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SPECIAL ARTICLE

The link between alterations in circadian rhythms and lipid metabolism in bipolar disorder: the hypothesis of lipid droplets

Ana Catarina **Pereira**,[1,2,3,4] Laura **Serrano-Cuñarro**,[1,2] Maria Teresa **Cruz**,[1,2,4,5] Cláudia **Cavadas**,[1,2,5] Cláudia Maria Fragão **Pereira**[1,2,3,4]

[1]*Centro de Neurociências e Biologia Celular, Universidade de Coimbra (UC), Coimbra, Portugal.* [2]*Centro de Inovação em Biotecnologia e Biomedicina (CIBB), UC, Coimbra, Portugal.* [3]*Faculdade de Medicina, UC, Coimbra, Portugal.* [4]*Centro Académico Clínico de Coimbra, Coimbra, Portugal.* [5]*Faculdade de Farmácia, UC, Coimbra, Portugal.*

Bipolar disorder (BD) is a neuropsychiatric illness characterized by recurrent episodes of mania and depression, leading to significant cognitive and functional impairments, psychiatric and metabolic comorbidities, and substantial healthcare costs. The complex nature and lack of specific biomarkers for BD make it a daily challenge for clinicians. Therefore, advancing our understanding of BD pathophysiology is essential to identify novel diagnostic biomarkers and potential therapeutic targets. Although its neurobiology remains unclear, circadian disruption and lipid alterations have emerged as key hallmarks of BD. Lipids are essential components of the brain and play a critical role in regulating synaptic activity and neuronal development. Consequently, alterations in brain lipids may contribute to the neuroanatomical changes and reduced neuroplasticity observed in BD. Lipid droplets, which regulate the storage of neutral lipids, buffer the levels of toxic lipids within cells. These dynamic organelles adapt to cellular needs, and their dysregulated accumulation has been implicated in several pathological conditions. Notably, lipid droplets and different classes of lipids exhibit rhythmic oscillations throughout the 24-hour cycle, suggesting a link between lipid metabolism, circadian rhythms, and lipid droplets. In this review, we explore the impairment of circadian rhythms and lipid metabolism in BD and present evidence that circadian clocks regulate lipid droplet accumulation. Importantly, we propose the ‘‘hypothesis of lipid droplets for BD,’’ which posits that impaired lipid metabolism in BD is closely linked to alterations in lipid droplet homeostasis driven by circadian clock disruption.

Keywords: Bipolar disorder; lipid droplets; lipid metabolism, circadian clocks

Introduction

Bipolar disorder (BD) is a neuropsychiatric illness characterized by cyclical mood swings. These oscillations range from manic episodes, characterized by increased energy, heightened activity levels, grandiosity, and irritability, to depressive episodes, characterized by decreased mood, energy, and activity. Between these extremes, individuals may experience periods of euthymia in which clinically significant mood disturbances are notably absent.[1] Patients diagnosed with BD tend to have high rates of divorce, unemployment, drug abuse, criminality, and suicide.[2] Affecting approximately 1-2% of the world’s population, BD significantly impairs quality of life and represents a substantial economic burden.[3-5] This mood disorder is the 6th leading cause of disability worldwide, and patients with BD are at increased risk of metabolic and cardiovascular comorbidities,[6-8] which are associated with increased premature mortality in these individuals.[9] Notably, these medical comorbidities are associated with significant alterations in lipid metabolism.[10] Furthermore, BD leads to cognitive and functional impairments that require lifelong treatment; however, current therapeutic options have significant side effects and are effective in only 40%-60% of cases.[11,12] The lack of specific biomarkers contributes to the misdiagnosis of BD due to the overlap of symptoms with other mood disorders, such as major depressive disorder (MDD).[13] Therefore, the identification of specific biomarkers for BD is of utmost importance to increase diagnostic accuracy and allow early clinical intervention in the early stages of BD to prevent progression to a full-blown disease state.[14,15]

Over the years, the pathophysiology of BD has been closely linked to the dysfunction of circadian clocks.[16]

