difficult to interpret in practice [206]. In mice, ABA and a food-restrictive control (no running wheel) showed similar dysbiosis, highlighting the importance of nutritional status [195].

Methanobrevibacter smithii was inversely correlated with BMI [199,200]. Patients with AN had a higher abundance of *M. smithii* than controls that may partly explain GI disorders attributed to CH₄ production [207]. Furthermore, the abundance of *Roseburia*, a short chain fatty acids (SCFA)-producing bacteria, was decreased in patients with AN [16,204,208]. *Agathobacter* genus belongs to the Lachnospiraceae family, known for its ability to produce butyrate, a SCFA essential for intestinal health and neuro-immune functions. Recent research has shown a significant reduction in the abundance of these bacteria in the fecal microbiota of patients

suffering from AN [16,199]. The abundance of *Lactobacillus* genus was often elevated in patients with AN [15,16]. *Lactobacillus* abundance was also increased in male and female ABA mice, without changes in *Roseburia* and *M. smithii* [137,195]. In a counterintuitive way in several points, the *Lactobacillus* genus has been commonly known as beneficial [209], although numerous functions can be observed in these bacteria, especially for *L. plantarum* [210] and a close correlation with BMI, positive or negative in a strain-dependent manner [211]. A counterintuitive point is the use of *Lactobacillus* to induce weight gain in malnourished mice [212] and in the livestock industry since 2000 [213]. The *Lactobacillus* genus, the most increased genus in AN [16], has been suggested in the literature to be associated with a risk factor of pathology as suggested by bioinformatic analyses [205] and whole microbiota fecal transplantation in germ-free mice [16]. However, in ABA mice, female have higher *Lactobacillus* than males but are more resistant to the model [137], we may thus wonder whether *Lactobacillus* genus is really detrimental for patients with AN or whether it is an adaptive phenomenon due to the malnutrition and therefore has beneficial properties.

In the ABA model, depletion of the microbiota by antibiotic therapy or the use of germ-free mice shows that the microbiota has an impact on feeding behaviour and physical activity in the C57BL/6 and BALB/c strains [36,214]. In the latter strain, these microbial alterations also induced hypothalamic alterations in the expression of neuropeptides involved in the regulation of food intake [214].

Metabolites from the gut microbiota themselves have beneficial functions. For example, butyrate has anti-inflammatory effects as recently demonstrated in human GI disease [215]. With regard to AN, there is an alteration of fecal SCFA [199,208,216] and in a recent study, plasma SCFA were also found to be altered on 109 patients with AN compared with healthy controls [217]. For instance, butyrate and acetate in stool of AN patients were decreased [199]. Plasma iso-valeric, iso-butyric and butyric acid levels were lower in patients with AN compared to healthy patients. Interestingly, there is a correlation between BMI and plasma SCFA levels [217]. The impact on neurotransmitters in the gut was also observed, with a decrease in serotonin, GABA and dopamine levels in the faecal content of patients suffering from AN [199].

1.3.6. Inflammation

1.3.6.1. Peripheral inflammation. Chronic, low-grade, peripheral inflammation has been described in patients with AN and in the ABA model [98]. It results in increased plasma levels of pro-inflammatory cytokines levels such as TNF α , IL-6, IL-1 α , IL-17 and IL-65 in humans [200,218]. Clinical treatments can improve blood IL-6 mRNA but not TNF α [219]. Interestingly, these changes were not found in patients who had been ill for less than a year [218]. It is therefore possible that inflammation is only associated with a maintenance phase of the disease. In the ABA model, TNF α and IL-1 β mRNA expression is increased in the colon while IL-6 is not affected [220]. Interestingly, the toll-like receptor 4 (TLR4) expression on colonic epithelial cells is increased in ABA mice [220] and an inducible knock-out (KO) specifically in these cells limits the body weight loss in ABA mice [64]. Further studies are needed to establish a cytokine profile in anorexia models. Interestingly, patients with eating disorders have a higher prevalence of autoimmune diseases [218], and the adaptive component of immunity has been shown to be impaired [98]. Most of these effects are reversed by refeeding, highlighting the role of malnutrition in these inflammatory phenomena [98].

