Review

Physiological and Pathological Insights into the Circadian Rhythm of Polyunsaturated Fatty Acids Metabolism

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Abstract: Polyunsaturated fatty acids (PUFAs) are essential lipid components that maintain human health and take part in various physiological and pathological processes. PUFAs are metabolized to bioactive mediators, such as prostaglandins (PGs), leukotrienes (LTs), epoxyeicosatrienoic acids (EETs), and hydroxyeicosatrienoic acids (HETEs), which play critical roles in cardiovascular function, metabolic homeostasis, neural activity, and inflammatory responses. Emerging evidence has shown that the circadian clock regulates the metabolism of PUFAs, exhibiting marked circadian rhythms varying across different disease states. This review explores the circadian dynamics of PUFAs metabolism and its implications in cardiovascular disease, metabolic disorders, neurodegenerative conditions, and immune diseases. Special attention is given to the circadian expression changes in PUFAs metabolic enzymes, like cyclooxygenases (COXs), lipoxygenases (LOXs), and cytochrome P450s (CYPs), and their potential mechanisms in disease development. In addition, the review discusses the application of circadian rhythms of PUFAs metabolism to optimize clinical strategies such as chronotherapy and personalized medicine. Understanding the circadian regulation in PUFAs metabolism could unveil new insights into disease mechanisms and inspire innovative approaches for the prevention and treatment of multiple diseases.

Keywords: polyunsaturated fatty acids (PUFAs); cyclooxygenases (COXs); lipoxygenases (LOXs); cytochrome P450s (CYPs); circadian rhythm

1. Introduction

PUFAs are a class of essential fatty acids characterized by two or more *cis* carbon-carbon double bonds arranged in a divinylmethane pattern. They are primarily divided into two major groups, ω-3 and ω-6, based on the location of the terminal double bond [1]. Since most ω-3 and ω-6 fatty acids cannot be synthesized endogenously, they must be obtained through dietary sources. Key ω-3 fatty acids include α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), commonly found in deep-sea fish oils, flaxseed oils, and certain vegetable oils. In contrast, ω-6 fatty acids, such as linoleic acid (LA), γ-linolenic acid (GLA), and arachidonic acid (AA), are primarily sourced from vegetable oils [2]. The metabolism of PUFAs is largely mediated by three enzymatic pathways: COXs, LOXs, and CYPs [3] (Figure 1). Although ω-3 and ω-6 fatty acids undergo similar metabolic pathways, their metabolites play pleiotropic roles in immune response, neuroprotection, vascular function and insulin signaling [4]. For instance, metabolites derived from ω-6 fatty acid, such as prostaglandins (PGs), thromboxanes (TXs), and leukotrienes (LTs), play significant roles in pro-inflammatory responses [5], while metabolites derived from ω-3 fatty acid tend to exhibit notable anti-inflammatory properties. Such as metabolites derived from EPA and DHA, E-series and D-series specialized pro-resolving mediators (SPMs) like resolvins, protectins, and maresins, are recognized as potent anti-inflammatory and pro-resolving agents [6]. These SPMs suppress the production of inflammatory mediators, facilitate tissue repair, and promote the resolution of inflammation [7]. The diverse functions of PUFAs metabolites are essential for maintaining normal physiological functions. However, dysregulation in PUFAs metabolism can trigger various pathological

conditions. For example, excessive production of specific ω-6 metabolites can lead to acute and chronic inflammation, whereas a deficiency in specific ω-3 metabolites may weaken the body's anti-inflammatory capacity, raising the risk of chronic diseases [8,9]. Recent studies have shown that PUFAs metabolism follows a circadian rhythm, suggesting that it may be regulated by the circadian clock [10].