Correspondence: Ana Catarina Pereira, Centro de Neurociências e Biologia Celular, Polo I, Faculdade de Medicina, Universidade de Coimbra, 3004-504, Coimbra, Portugal.
E-mail: anacatarinajpp@gmail.com
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These molecular mechanisms regulate various physiological functions, including body temperature, hormone levels, day/night or sleep-wake cycles, mood, and cognition. This cell-autonomous transcription-translation feedback mechanism operates in 24-hour cycles, commonly referred to as circadian rhythm. In mammals, the core machinery of circadian clocks consists of molecular feedback loops involving genes such as the circadian locomotor output cycles kaput (*Clock*), the brain and muscle ARNT-like 1 known as *Bmal1*, Period 1, 2 and 3 (*Per1*, *Per2*, *Per3*), cryptochrome 1 (*Cry1*), and cryptochrome 2 (*Cry2*).[17-20] The master clock is located in the hypothalamic suprachiasmatic nucleus of the central nervous system, while secondary clocks are located peripherally, such as in the liver, adipose tissue, and muscles.[21-24] Recent findings show that lipid metabolism is regulated by molecular circadian clocks,[25] and alterations in lipid metabolism have been identified as a key hallmark of BD.[26] Pioneering evidence of defective lipid metabolism in BD came from magnetic resonance spectroscopy (MRS) studies, which have shown abnormalities in membrane phospholipids in patients with BD.[27,28] This impairment was further confirmed by the increasing body of data obtained from mass spectrometry (MS)-based approaches, which revealed significant alterations in levels of fatty acids and several classes of phospholipids in patients with BD.[29,30] Although MS-based lipidomics approach is the least explored "omics" platform in the field of neuropsychiatric diseases, it has advanced the understanding of the BD-associated lipid signature and has gained relevance in the discovery of biomarkers for BD.[31,32]

Lipids are essential components of cell membranes, powerful sources of energy, and important mediators of cell signaling. In the brain, they are the predominant biomolecules, critical for neuronal development and function by modulating neuronal synapses.[33,34] Thus, disturbances in brain lipid metabolism may underlie the pathological changes in neuroanatomical structure and synaptic plasticity observed in individuals with BD.[35] Beyond the brain, lipids, particularly phospholipids, are ubiquitous in all living cells and serve as the fundamental building blocks of cellular membranes. Because of their central role in maintaining biomembrane integrity, phospholipids play a critical regulatory role in essential cellular processes such as cell signaling and division, energy homeostasis, vesicular trafficking, and intercellular communication.[30,36] Phospholipids also act as intermediate precursors of triglycerides (TGs) and lipid droplets, which are dynamic organelles characterized by a neutral lipid core surrounded by a surface phospholipid monolayer. Lipid droplets exhibit a remarkable day-night rhythmicity of approximately 24 hours. Moreover, they can communicate with other organelles, including the endoplasmic reticulum (ER) and mitochondria, to participate in lipid metabolism and contribute to cellular homeostasis.[37-40] Recent research has highlighted the dynamic nature of lipid droplets, revealing their ability to adjust in number and size in response to cellular stressors such as ER stress, oxidative stress, and inflammation.[41,42]

Despite the growing body of scientific research on lipids, the content and modulation of lipid droplets in neuropsychiatric disorders, particularly BD, remains largely unexplored. To address this gap, the present review focuses on the close link between circadian clocks and lipid metabolism, with a special emphasis on lipid droplets. For the first time, we propose the "hypothesis of lipid droplets for BD."

Circadian clocks alterations in bipolar disorder

In recent years, genetic variations in several circadian genes have been reported in patients with a diagnosis of BD. Nievergelt et al.[43] identified a significant association between single nucleotide polymorphisms (SNPs) in the *Per3* and *Bmal1* genes and the pathophysiology of BD. Concomitantly, Mansour et al.[44] found a remarkable link between the clock genes *Bmal1* and *Timeless* and BD. Supporting these findings, a large-scale genome-wide association study (GWAS) has established clock genes as core genetic substrates in BD, with *Bmal1* being one of the key genes showing robust evidence of association with BD.[45]

The presence of polymorphisms in the molecular clock machinery appears to influence the response to the treatment and symptomatology of BD as well as the response to sleep deprivation.[46,47]

Sleep disturbances are one of the major symptomatic features of mood disorders, often preceding mood episodes and worsening in the days leading up to them. The severity of these symptoms appears to be related to alterations in circadian rhythms. Patients with BD continue to experience sleep disturbances even during periods of remission. These problems include not only common insomnia but also delayed sleep-wake cycles that vary depending on disease stage.[17,46] A SNP in the human *Clock* gene (thymine [T] → cytosine [C] nucleotide substitution at position 3,111 of the DNA sequence [3111C variant]) is associated with increased evening activity and delayed sleep pattern in BD-depressed patients (Figure 1).[48] Additionally, a SNP in the clock gene *Per3* has been associated with chronotypes due to a tandem repeat polymorphism of a segment formed by a 54-nucleotide coding region. When repeated four times, this polymorphism leads to a delayed sleep phase and is linked to later onset of BD. When repeated five times, it is associated with extreme morning chronotypes and early onset of BD.[47,49] Interestingly, patients with early-onset BD are less responsive to lithium treatment than patients with late-onset BD.[50] A study by Bengesser et al.[51] suggested a link between *Bmal1* and the different affective states in BD, finding that *Bmal1* expression was higher in the euthymic state than in the depressive state. Further investigation of the *Bmal1* gene revealed increased methylation at the CG site cg05733463 in patients with BD compared to controls, suggesting repression of the *Bmal1* gene and its influence on mood regulation.[52] This methylation and subsequent silencing or repression of *Bmal1* may result in decreased transcription of monoamine oxidase A (MAO-A), a mitochondrial enzyme that breakes down catecholamines and is regulated by the circadian clocks. This leads to increased neurotransmitter levels in the manic stage of BD.[53,54]