The intestinal barrier, which is involved in optimizing nutrient absorption, immune defence and structural integrity of the intestine [221], is altered in inflammatory situations. Intestinal

hyperpermeability has been reported both in severely malnourished anorexic patients [69] and in the ABA model [130] but not in patients with AN with a mean BMI of 16.97 [222]. Interestingly, the comparison of ABA and control groups subjected to the same malnutrition (pair-fed group), showed the crucial protective role of physical activity in establishing intestinal hyperpermeability [130]. Increased intestinal permeability would also contribute to the dysregulation of the microbiota–gut–brain axis [69].

The peripheral inflammation is thought to contribute to the negative energy balance seen in AN in several ways. First, the IL-6 signalling pathway has been shown to be involved in the regulation of body weight [223]. TNF α induces catabolic effects, and at very high concentrations, suppresses food intake [219]. Circulating cytokines can also lead to sickness behaviour *via* vagus nerve stimulation, [224], *i.e.* an adaptive evolutionary behaviour including reduced food intake, hypoactivity, apathy and other behaviours aimed at optimizing the fight against pathogens, both from an individual and collective point of view [225]. Therefore, the immune system may be involved in the development of AN [218]. On the other hand, negative energy balance has also been shown to influence inflammation. Malnutrition for example, would alter the proper functioning of the immune system by affecting the composition and thus the activity of immune cells [218]. Fatty acids are part of the composition of lymphocytes, and antioxidant nutrients are involved in protecting immune cells from oxidative stress [226], as is leptin in immune cell efficiency [227].

1.3.6.2. Central inflammation. There is some evidence that neuroinflammation, the inflammation of the central nervous system (CNS), is involved in the pathophysiology of AN [42,228]. In fact, it has been shown that peripheral inflammation can be transmitted to the CNS by mechanisms that are not yet elucidated [229]. For example, circulating cytokines are able to cross the blood–brain barrier and thus induce an inflammatory phenotype in the brain [229,230]. Other mechanisms that are independent of the blood–brain barrier are also thought to be involved. In addition, several elements seem to link psychiatric disorders and infections: a common genetic susceptibility, the association of certain pathogens with an increased risk of developing psychiatric disorders [231], or the excessive activation of the immune system in certain psychiatric disorders. Furthermore, the prevalence of autoimmune diseases is higher in patients with eating disorders than in the general population [218]. We can also wonder if, in some cases, an infection could be the cause of the pathology with induction of neuroinflammation.

Neuroinflammation, acting through the activation of microglial and astrocytic cells, can affect food intake. Firstly, through sickness behaviour described above, but also directly through glial cells expressing food intake-related receptors. Microglial cells are able to regulate food intake [232], *via* TLR2 [233] and TLR4 [234] receptors, or by sensing glucose levels in the hypothalamus [235]. Regarding astrocytes, they are activated under glucose restriction conditions *in vitro* [175]. However, they can also directly regulate food intake through their reciprocal interactions with AgRP neurons [236] and PVN neurons [237]. More specifically, the hypothalamus is particularly sensitive to inflammation because it is the region that expresses the most cytokine receptors. Activation of these receptors therefore leads to a dysregulation of the food intake circuits [238]. Rovère and colleagues have shed light on chemokines that can modulate neuronal activity and therefore feeding behaviour, such as chemokine ligand 2 (CCL2), which would lead to a decrease in food intake by interacting with melanin-concentrating hormone neurons [239].