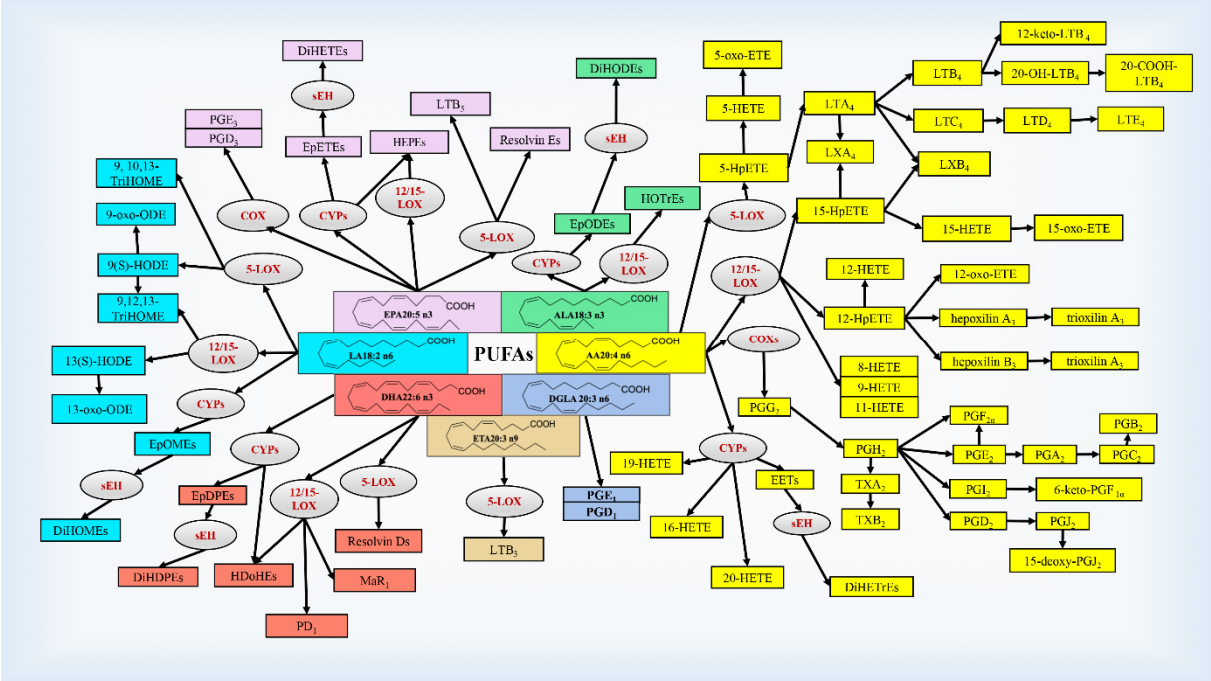

Figure 1. A brief scheme of metabolism of PUFAs. PUFAs are metabolized by LOXs, COXs, and CYPs to produce different metabolites. The metabolic flow of each PUFAs is shown using the same colors. The abbreviations are defined in the abbreviation table. The figure was cropped from *Pharmacology & Therapeutics* **2024**, *256*, e108612 by courtesy of the journal.

Circadian rhythms are intrinsic physiological cycles in organisms, typically following an approximately 24-h period. These rhythms are prevalent across species, from single-celled organisms to complex multicellular systems, and regulate a wide array of physiological processes, including sleep, metabolism, body temperature, and hormone secretion [11]. Importantly, circadian rhythms are not merely passive responses to environmental cues, such as light-dark cycles, but are actively regulated by an internal circadian clock [12,13]. The molecular mechanism of the circadian clock is primarily composed of a set of highly conserved genes and proteins that form a complex transcription-translation feedback loop. Within this loop, core transcription factors like CLOCK and BMAL1 form dimers, binding to the promoter regions of circadian genes to activate the transcription of negative feedback regulators, including PER and CRY. These feedback regulators subsequently accumulate in the nucleus and inhibit the activity of the CLOCK-BMAL1 complex, establishing a roughly 24-h oscillation in gene expression (Figure 2) [12].

The circadian clock directly influences fluctuations in metabolic processes by modulating the expression of metabolism-related genes, thereby optimizing energy efficiency and maintaining metabolic homeostasis across varying environmental conditions [14]. Specifically, the circadian clock can regulate the activity of enzymes involved in PUFAs metabolism through core clock genes such as CLOCK and BMAL1 by multi-tiered regulation, imparting rhythmicity to PUFAs metabolic pathways throughout the circadian cycle [15,16]. However, disruptions in modern lifestyles, such as shift work, insomnia, jet lag, and irregular routines, can disturb these metabolic rhythms, leading to metabolic disorders and related health issues [17]. These chronic diseases can further disrupt circadian regulation, leading to weakened metabolic cycles [18]. Therefore, it is crucial to elucidate the effects of the circadian clock on PUFAs metabolism to understand the mechanisms of these diseases.