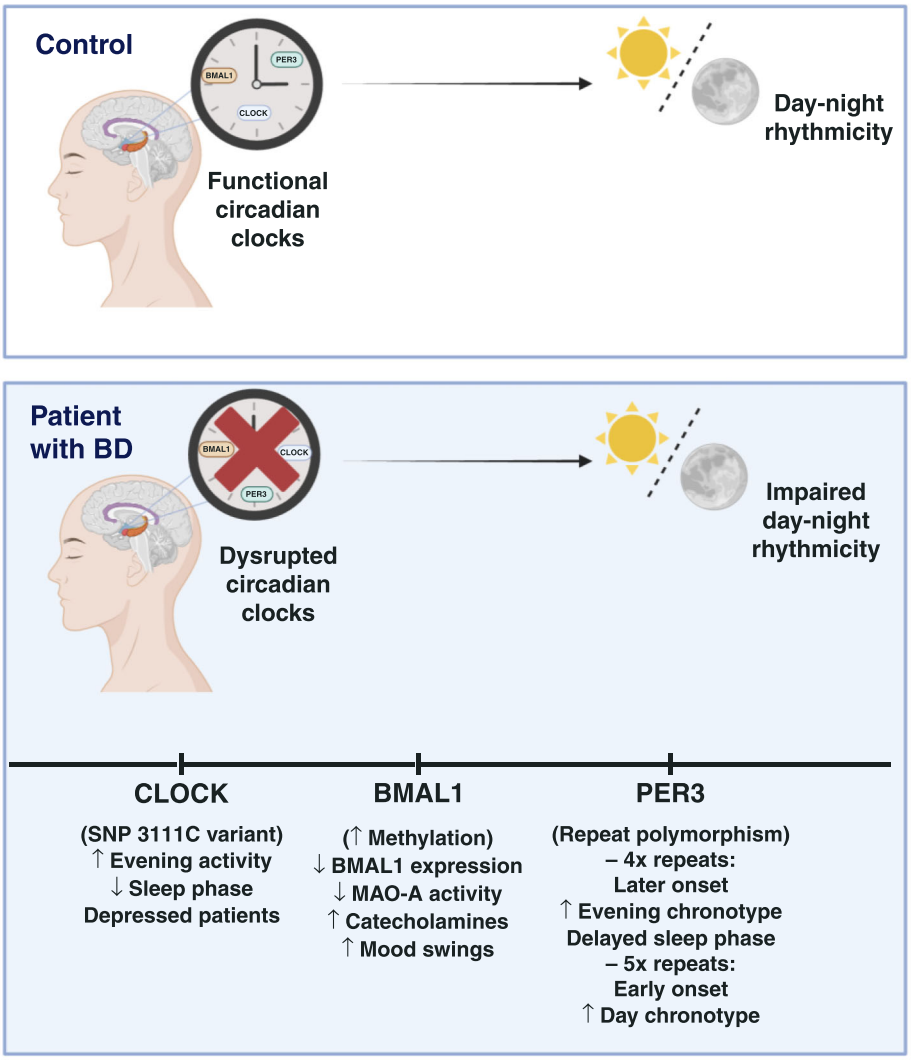

Figure 1 Impaired day-night rhythmicity in patients with bipolar disorder. BMAL1 = brain and muscle ARNT-like; CLOCK = circadian locomotor output cycles kaput; PER3 = period 3; MAO-A = monoamine oxidase A; SNP = single nucleotide polymorphisms.

Lipid metabolism alterations in bipolar disorder

Pioneering evidence for abnormal lipid metabolism in the pathophysiology of BD has been provided by MRS studies. These studies have shown that euthymic patients with BD have lower levels of cerebral metabolites, particularly precursors of membrane phospholipids.[28] In addition, manic/depressed patients show reduced concentrations of N-acetyl aspartate (NAA) and choline (Cho) in the frontal lobe of the brain (Table 1).[55] This hypothesis was further supported by a high-throughput lipidomic study that found higher levels of free fatty acids, phosphatidylcholines (PC), and ceramides (Cer) in the prefrontal cortex of patients with BD.[56] In agreement with this theory, decreased levels of fatty acids (e.g., omega-3 docosahexaenoic acid [DHA], omega-6 arachidonic acid [AA], and stearic acid) have been reported in the postmortem orbitofrontal cortex of these patients.[57] Conversely, other studies of postmortem prefrontal cortex have not found significant BD-associated alterations in the levels of the omega-3 DHA.[58,59]