Various models of AN have shown evidence of neuroinflammation: increased hypothalamic IL-1 β [220] and decreased density of glial cells in the corpus callosum, cortex and SCN in ABA [45,46,240], a reactive microglial phenotype in the prefrontal cortex [98] and hippocampus [241], a decreased density of astrocytes in the corpus callosum, cortex and hippocampus associated with a deramification in DIA rats or increased expression of proinflammatory cytokines in the prefrontal cortex in the same model [228]. Some discrepancies in the microglia phenotype are reported but can be explained by the diversity of animal models, restriction protocols, and brain regions studied [23,46,241]. Altered hypothalamic mitochondrial respiration associated with ROS and oxidative stress supports the neuroinflammation and neurodegeneration hypothesis in *anx/anx* mice [187]. Additional analyses are needed to characterize astrocytes and microglia at different levels of complexity (metabolomic, proteomic, transcriptomic ...) [242] and thus clarify the nature of a potential inflammation of the central nervous system.

All these comorbidities contribute to the maintenance of an altered energy balance in patients with AN. A better understanding of how these disorders contribute to the pathophysiology of AN is an important issue that would ultimately improve patient management. Interestingly, preclinical models are able to recapitulate some of the clinical features of AN, as described below, and are therefore helpful in unravelling the pathophysiology of AN.

1.4. Connecting the dots

1.4.1. Circadian rhythms and physical activity

Sleep disorders and other circadian dysfunctions have been described in AN but the underlying mechanisms remain elusive. Patients with AN showed sleep disturbances with a 60 min average of waking up events per night [243]. Interestingly, it is well described that the rodent models of anorexia present FAA, based on the restriction of food availability at the same time each day. For instance, this can occur during resting phase in male and female mice [35]. Interestingly, this FAA seems to be linked to circadian rhythms. It is worth noting that, SIRT1 can modulate the circadian rhythm in the SCN to modulate physical activity [244]. Modulation of SIRT1 expression can bidirectionally modulate FAA but specific inactivation on POMC neurons did not affect FAA. A study reported that *Per2* mutant mice did not show FAA in response to timed food restriction [133]. We might ask whether ABA rodents with FAA present SIRT1 and PER2 dysregulation in the SCN.

1.4.2. Circadian rhythms and gut microbiota

The notion of microbiota stability is being challenged in several ways. First, it has been clearly shown that the composition of the microbiota varies with the type and rhythm of food intake. The latter is the main source of variation in the microbiota. Diurnal oscillations have also been demonstrated affecting up to 20 % of the abundance of commensal gut microbiota species in both mice and humans. These reflect different functional profiles of the microbiota during the day: during the waking phase, activities are directed towards energy production, cell growth and repair of genetic material, whereas during the resting phase, detoxification and chemotaxis are favoured [245]. The observed oscillations are both quantitative and qualitative. For example, *Bacteroidetes* and *Firmicutes* show maximum abundances twice a day at 11 am and 11 pm, and 3 am and 7 am, respectively [246]. Furthermore, circadian rhythm disruption in mice alters the gut barrier, bacteria recognition pathway and gut microbiota composition in mice submitted to an exclusive light exposure for 4 weeks. For example, there was a decrease in *Lactobacillus johnsonii*, known to contribute to intestinal integrity [247]. In mice, the abundance of

Lactobacillus reuteri increases during the day and decreases during the night [248]. The rhythm of the microbiota is aligned with that of the host's food intake and therefore depends on its clock, it is not intrinsic to the microbiota. Indeed, in KO mice for the clock genes *Per* [248] or *Bmal1* [246], microbiota remains constant throughout the day. Temporal information is therefore transmitted from the host to the microbiota, and alteration of this clock leads to dysbiosis [245,249].

It has also been shown that the rhythm of the microbiota exerts a feedback control on the host clock, *via* cyclically secreted metabolites. In particular, SCFAs and H₂S, directly affect the expression of clock genes, especially in the liver. Thus, the transcriptome of the hepatic clock is altered in dysbiosis. In addition, depletion of the gut microbiota with antibiotics alters the circadian clock genes mRNA level in the ileum and colon, particularly for *Nr1d1* [249]. The microbiota is then identified as a new element in maintaining the body's circadian rhythms [250]. Whether dysregulation of SCFA and clocks genes occur in patients with AN with sleep disorders remains to be investigated.