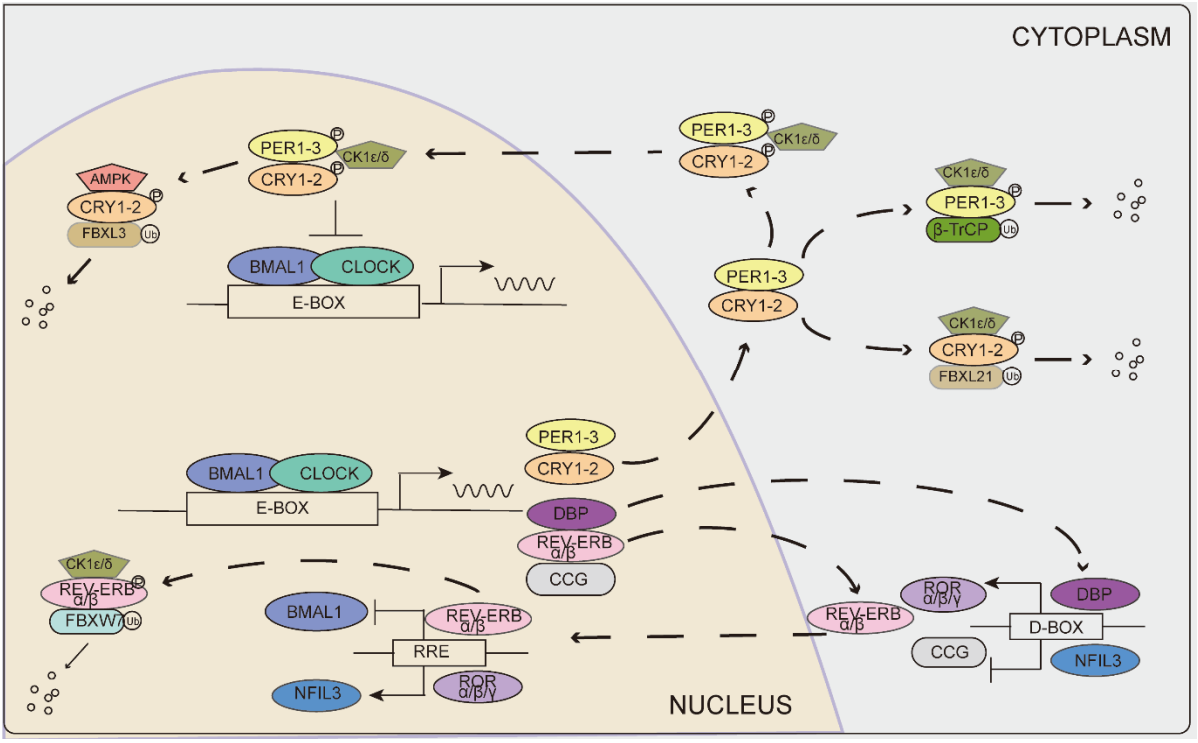

Figure 2. Molecular transcriptional and translational feedback loops of the mammalian core circadian clock. The mammalian circadian clock orchestrates daily rhythms through a sophisticated core mechanism, driven by a network of activators and repressors organized into interconnected feedback loops and multiple regulatory layers. These layers encompass transcriptional control, post-translational modifications, and dynamic cytoplasm–nucleus translocation processes. At the heart of the primary loop, the transcriptional activators BMAL1 and CLOCK bind to E-box motifs in DNA, initiating the expression of repressor proteins, including the PERIOD (PER1, PER2, PER3) and CRYPTOCHROME (CRY1, CRY2) families. As PER and CRY proteins accumulate, they form complexes and undergo phosphorylation by casein kinase 1δ/ε (CK1δ/ε), facilitating their translocation into the nucleus. Once inside, they inhibit BMAL1 and CLOCK activity, effectively suppressing their own transcription and completing the feedback loop. Post-translational mechanisms further refine this rhythmicity: AMPK and FBXL3 mediate CRY degradation in the nucleus, while CK1δ/ε and FBXL21 regulate CRY turnover in the cytoplasm. Similarly, PER proteins are targeted for cytoplasmic degradation upon phosphorylation by CK1δ/ε and β-TRCP. A secondary feedback loop involves BMAL1 and CLOCK activating the expression of REV-ERBα/β and RORα/β/γ, which act as transcriptional repressors and activators, respectively. These proteins rhythmically modulate BMAL1 expression, adding another layer of regulation. CK1δ/ε and FBXW7 control the degradation of REV-ERBα/β, further enhancing the precision of the circadian clock. Abbreviations: P, phosphorylation; Ub, ubiquitin.

2. Risk Assessment of PUFAs Dysregulation in Chronic Diseases

Dysregulation of PUFAs is strongly associated with an increased risk of chronic diseases such as cardiovascular disease, metabolic syndrome, type 2 diabetes, neurodegeneration, and immune diseases. Low omega-3 PUFAs levels (EPA/DHA) are associated with an increased cardiovascular risk, whereas a 5% increase in dietary omega-3 PUFAs intake has been shown to reduce cardiovascular mortality risk by 15–20% [19]. ω-3 supplementation (2–4 g/day) effectively lowers blood triglycerides by 25–30%, thereby decreasing the risk of atherosclerosis [20]. Furthermore, a higher omega-6/omega-3 ratio (>10:1) has been linked to a 1.8- to 2.5-fold increased risk of coronary artery disease, primarily due to elevated TXA_2 and LTB_4 levels derived from PUFAs metabolism, which contribute to thrombosis and vascular dysfunction [21]. PUFAs imbalances also play a significant role in metabolic disorders, contributing to insulin resistance, obesity, and hepatic lipid accumulation. Individuals with a low omega-3 intake and high omega-6 intake have a 3.2-fold increased risk of developing metabolic syndrome [22]. PUFAs-driven inflammation further exacerbates this risk, increasing the likelihood of Type 2 diabetes, particularly in individuals with low DHA levels [23,24]. Notably, omega-3 supplementation (EPA/DHA 3–4 g/day) can improve insulin sensitivity by 12–15% in prediabetic individuals [19]. Low DHA levels are also associated with an increased risk of neurodegenerative diseases such as Alzheimer's and Parkinson's [25]. PUFAs-driven inflammation exacerbates oxidative stress and accelerates neurodegeneration,