The impairment of lipid metabolism in BD is further supported by emerging evidence of altered levels of fatty acids in the peripheral tissues of these patients. Specifically, an increased ratio of omega-6/omega-3 fatty acids has been found in the plasma of patients with BD when compared to controls, with lower omega-3 ratios associated with depressed mood.[68] In line with this, Scola et al.[29] conducted a study comparing the serum levels of fatty acids in depressed or euthymic patients with BD and healthy controls. Although they did not find significant differences in the levels of fatty acids among the three experimental groups, they reported higher ratios of omega-6/omega-3 fatty acids: AA:eicosapentaenoic acid (EPA) and AA:EPA + DHA in patients with depression compared with euthymic patients and healthy controls.

On the other hand, a study aimed at determining the overall plasma fatty acid profile in patients with BD observed higher levels of all fatty acids, including AA and EPA, and diminished levels of DHA.[69] Subsequent research confirmed the deficit of omega-3 fatty acid DHA in BD, as evidenced by a significant decrease in DHA levels in erythrocyte membranes of type I patients with BD compared to healthy individuals.[67] This DHA deficiency prompted the development of clinical trials to investigate the impact of DHA supplementation on the clinical features of BD. A reduction in BD-associated depressive symptoms was observed when conventional mood stabilizers were administrated in combination with omega-3 DHA.[72,73] Furthermore, a growing body of evidence supports the antidepressant effect of DHA supplementation compared to conventional therapy alone for the treatment of depressive symptoms in other psychiatric disorders (e.g., unipolar disorder and MDD), as well as a reduction of psychotic episodes in schizophrenia.[74,75]

Remarkably, GWAS studies have demonstrated that the fatty acid desaturase (FADS) locus, which encodes FADS1/2 enzymes, confers susceptibility to BD. FADS1/2 are rate-limiting enzymes involved in the metabolism of long-chain polysaturated fatty acids, including EPA and DHA.[76-78] Recently, Yamamoto et al.[79] developed a Fads1/2 knockout mice model to elucidate how lipid metabolism influences the pathogenesis of BD. Their findings suggest that Fads1/2 mutant mice are a novel *in vivo* model of BD, as these mice exhibited bipolar swings in their activity, displaying episodes characterized by hyperactivity and hypoactivity, which were accompanied by abnormal circadian rhythms. Analysis of the brain lipid profile in these mutant mice revealed overall changes in cerebral lipid composition, particularly in PC and phosphatidylserines (PS) lipid classes, despite the absence of changes in the levels of DHA or EPA. Interestingly, bipolar swings were prevented when those mice were supplemented with DHA or a mixture of DHA + EPA.[79]

Over the last few years, lipidomic analysis of plasma and serum samples has emerged as a key tool to study lipid metabolism in several pathological conditions, including BD. This approach allows the identification of unique lipid signatures, thereby contributing to the discovery of potential peripheral biomarkers for BD.[71] Ribeiro et al.[31] pioneered the use of a liquid chromatography-MS (LC-MS) lipidomic approach to study the serum lipid profile of patients with BD. Their results showed significant differences in 121 lipids between patients diagnosed with BD and healthy individuals, particularly in the distribution of phospholipids, glycerolipids, and sphingolipids.[31] Furthermore, this study identified phosphatidylinositol (PI) as the most significantly altered lipid in the serum of patients with BD.[31] Consistently, PI was identified as the most heritable serum lipid class and was strongly associated with the risk for BD.[30] Notably, higher levels of Cer were found in the plasma of patients with BD, particularly in males.[70] Additionally, Guo et al.[71] compared 31 lipid classes between women with BD and healthy controls. Their results showed that women with BD had depletion of several lipid classes, including acylcarnitine (CAR), sphingomyelin (SM), PS, and phosphatidylethanolamine (PE), as well as upregulation of PI, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylinositol, Cer, and TG. Besides analyzing different molecular lipid classes, they also investigated the fatty acid chain lipid profile in women with BD.[71] Results highlighted changes in the composition of long-chain fatty acids and in the degree of fatty acid saturation between patients with BD and healthy controls. Specifically, women with BD had higher plasma levels of saturated fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids with five, eight, or nine double bonds, and reduced levels of polyunsaturated fatty acids with six or more than nine double bonds. Finally, they identified nine lipids that together could potentially serve as plasma biomarkers for BD diagnosis, including PS 42:9, diacylglycerol (DG) 21:5, PC 36:6, PC 14:0, PS 38:5, TG 54:7, TG 58:9, TG 57:7, and TG 46:4.[71]