The interdependence of the host and gut microbiota clocks allows us to introduce the concept of a multidomain ecosystem to describe the organism. Notably, the activities of the host cells and gut microbiota are coordinated with each other and respond in a synchronized manner to diurnal fluctuations in the environment [245]. Taken together, these data raise the question of whether and how circadian disruption and gut microbiota are linked in AN.

1.4.3. Circadian rhythms and mitochondrial dynamics

In 1981, Uchiyama et al., observed rat hepatocytes by electron microscopy and highlighted a significant difference in shape and mitochondrial density between the night and day phases [251]. They were the first to conclude that mitochondrial dynamics are organized according to a circadian rhythm (Fig. 3).

In particular, rhythms are found in the composition of the mitochondria, at the level of the proteome, the acetylome and the lipidome, and would act as a support for the diurnal functional variations of the mitochondria. The lipidome also varies according to the phases of food intake. Mitochondrial respiration and nutrient metabolism are also subject to diurnal rhythms, with higher O₂ consumption at night than during the day and a peak in carbohydrate consumption during the day in mice [252]. Furthermore, the membrane potential of mitochondria shows oscillations, the highest of which coincides with the fusion state, suggesting that fusion processes are membrane dependent [253]. The circadian component of mitochondrial morphology is well established [252–254]. The numerous oscillations observed in previous publications are supported by Jacobi et al., in 2015, who showed that the clock gene *Bmal1* regulates the rhythmicity of mitochondrial dynamics in the liver, including the expression of fission gene [255]. BMAL1 interacts with the translation machinery to regulate circadian rhythms of protein synthesis [256]. For instance, in cardiomyocytes, BMAL1 deficiency showed altered mitochondrial dynamics (higher MFN2 expression, hyperfused microscopy observations, lower mitophagy) and respiration dysfunctions with lower maximal respiration capacity [257]. BMAL1/CLOCK dimer binds the E-box of *BNIP3* to induce mitophagy, an important process to control the mitochondria quality [257]. Genes related to mitochondrial function would be one of the main transcriptional targets of the hepatic clock, allowing to anticipate the influx of nutrients to optimize metabolism [255]. It is also been shown that DNM1L serine 637 phosphorylation, classified as a fission inhibitory mark, occurs in a circadian manner and is essential for rhythmic ATP production but also acts as a feedback control on the molecular clock [258,259]. Indeed, DNM1L KO cells lose the oscillations in ATP synthesis and in the expression of the