with individuals who have low DHA levels exhibiting a 47% higher risk of developing Alzheimer's disease [26]. ω-3 supplementation (DHA 1–2 g/day) has been shown to improve cognitive function scores by 10–15% in early-stage neurodegenerative disease patients [19]. Chronic inflammation in autoimmune diseases is exacerbated by pro-inflammatory eicosanoids such as PGE_2, TXA_2, and LTB_4 [27], whereas SPMs derived from PUFAs, including resolvins and protectins, play a crucial role in inflammation resolution [28]. Elevated PGE_2 levels correlate with a 3.5-fold increased risk of chronic inflammatory diseases such as RA and IBD [29]. Additionally, individuals with low DHA levels exhibited a higher risk of systemic inflammation linked to increased NF-κB activation [30]. ω-3 supplementation (2–3 g/day) has been found to reduce inflammatory cytokine levels by 25–30% in rheumatoid arthritis patients [19].

3. Diurnal Changes in the Enzymes and Metabolites Associated with PUFAs Metabolism

The metabolism of PUFAs involves a series of enzymatic reactions, primarily mediated by COXs, LOXs, and CYPs. These enzymes show circadian rhythms in expression and activity, influencing the production of downstream metabolites in alignment with the body's circadian cycle.

3.1. Circadian Rhythmicity of COXs

Circadian rhythms are regulated by endogenous clocks that are synchronized with the circadian cycle of the environment. It has been found that the expression and activity of COXs show circadian fluctuations. Core circadian clock genes regulate the circadian expression of COX-2, which has been observed across various tissues, including the liver, adipose tissue, and vascular endothelium [31–33]. Studies have shown that COXs expression is higher at night than in daytime, which is consistent with the increased production of PGs and TXs during nighttime hours [34]. PGI_2 and TXA_2 have converse effects on the cardiovascular system, with PGI_2 playing a role in vasodilatation, peaking during the active phase, while TXA_2 dominates during rest, increasing the risk of thrombosis by promoting platelet aggregation and vasoconstriction [35]. Such time-dependent variations in metabolite levels are thought to contribute to the observed nocturnal increase in cardiovascular events, like myocardial infarctions, occurring in individuals with disrupted sleep cycles or irregular lifestyles [36]. In the nervous system, the rhythmic expression of COX-2 may also influence neuroinflammatory processes by the excessive production of PGE_2 and TXA_2 at night, impacting brain health and responses to environmental stressors [37].

3.2. Circadian Rhythmicity of LOXs

Similar to COXs, LOX enzyme expression and activity exhibit pronounced circadian rhythmicity under regulating circadian clock genes [38]. There are several isoforms of LOX enzymes, with 5-LOX, 12-LOX, and 15-LOX being the most studied ones. While 5-LOX catalyzes the formation of pro-inflammatory LTs, it also produces anti-inflammatory lipoxins, orchestrating with 12-LOX and 15-LOX [3]. The activity of 5-LOX ends to peak during early morning hours, coinciding with increased inflammatory responses, as LTs levels rise in response to circadian signals [39]. Lipoxins, which are anti-inflammatory, also show rhythmic production, generally balancing the pro-inflammatory effects of LTs and other mediators [40]. This balance helps maintain physiological homeostasis in tissues and plays a role in resolving inflammation after acute responses [41]. When circadian rhythms are disrupted, such as through extended wakefulness or irregular sleeping patterns, the rhythmic expression of LOX enzymes can become desynchronized, leading to an imbalance in LTs and lipoxins production [42]. This desynchronization may contribute to chronic inflammatory diseases, suggesting a crucial role of LOX enzyme rhythmicity in inflammatory homeostasis and potential therapeutic targets for conditions like asthma and atherosclerosis [43,44].