Lipids have been identified as potential diagnostic biomarkers for BD. However, determining the lipid profile of these patients is challenging due to numerous potential confounders. Table 1 shows that published studies vary considerably in terms of inclusion criteria, sex, and medication status. In addition, many studies often lack cause-and-effect analyses that specifically address the variables of sex and medication.[31,56] Population heterogeneity is also a confounder, with some studies including only type I patients with BD[55] and others including both type I and type II patients.[69] Recently, significant efforts have been made to correlate the severity of lipid alterations with BD-related mood states.[29,68] Methodological diversity in lipid analysis further complicates interpretation. MRS is the primary method for studying brain lipids (Table 1),[28,55,60-66] while gas chromatography (GC) or GC-MS is used to assess fatty acid composition.[57,68] LC-MS is critical for the comprehensive identification of thousands of lipid molecular species in tissues and peripheral blood sources such as serum and plasma.[31] However, heterogeneity in sample preparation procedures across studies adds another layer of complexity to the consistency of lipid analysis.[68,69] Regarding medication effects, recent evidence has shown that the administration of antipsychotic and antidepressant drugs generally perturbs lipid homeostasis, with notable alterations in TGs and low-density lipoprotein (LDL).[26]

Crosstalk between circadian rhythms and lipid metabolism

A growing body of evidence obtained from *in vitro* and *in vivo* studies has demonstrated that dysfunction of molecular circadian clocks compromises lipid metabolism and impairs lipid droplet accumulation.

Shimba et al.[80] showed that the molecular clock gene *Bmal1* regulates adipogenesis and lipid metabolism. Particularly, they found that disrupting *Bmal1* in 3T3-L1 adipocytes and mouse embryonic fibroblast cells (MEFs) *in vitro* resulted in the accumulation of minimal amounts of lipid droplets. Furthermore, restoration of normal *Bmal1* expression in these cells resulted in a significant increase in lipid droplet accumulaton.[80] According to Li et al.,[81]

Table 1 Central and peripheral lipid changes observed in patients diagnosed with BD

Lipid metabolism alterations in patients with BD	Mood state	Age range (years)	Sex	Method	Psychiatric medication
Patients with BD have lower levels of brain cerebral metabolites.[28,55,60-66†]	Euthymic	40-44	F/M	MRS	Free/treated
Patients with BD exhibit reduced NAA and Cho brain concentrations.[55]	Manic/mix episodes	16-35	F/M	MRS	Treated
Patients with BD have increased brain levels of Cer, FFA, and PC.[67]	N/R	33-60	F/M	LC-MS	Free/treated
Patients with BD display lower levels of DHA, AA, and stearic acid.[57]	N/R	25-55	F/M	GC	Free/treated
Patients with BD exhibit normal brain DHA levels.[58,59]	N/R / N/R	44-72/27-90	F/M	GC	Free/treated
Patients with BD display increased plasma ratio of omega-6/omega-3 FA than controls; lower ratios of omega-3 were associated with depressed mood.[68]	Manic/ depressed	24-56	F/M	GC-MS	Free
Depressed patients with BD exhibit higher serum ratios of AA:EPA, and AA:EPA + DHA when compared with euthymic patients and healthy controls.[29]	Euthymic or depressed	22-41	F/M	GC	Free/treated
Patients with BD display higher plasma levels of AA and EPA and diminished levels of DHA.[69]	Euthymic or depressed or manic	36-54	F/M	GC-MS	Free/treated
Patients with BD have decreased DHA levels in the erythrocyte membrane.[67†]	Euthymic or depressed or manic	14-42	F/M	GC	Free/treated
Patients with BD exhibit altered serum distribution of PL, GL, and SL; PI was the most significantly altered lipid class.[31]	Euthymic	18-65	F/M	LC-MS	Free/treated
Serum PI identified as a biomarker for BD liability.[30]	N/R	30-64	F/M	LC-MS	N/A
Patients with BD exhibit higher plasma levels of Cer.[70]	Euthymic or depressed or manic	20-67	F/M	LC-MS	Free/treated
Plasma biomarker set containing nine lipids for BD.[71]	N/R	22-58	F	LC-MS	N/R

AA = arachidonic acid; BD = bipolar disorder; Cer = ceramides; Cho = choline; DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid; FA = fatty acids; FFA = free fatty acids; F = female; GC = gas chromatography; GC-MS = GC-mass spectometry; GL = glycerolipids; LC-MS = liquid chromatography-mass spectrometry; M = male; MRS = magnetic resonance spectroscopy; N/A = not applicable. N/R = not reported; NAA = N-acetyl-aspartate; PC = phosphatidylcholine; PI = phosphatidylinositol; PL = phospholipids; SL = sphingolipids.
† Meta-analysis study.