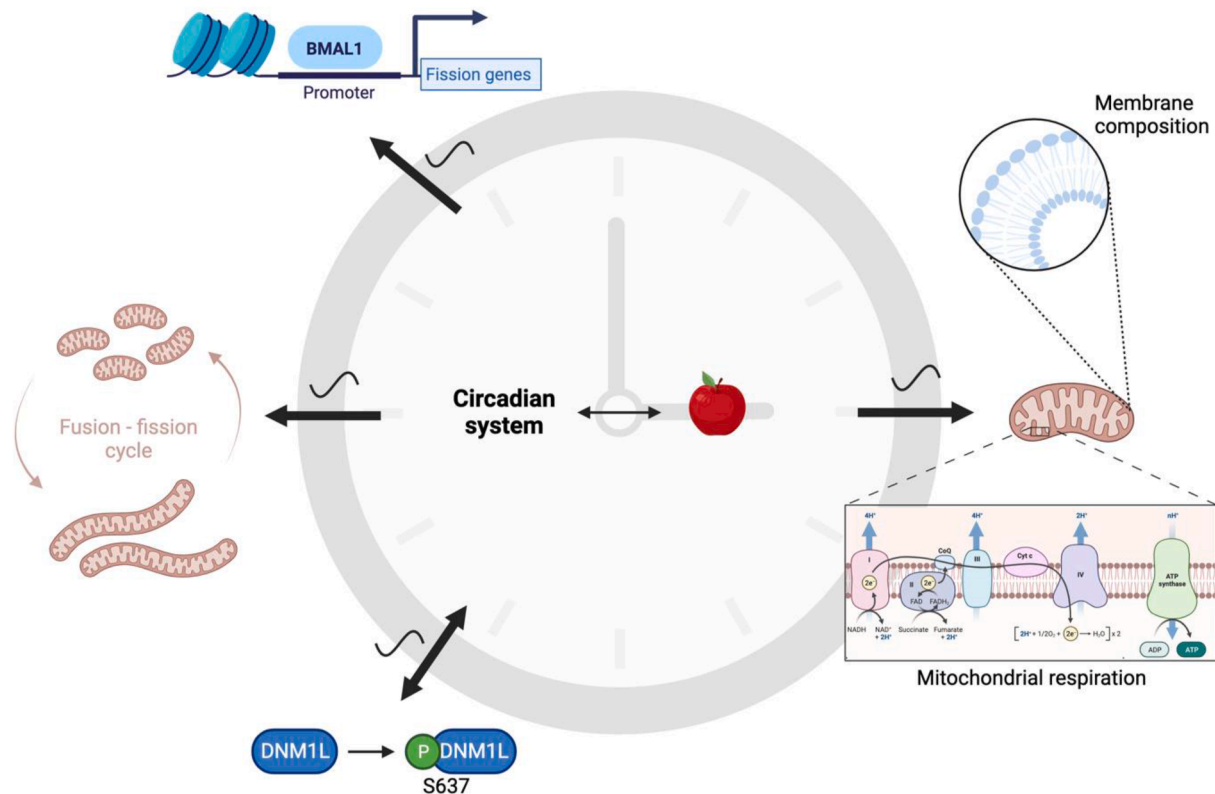


Fig. 3. Circadian function of the mitochondria.

Circadian rhythms are observed in mitochondrial membrane composition (which also follows the rhythms of food intake), in the functioning of the respiratory chain, in mitochondrial dynamics per se and also in the phosphorylation of DNM1L serine 637. This phosphorylation also acts as a retrograde signal on the molecular clock, highlighting the essential nature of factors in mitochondrial dynamics for the correct functioning of the clock. It has also been observed that the *Bmal1* clock gene product activates the transcription and translation of fission genes by binding to their regulatory regions.

The circadian system is therefore essential for maintaining operational mitochondrial dynamics. These two factors are closely interconnected.

clock genes *Bmal1* and *Per*. Mitochondrial dynamics factors are thus essential for clock function. In A172 glioma cell cultures synchronized with rhythmic cycle of BMAL1, P-637 DNM1L shows cyclic protein level, with a peak at 24 h after synchronization and lower level at 12 h, which correlates with mitochondrial length. The siRNA *Per1/Per2* transfection blunted the circadian expression of P-637 DNM1L [259].

Furthermore, studies of mutant models for clock genes all conclude that the circadian rhythm is essential for the maintenance of functional mitochondrial activity [252,254,255,257,258], demonstrating the link between these two factors. In AN, the links between mitochondrial dysfunction and circadian disruption remain poorly documented.

1.4.4. Mitochondria and microbiota-gut-brain-axis

Due to their phylogeny, mitochondria share many structural and functional characteristics with prokaryotes that are the bacteria of the gut microbiota. It is also important to study their interactions within organisms is also relevant. Firstly, a correlation between the quality and diversity of the microbiota and mitochondrial function has been highlighted [260,261]. SCFAs have shown to have beneficial effects on mitochondrial activities [260]. For example, the satiety stimulator butyrate stimulates fusion in the liver by activating the AMP-activated protein kinase (AMPK) pathway [262]. Other microbiota metabolites are involved in the regulation of transcription factors and enzymes of mitochondrial metabolism and biogenesis [261,263]. They are also involved in the modulation of ROS synthesis [263]. The communication between gut microbiota and mitochondria contributes to the energy balance and, in