3.3. Circadian Rhythmicity of CYPs

The CYP enzyme family is central to lipid metabolism, drug metabolism, and the synthesis of signaling molecules, with circadian rhythms observed in their expression and activity [45]. CYP enzyme expression fluctuates over the circadian cycle in tissues such as the liver, adipose tissue, and vasculature, playing a key role in lipid metabolic processes and metabolic health [46]. Certain isoforms, such as CYP2J and CYP4A, exhibit peak activity at night or early morning, coinciding with shifts in the body's metabolic demands [47,48]. Among various CYP isoforms, CYP2C and CYP2J are actively involved in PUFAs metabolism, particularly in generating EETs, which are released by astrocytes, neurons, and vascular endothelial cells [3]. The circadian regulation of CYP enzymes significantly affects EETs production, which influences vascular function, as well as inflammatory

responses [49,50]. Disruptions in the circadian rhythm of CYP activity, due to factors like irregular sleep or dietary patterns, can decrease EETs production, potentially impairing vascular health and increasing the risk of conditions such as hypertension and atherosclerosis [51,52].

4. Multi-Level Regulation of PUFAs Metabolism by Circadian Clock

The circadian clock is a complex system driven by endogenous biorhythm genes that regulate the physiological rhythms of the body, including sleep, metabolism, and immune responses. Circadian clocks regulate physiological processes through various regulatory mechanisms, including transcriptional, epigenetic, and post-transcriptional regulation. The rhythm of these physiological processes can also be affected by variations in clock genes and environmental factors. The enzymes mediating the metabolism of PUFAs, such as LOXs, COXs, and CYPs, are regulated by the circadian clock at multiple levels [45,53] (Figure 3).