brown adipocytes from *Bmal1*-deficient mice exhibit overall extensive accumulation of lipids and display an increased content of lipid droplets. Monjes et al.[36] also found a robust crosstalk between circadian clocks and lipid metabolism by showing that the disruption of intrinsic molecular clocks induced by downregulation of *Bmal1* in the human hepatocellular carcinoma-derived cell line (HepG2) is associated with a significant decrease in TG content, as well as time-dependent variations in the levels of PC, PE, and in PC/PE ratio. *Bmal1*-deficient cells also showed rhythmic changes in the expression of the lipid synthesizing enzymes ChoKα, Pcyt2, and Lipin1, which are involved in the biosynthesis of PC and PE. Additionally, when compared to controls, HepG2 cells with disrupted molecular clocks show a significant reduction in the size and area of lipid droplets as well as a decrease in their number compared to controls.[36] More recently, Fan et al.[82] observed that 1,3-dichloro-2-propanol causes lipid droplet accumulation in HepG2 cells by suppressing neutral lipases via inhibition of the *BMAL1* pathway.

Regarding the *Per2* genes, studies have shown that *Per2*-deficient mice have impaired lipid metabolism, with a significant decrease in TG and fatty acids.[83] Importantly, Neufeld et al.[84] demonstrated that the activity of rate-limiting mitochondrial enzymes involved in lipid processing is dependent on the clock proteins Per1/2. Furthermore, Jing et al.[85] found that *Per2*-deficient bovine mammary epithelial cells have impaired lipid metabolism, as demonstrated by the significant decrease in both the number and density of lipid droplets in these cells.

In *Clock* mutant mice, peripheral adipose clocks fail to promote normal lipid breakdown from lipid droplets and subsequent release of free fatty acids and glycerol into

the blood. This leads to excessive accumulation of TGs in adipose tissue, resulting in dysregulated feeding behavior.[86]

These findings were further supported by significant circadian-dependent alterations in lipid metabolism, particularly in lipid droplets, observed in healthy individuals. Chua et al.[40] revealed that plasma lipids display circadian rhythmicity over the 24-hour cycle. Moreover, they found remarkable interindividual variability in the circadian rhythms of different types of lipids, such as phospholipids and sphingolipids. In accordance, Held et al.[39] described that lipid metabolism in skeletal muscle of healthy people follows a day-night rhythmicity, as shown by the rhythmic oscillations over the 24-hour period found in most lipid classes and lipid droplets.

Collectively, these findings demonstrate that molecular circadian clocks are intimately involved in the regulation of lipid droplet homeostasis.

Lipid droplets: physiological and pathological roles

Lipid droplets are intracellular vesicles containing a hydrophobic core of neutral lipids, predominantly TG and cholesterol esters, surrounded by a phospholipid monolayer. Compared to other biomembranes, the lipid composition of their monolayer is enriched in PC and PE, while exhibiting relatively low levels of PS and SM.[41,87,88]

Initially, lipid droplets were described as universal storage sites for lipids, especially during periods of nutrient abundance. These stored lipids are mobilized to produce energy during starvation or are used for phospholipids synthesis when there is a high demand for cell membrane formation. Moreover, lipid droplets play a critical role in buffering cellular levels of potentially toxic lipids, thereby preventing lipotoxicity — the harmful effects of improperly stored lipids within cells.[89] While the primary function of lipid droplet biogenesis is to mitigate cellular lipotoxicity by sequestering toxic lipids, our understanding has evolved to recognize them as highly dynamic cellular organelles critical for normal cell physiology. Generated from the ER, lipid droplets are able to establish contact sites with other cell organelles, including mitochondria and lysosomes. These interorganelle communications are crucial for maintaining the normal cell life cycle. Recent studies have shown that although lipid droplets are present in all cells, their number and size are adapted according to cellular conditions to alleviate cellular stress and maintain energy homeostasis.[38,41,90] In addition to lipotoxicity, various cellular stress conditions promote the accumulation of lipid droplets. Inflammation, ER stress, and oxidative stress are well-established triggers that drive lipid droplet biogenesis and accumulation.[42]

Lipid droplet dysregulation in disease

Because of their role as central hubs of cellular metabolism, dysregulated accumulation of lipid droplets is closely associated with various diseases.[89,91]

Obesity is characterized by excessive accumulation of lipids in lipid droplets in adipose tissue and ectopically in the liver, heart, and skeletal muscle. This leads to secondary metabolic complications such as type 2 diabetes mellitus, cardiovascular disease, and nonalcoholic fatty liver disease (NAFLD). Cardiovascular diseases can arise from the excessive accumulation and enlargement of lipid droplets in cardiomyocytes and macrophages foam cells. Increased lipid droplet deposition in cardiomyocytes promotes cardiomyopathy and heart failure, whereas in macrophage foam cells it leads to atherosclerosis. When excessive accumulation occurs in hepatocytes, the result is NAFLD.[37,89,91,92] Notably, all of these diseases characterized by excessive lipid droplet content are closely associated with lipotoxicity and oxidative stress.[70]