particularly, in the control of physical activity [263], an interesting point for the consideration of AN. Metabolism is not the only mitochondrial function affected by the microbiota, effects on mitochondrial dynamics have also been demonstrated [264]. Colanic acid secreted by *E. coli* in the *C. elegans* model stimulates fission in host intestinal epithelial cells [265]. In 2020, McKay et al., have shown that infection of the gut by pathogens leads to excessive fission and cell death [266]. They then hypothesize that pathogenic bacteria alter the fusion-fission balance, whereas symbiotic microorganisms residing in our gut lumen favour the stabilization of mitochondrial dynamics. Thus, gut dysbiosis is associated by mitochondrial hyper-fragmentation. In addition, mitochondrial activity can also modify the microbiota, notably through the production of ROS and the maintenance of the gut barrier integrity [263].

All these data highlight the existence of a bidirectional communication between the gut microbiota and host mitochondria [260,261,263,264]. This would rely on endocrine, immune and humoral pathways [263]. The alteration of this communication is at the origin of the organism's dysfunction and associated pathologies [260,267]. An alteration of colonic and hypothalamic mitochondrial dynamics in the ABA model and gut microbiota dysbiosis raises the question of a role of the gut microbiota in this mitochondrial parameter.

1.4.5. Mitochondrial dynamics and putative neuroinflammation

Dysfunction of mitochondrial dynamics is observed in many diseases associated with neuroinflammation, such as postoperative cognitive dysfunction [268], or neurodegenerative diseases [269]. Moreover, genes related to mitochondria and their functions are

among those most implicated in neurodegenerative diseases [270]. An alteration of hypothalamic mitochondrial dynamics has also been shown in the ABA model [32,167,186], supporting the hypothesis of a neuroinflammation in AN. Nilsson et al., even speculate that the hypothalamic neuroinflammation observed in the anx/anx model may be a consequence of a mitochondrial dysfunction [20]. Mitochondrial dynamics is essential for the proper functioning of the CNS. Astrocytes and microglia require a lot of energy for their inflammation-regulating functions, which implies a functional metabolism and thus a functional mitochondrial dynamics [271]. Mitochondrial dynamics regulates, for example, the production of IL-10, TNF α , but also mitochondrial ROS and DNA secreted following apoptosis; these molecules activate the NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome [271]. Mitochondrial dynamics in microglia is a well-studied process and follows the understanding of the same mechanism in macrophages, of which microglia cells are a subtype [272]. *In vitro* stimulation of microglia to a pro-inflammatory state results in increased fission, which correlates with increased ROS secretion [273]. This phenomenon is also shown *in vivo* in astrocytes [274]. Recently, a specific subset of GABAergic neurons, expressing the $\alpha 5$ GABA receptor subunit in the LHA, has been shown to modulate thermogenesis in brown adipose tissue. These neurons are tonically inhibited by GABA released from astrocytes, especially when astrocytes are reactive [170]. The involvement of these cells in AN remains unknown (Fig. 1).

Park et al., in 2013, demonstrated the regulation of ROS production and the expression of pro-inflammatory mediators by mitochondrial fission itself. Activation of microglia in a pro- or anti-inflammatory state is also accompanied by a preferential use of metabolic pathways, glycolysis or phosphorylating oxidations, respectively. The shift to glycolysis, called the Warburg effect, observed in pro-inflammatory conditions [276], allows a metabolic profiling of microglia in order to characterize its activation state [277]. Whether this switch to glycolysis depends on mitochondrial fission [278] or not [279] is still unclear. Montilla et al., conclude that DNM1L-mediated fission contributes to the expression of pro-inflammatory genes but not to the change of metabolic phenotype in an *in vitro* study. However, only the phosphorylating oxidative pathway has been evaluated using the Seahorse method, and not glycolysis, in contrast to the study by Nair et al., which also showed similar results *in vitro* and in an *in vivo* mouse model of neuroinflammation [278]. The alteration of these mitochondrial dynamics leads to numerous consequences at the cellular and molecular level, such as the secretion of cytokines [271] or an increase in the permeability of mitochondrial membranes leading to apoptosis and sometimes to the release of mitochondrial damage-associated molecular patterns which then activate other microglial cells, creating a vicious circle [274]. Mitochondrial dynamics is therefore well established as a factor regulating the response of microglia to inflammatory conditions.