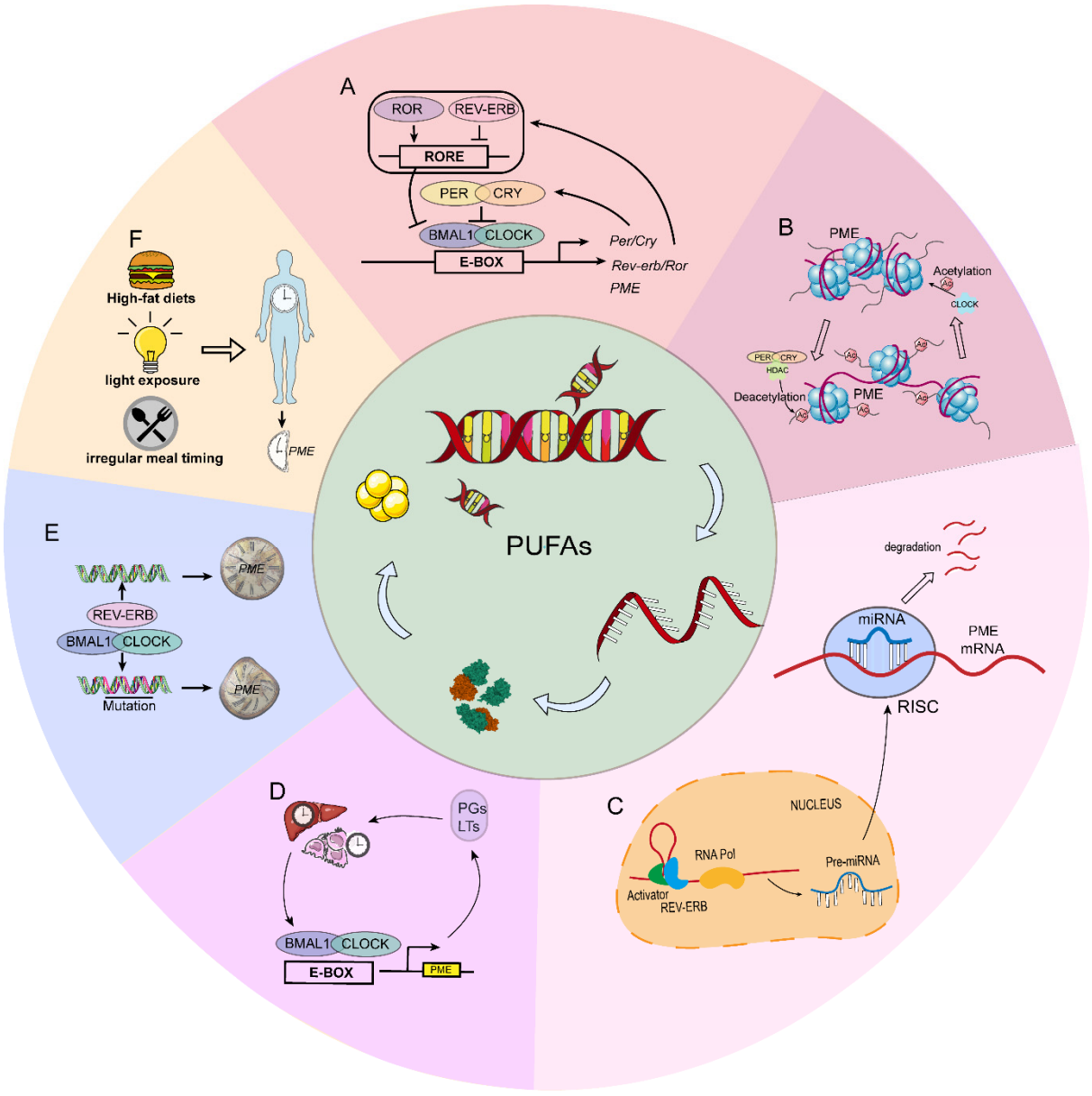

Figure 3. Multi-level Regulation of Polyunsaturated Fatty Acid (PUFAs) Metabolism by the Circadian Clock. (**A**) The circadian clock regulates the transcription of polyunsaturated fatty acid-metabolizing enzyme (PME) genes through several key transcription factors, including CLOCK/BMAL1, REV-ERB, and the PER/CRY complex. These transcription factors rhythmically bind to the promoter regions of PME genes, modulating their expression across the circadian cycle. (**B**) Circadian clock-related factors regulate PME gene activity through histone modifications. CLOCK, which has histone acetyltransferase (HAT) activity, rhythmically activates PME transcription by acetylating histones near these genes. In contrast, histone deacetylases (HDACs) collaborate with the PER/CRY complex to deacetylate histones, reducing PME gene activity cyclically. (**C**) REV-ERBα, a core

circadian transcription factor, rhythmically regulates the expression of pre-microRNAs (premiRNAs). These premiRNAs are exported from the nucleus, pairing with PME mRNAs in the cytoplasm to form RNA-induced silencing complexes (RISC), which mediate target mRNA degradation. (**D**) PUFAs metabolites, including LTs and PGs, also exert feedback on circadian clocks in peripheral tissues, influencing the expression of core circadian genes and modulating PUFAs metabolite production rhythmically. (**E**) Variations in clock genes, such as CLOCK, BMAL1 and REV-ERBα, significantly influence PME transcription and disrupt the diurnal regulation of PUFAs metabolism. (**F**) External factors, including High-fat diets, irregular meal timing and light exposure exert a profound influence on circadian clock, consequently modulating PUFAs metabolism. Abbreviation: PME: PUFAs metabolizing enzymes; RISC: RNA-induced silencing complex.

4.1. Transcriptional Regulation of PUFAs Metabolizing Enzymes by the Circadian Clock

The circadian clock controls gene transcription of PUFAs-metabolizing enzymes via key transcription factors, including CLOCK, BMAL1, REV-ERB, and the PER/CRY complex. The BMAL1/CLOCK heterodimer binds to E-box elements in the promoters of PUFAs-metabolizing enzymes, driving their rhythmic transcription. This process directly upregulates COX-2 and 5-LOX gene expression, promoting the synthesis of PGs and LTs [4,54]. REV-ERBα functions as a transcriptional repressor by binding to RORE elements, inhibiting the expression of BMAL1 and its downstream targets. This mechanism prevents excessive production of pro-inflammatory mediators such as PGs and LTs during the inactive phase [55]. Similarly, PER and CRY form a repressor complex that inhibits BMAL1/CLOCK transcriptional activity, reducing inflammatory lipid production during the resting phase [56]. Meanwhile, RORα competes with REV-ERBα for binding to RORE elements, thereby promoting BMAL1 expression and enhancing PUFAs metabolism [4]. Notably, Das reported that RORα-deficient mice exhibit reduced levels of anti-inflammatory lipid mediators, leading to prolonged inflammation [54].

4.2. Epigenetic Regulation of PUFAs Metabolism

Through histone acetylation and deacetylation, transcription factors related to circadian clock regulation could precisely regulate the transcriptional activity of PUFAs metabolizing enzyme genes. CLOCK, which serves as a core circadian regulator and a histone acetyltransferase (HAT), activates gene transcription by acetylating histones near LOX and COX genes [57]. This modification is rhythmic, as CLOCK/BMAL1 complex activity varies over the circadian cycle, synchronizing enzyme expression with circadian demands [58]. Conversely, histone deacetylation suppresses the transcription of PUFAs-metabolizing enzymes. Histone deacetylases (HDACs) work in tandem with circadian rhythm-associated proteins, such as PER and CRY, to downregulate enzyme activity, ensuring reduced production of PUFAs metabolites during certain periods of the day [59].

4.3. Post-Transcriptional Regulation

Beyond transcriptional and epigenetic controls, the circadian clock also regulates the stability of mRNA transcripts encoding PUFAs-metabolizing enzymes [60]. REV-ERBα, a core circadian transcription factor, rhythmically influences the production of precursor microRNAs (pre-miRNAs). These pre-miRNAs are exported from the nucleus, where they pair with mRNAs of PUFAs-metabolizing enzymes, forming RNA-induced silencing complexes (RISC) that mediate target mRNA degradation [61]. Circadian genes and miRNAs act in concert to maintain specific mRNA stability of PUFAs-metabolizing enzymes at different circadian phases, thus influencing enzyme translation in alignment with physiological demands [62]. This regulation allows PUFAs-metabolizing enzyme protein levels to adapt to the body's metabolic needs throughout the circadian cycle, ensuring efficient metabolic processes [63].