Lipid droplets also play a crucial role in neurodegenerative diseases, particularly Alzheimer's disease (AD) and Parkinson's disease (PD).[91] Under physiological conditions, they accumulate primarily in microglial cells.[93] However, stressful conditions such as oxidative stress and inflammation lead to their ectopic deposition in other brain cells, such as neurons, astrocytes, and oligodendrocytes.[42] To protect neurons from oxidative stress, peroxidized lipids generated via reactive oxygen species (ROS) are stored within the lipid droplets of glial cells through the action of apolipoproteins E (ApoE) and D (ApoD).[94,95] The presence of the ApoE-ε4 allele, a known risk factor for AD, decreases the lipid transfer capacity and thus impairs the formation of glial lipid droplets in AD.[94-96] In PD, the pathological α-synuclein protein binds to the surface of lipid droplets, preventing their lipolysis and promoting their accumulation.[97,98]

In summary, while lipid droplets play a vital physiological role, their dysregulation can lead to cytotoxicity and contribute to disease progression.

The hypothesis of lipid droplets for bipolar disorder

Collectively, the findings outlined in this review underscore that lipid abnormalities and circadian clock dysfunction are intrinsic features of BD.[26,99] Notably, despite significant advances in lipid research in BD, to the best of our knowledge, no study to date has examined the role of lipid droplets in this neuropsychiatric disorder.

Based on the intricate relationship between molecular circadian clocks and the regulation of lipid metabolism, with a particular focus on lipid droplet accumulation, this critical review introduces the "the hypothesis of lipid droplets for BD" (Figure 2). This hypothesis proposes that lipid droplet homeostasis may be dysregulated in BD, primarily due to disruptions in molecular circadian clocks, which may play a significant role in the pathophysiology of this severe mental disorder.

In addition to the BD-associated circadian dysfunctions described above, lipid droplet dysregulation in BD may be further promoted by disruptions in several molecular events that have been identified as key modulators of lipid droplet homeostasis, namely:

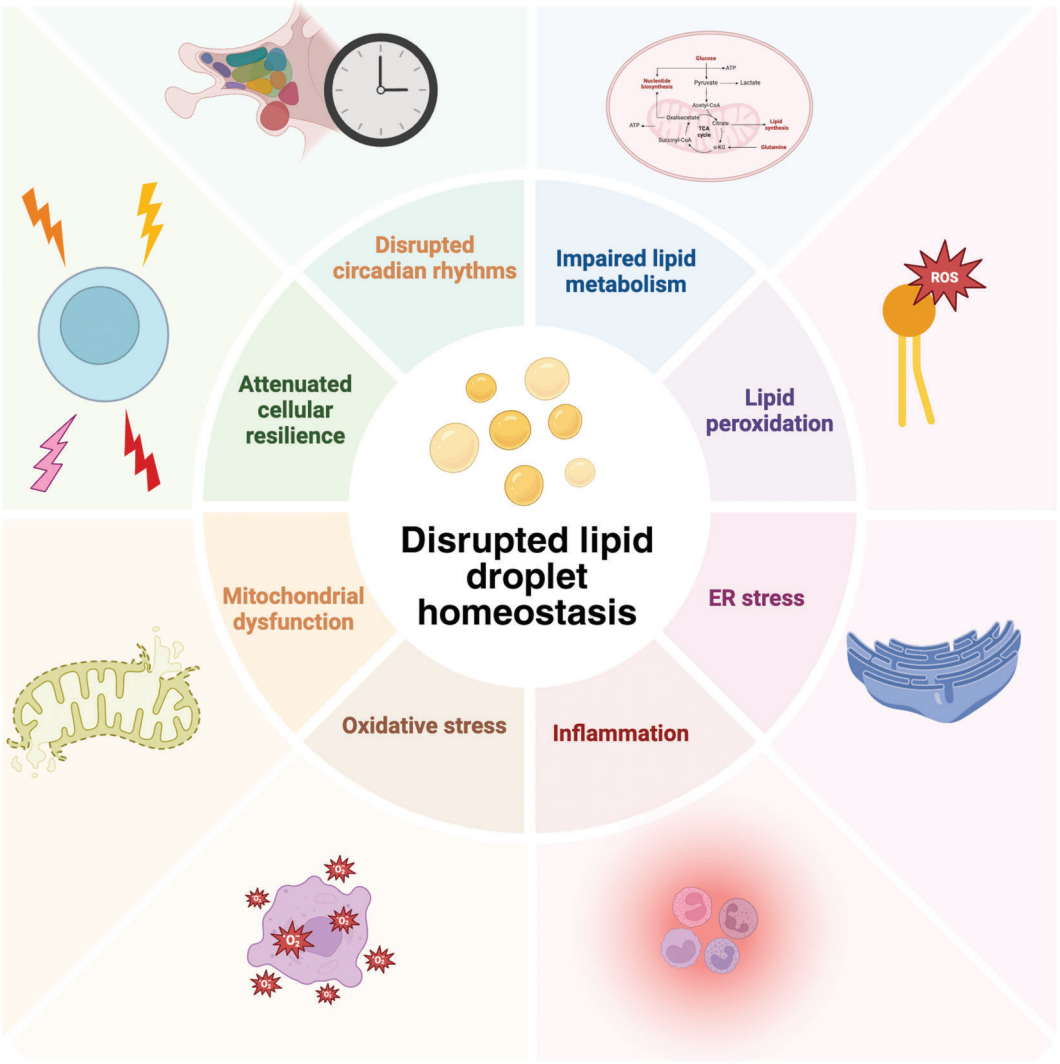

Figure 2 Lipid droplet hypothesis for bipolar disorder. ER = endoplasmic reticulum.

Alterations in lipid metabolism and increased lipid peroxidation

Patients with BD exhibit a notable increase in the levels of fatty acids and several classes of lipids, such as phospholipids and TG, which are components of lipid droplets.[29,30,56] Elevated fatty acids levels, along with increased lipid peroxidation markers in these patients, suggest a possible activation of lipid droplet biogenesis in BD as an attempt against lipotoxicity.[56,100-102] This is corroborated by the fact that BD is associated with medical comorbidities such obesity and cardiovascular diseases, which are linked to the accumulation of lipid droplets.[8,91]

Endoplasmic reticulum stress and inflammation

The involvement of cellular events such as ER stress and inflammation in the pathophysiological landscape of BD strongly supports an increased lipid droplet content in these patients.[42,103,104] In fact, recent evidence has shown that lipid droplets are essential organelles for metabolic and inflammatory responses.[105] Futhermore, the induction of ER stress is often associated with increased lipid droplet biogenesis and accumulation in various cell types.[106-108]

Oxidative stress and mitochondrial dysfunction

Alterations in oxidative phosphorylation and oxidative stress observed in patients with BD, as evidenced by decreased mitochondrial oxygen consumption rate (OCR) and increased ROS production, may be directly related to the formation of lipid droplets.[109,110] Indeed, oxidative stress resulting from increased ROS production has been shown to promote the accumulation of lipid droplets.[111] Furthermore, reduced OCR and elevated ROS levels are markers of mitochondrial dysfunction, which may drive

increased lipid droplet biogenesis as an adaptive cellular response to stress or by disrupting the communication between lipid droplets and mitochondria.[112,113]

Impaired cellular resilience

Impaired neural plasticity and diminished cellular resilience at multiple levels in BD further strengthen the theory of dysregulated lipid droplets in this disease.[35,114] Lipid droplets are essencial to the cellular stress response, being mobilized according to specific needs to protect against different types of stress. In patients with BD, cells are inherently more vulnerable due to compromised stress coping mechanisms. As a result, under BD-related stressful conditions such as oxidative and ER stress, there may be a stimulation of lipid droplet production to help maintain cellular homeostasis.[115]

Conclusions

The comprehensive assessment of the clinical symptoms observed in patients diagnosed with BD, including both neuropsychiatric and non-neuropsychiatric manifestations, has inspired scientific research aimed at uncovering the cellular dysfunctions underlying this pathology. Consequently, dysfunctional circadian rhythms and abnormal lipid metabolism have emerged as key biological mechanisms in BD.

Despite extensive efforts in lipidomic profiling of patients with BD, lipid droplets have never been studied in this population. This gap in knowledge led to the proposal of the "lipid droplet hypothesis for BD," which suggests that patients with BD may have alterations in the cellular content of lipid droplets due to dysfunctional circadian clocks. This theory is reinforced by the involvement of other cellular processes, including mitochondrial dysfunction, ER stress, and oxidative stress, in the pathophysiology of BD.

In conclusion, this critical review highlights the importance of investigating the role of lipid droplets in the pathophysiology of BD and provides new avenues for research. The clinical implications of lipid alterations in BD extend beyond diagnosis to treatment optimization, which is particularly relevant in the era of precision medicine tailored to mood disorders. Integrating lipidomic data, including insights into lipid droplets, into routine clinical practice could help prevent BD-associated medical comorbidities and uncover new therapeutic targets. This approach has the potential to significantly enhance patient care and outcomes for individuals with BD.

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The authors report no conflicts of interest.

Author contributions

ACP: Writing – original draft, Writing – review & editing.
LS-C: Writing – original draft.
MTC: Writing – review & editing.
CC: Writing – review & editing.
CMFP: Writing – review & editing.
All authors have read and approved of the final version to be published.

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