A dysfunction of mitochondrial dynamics at the neuronal level is also highlighted in several neurodegenerative diseases [275]. This would lead to an energy deficiency and consequently to neuronal loss [280]. At the neuronal level, the MFN2 fusion protein has been shown to have a repressive effect on microglia [281]. This shows the involvement of mitochondrial dynamics not only in the activation of microglia but also in the communication between the different actors of the CNS. All these data again support the hypothesis of a neuroinflammation associated with AN.

1.4.6. Gut microbiota and putative neuroinflammation

Gut microbiota and its metabolites can modulate the actors of neuroinflammation. In patients, a reduction in the genera that produce short-chain fatty acids [16,199,204] and

neurotransmitters and a modulation of autoantibodies involved in eating behaviour are implicated in the pathophysiology of AN [282]. Since SCFAs are able to cross the blood–brain barrier and even modify its structure [283] they can directly regulate inflammation at the central level [284]. For example, butyrate has been shown to reduce the activation of primary microglial cells [285], whereas propionate induces reactive gliosis *in vivo* [286]. Tryptophan and its metabolites are also known to influence food intake and glial activation [283,287,288]. Activation of microglial TLR4 by intracerebral or intravenous injection of lipopolysaccharide (LPS) also results in a shift to the macrophage M1 phenotype [289]. Following these findings, numerous teams have been able to modulate the neuroinflammatory response using pro- and pre-biotics [290].

It is therefore interesting to investigate the effect of altered gut microbiota on neuroinflammation. Firstly, dysbiosis is associated with an increase in the permeability of the blood–brain barrier and an activation of the inflammasome in the brain, *via* mechanisms that are not yet understood [283]. More specifically, the microbiota, and SCFAs in particular, have been shown to be necessary for the microglial homeostasis throughout life. For example, in germ-free mice, a decrease in the microglial population, an immature phenotype and consequently a dysfunction of the immune response are observed [291]. Neuroinflammation in AN remains elusive, but the function of astrocytes is certain. Notably, a decrease in the number of astrocytes is described in the ABA model, which could be responsible of the reduced brain volume. These authors highlighted the potential role of gut microbiota in the brain volume changes observed in patients with AN. Indeed, they showed a dysbiosis with a significant increase in *Lactobacillus*. Some correlations between brain volume and bacteria have been observed, which interestingly are at least partially restored by refeeding, as observed in patients [42,196,197]. Taken together, the above data support the hypothesis of a neuroinflammation associated with AN and again emphasize the importance of the gut microbiota.

2. Conclusion

The pathophysiology of AN is complex and involves many processes that are only partially documented. Some preliminary data suggest that mitochondrial metabolism and dynamics, circadian rhythms and the microbiota–gut–brain axis may interact to regulate energy metabolism and food intake. Taken together, these studies highlight the importance of further experimental and clinical research to better characterize the role of mitochondrial dynamics and circadian rhythms during AN both at the central and peripheral levels.

Author contribution

Léna Rousseau and Colin Salaün contributed equally to this work, they wrote original manuscript and made figures. Ludovic Langlois revised actively the review, especially concerning the neuroscience part. Najate Achamrah revised actively the review, especially concerning the clinical part. Moïse Coëffier revised actively the review entirely and led the project.

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Conflict of interest

The authors declare none.

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