4.4. Genetic Polymorphisms of PUFAs Metabolism

Genetic polymorphisms in CLOCK, BMAL1, and REV-ERBα significantly influence PUFAs metabolism, thereby modulating lipid mediator production and inflammatory responses. Variations in the CLOCK gene disrupt circadian lipid homeostasis, leading to dysregulated PUFAs-derived eicosanoids. For instance, the CLOCK mutation rs1801260 results in delayed gene expression, reducing PUFAs oxidation cycles and consequently shifting lipid mediator production [64,65]. Additionally, the rs3749474 variant affects the stability of the CLOCK-BMAL1 heterodimer, impairing COX-2 transcription and disrupting the diurnal regulation of PGE_2 [66]. BMAL1 plays a crucial role in controlling the diurnal expression of LOX and COX enzymes, thereby orchestrating the balance between pro- and anti-inflammatory PUFAs metabolites [67]. Specific BMAL1 mutations, such as rs3816358 and rs11022775, lead to decreased 15-LOX transcription, impairing the resolution of inflammation via

SPMs like LXA_4 and RvD1, thereby prolonging chronic inflammation [68,69]. Similarly, variations in REV-ERBα(rs2071427), disrupt the regulation of COX-2 and CYP4A genes, leading to elevated synthesis of PGE_2 and 20-HETE [70]. These mutations also interfere with the CLOCK-BMAL1 feedback loops, fostering a state of persistent inflammation [71].

4.5. Environmental Factors of PUFAs Metabolism

External factors, including diet composition, meal timing and light exposure, profoundly influence circadian rhythms, consequently modulating PUFAs metabolism. High-fat diets have been shown to shift the expression of LOX enzymes in a circadian-dependent manner, leading to an upregulation of pro-inflammatory PUFAs metabolites, particularly LTB_4 and 5-HETE [72]. This metabolic shift exacerbates systemic inflammation and contributes to chronic disease progression. Similarly, prolonged light exposure during nighttime suppresses BMAL1 and CLOCK activity, thereby impairing the conversion of DHA into neuroprotective mediators such as NPD1 and RvD1 [73]. This disruption fosters neuroinflammation and heightens the risk of neurodegenerative conditions [74]. Furthermore, irregular meal timing disrupts CLOCK-BMAL1 expression, altering EPA metabolism and increasing PGE2 synthesis, amplifying inflammatory responses and elevating disease susceptibility [75].

4.6. Metabolic Feedback Regulation: PUFAs Metabolites as Regulators of the Circadian Clock

Metabolites derived from PUFAs metabolism, such as PGs, LTs, and EETs, follow circadian regulation and exert feedback effects on the circadian clock itself. For instance, PGs, major metabolites of COX, have been shown to influence the expression of core circadian genes by acting on circadian centers in peripheral tissues, including in liver and macrophages [76,77]. This feedback mechanism allows PUFAs metabolites to impact circadian rhythms, further modulating metabolic and inflammatory responses. In addition, LTs affect the circadian clock by altering the expression of inflammatory mediators and modulating immune responses. For example, LTs can influence the rhythmic fluctuation of PUFAs metabolism by regulating immune cell activity and circadian gene expression at specific times [78,79]. This metabolic feedback mechanism suggests that PUFAs metabolites serve as reverse regulators of the circadian clock, highlighting their integral role in the interplay between circadian rhythms and PUFAs metabolism [80].

5. Roles and Mechanisms of Metabolic Rhythmicity of PUFAs in Multiple Diseases

PUFA metabolism exhibit circadian rhythmicity regulated by the circadian clock, which plays a crucial role in maintaining physiological homeostasis. Disruptions in the temporal regulation of PUFA metabolism have been increasingly implicated in the development and progression of various diseases, including cardiovascular disease, metabolic diseases, neurological disorders, and immune disorders (Table 1).

5.1. Cardiovascular Disease

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality globally. Emerging evidence underscores the significant roles of PUFAs and their metabolites in cardiovascular health, including PGs, LTs and EETs, which regulate cardiovascular processes such as vasodilation, inflammatory responses, and platelet aggregation [4]. PUFAs and their metabolites, particularly those derived through COX, LOX and CYPs, exhibit rhythmic fluctuations that profoundly influence cardiovascular health [81,82].

Circadian rhythms in the expression and activity of COX significantly contribute to daily blood pressure fluctuations and thrombosis [83]. Among the COX-derived metabolites, primarily PGs (PGI_2, PGE_2) and TXs (TXA_2, TXB_2), play a pivotal role in regulating vascular function and thrombosis. PGI_2 is a potent vasodilator and inhibitor of platelet aggregation, produced primarily by COX-2 in endothelial cells, counteracting TXA_2 to maintain vascular homeostasis and prevent thrombosis [84]. PGI_2 exerts its vasodilatory effects by binding to the IP receptor on vascular smooth muscle cells (VSMCs), activating adenylate cyclase (AC), which in turn increases the levels of cyclic AMP (cAMP) within the cell. The elevated cAMP levels reduce the concentration of intracellular calcium (Ca^{2+}) in VSMCs, resulting in vascular relaxation and a subsequent reduction in blood pressure [85]. The reduction of PGI_2 is often observed in myocardial infarction and stroke, contributing to endothelial dysfunction and atherosclerosis [86]. TXA_2 is a strong vasoconstrictor and activator of platelet aggregation, synthesized primarily by COX-1 in platelets. Excess TXA_2 leads to atherosclerosis and increased thrombotic risk [87]. TXA_2 binds to TP receptors on VSMCs, activating phospholipase C (PLC). This leads to an

increase in inositol triphosphate (IP_3) levels, which triggers calcium influx into the cells. This mechanism plays a key role in regulating vascular tone and blood pressure, especially under conditions that promote platelet aggregation and clot formation [88]. In acute coronary syndrome (ACS), TXA_2 spikes in the morning increase the risk of myocardial infarction [84]. PGE_2 has a dual role in vascular effects, with low concentrations inducing vasodilation and high concentrations leading to vasoconstriction. At low concentrations, PGE_2 binds to the EP2 and EP4 receptors, leading to vasodilation through the cAMP/PKA pathway. This results in the relaxation of vascular smooth muscle and decreased blood pressure [89]. At higher concentrations, PGE_2 binds to the EP1 and EP3 receptors, which activate PLC, leading to calcium release, vasoconstriction, and increased blood pressure [90,91]. Increased PGE_2 promotes vasodilation in atherosclerosis, but it can also destabilize atherosclerotic plaques, increasing the risk of acute cardiovascular events such as heart attacks or strokes [92]. PGE_2 levels are also elevated in heart failure, where they contribute to vascular dysfunction and fluid retention. This is primarily through EP3 receptor activation, which leads to vasoconstriction and worsens symptoms of heart failure by increasing vascular resistance and impairing cardiac output [93]. Endothelial dysfunction is a hallmark of hypertension. PGE_2 reduces eNOS expression, impairing NO-mediated vasodilation through EP3 receptor activation, while TXA_2 induces endothelin-1 (ET-1) secretion, promoting vasoconstriction. Furthermore, PGE_2 is also a pro-inflammatory prostaglandin derived from AA, exerting inflammatory effects by binding to EP2 and EP4 receptors on macrophages, activating NF-κB signaling and inducing the release of IL-1β, TNF-α, and IL-6. The balance between these metabolites, often influenced by circadian regulation, governs vascular homeostasis and thrombosis risk. These metabolites exhibit daily oscillations aligned with blood pressure rhythms. PGE_2 and PGI_2 levels peak during the active phase, enhancing vasodilation and antithrombotic effects, while TXA_2 dominates during rest, promoting platelet aggregation and vasoconstriction to minimize hemorrhagic risks [94]. REV-ERBα, a circadian repressor, inhibits the pro-thrombotic mediator TXA2 at night. Disrupted circadian cycles enhance TXA2 levels, increasing early morning thrombosis risk and contributing to myocardial infarction [95,96]. The occurrence of cardiovascular events exhibits a circadian rhythm, with incidents being more common during nighttime or early morning when blood pressure rises. This pattern may be linked to the rhythmic expression of COX enzymes and their metabolites [97].

Similarly, EETs, produced via CYP2Cs, CYP2J2, and CYP3A4 enzymes, follow a circadian pattern that aligns with cardioprotective functions, including vasodilation, anti-inflammatory effects, and myocardial protection against ischemic damage [98]. However, in CVD, particularly conditions like hypertension and atherosclerosis, EET production is often reduced, leading to impaired vasodilation and contributing to increased vascular resistance [99]. Studies suggest that EETs derived from the endothelium help maintain vascular integrity, and their reduction in atherosclerotic plaques contributes to increased thrombosis risk [100]. CYP2J2 and EETs play a protective role in preventing the pathological growth of cardiac tissue, and EET deficiency has been linked to worsened cardiac function in conditions such as heart failure [101]. Studies have demonstrated that EET levels fluctuate in a circadian pattern, with variations influencing vascular reactivity in the context of hypertension and CVD [102,103]. EETs activate potassium channels in cardiomyocytes, mitigating ischemia-reperfusion injury during peak activity periods [104]. Studies found that circadian rhythmicity of CYP2C and CYP2J are often disrupted in atherosclerosis. BMAL1 methylation reduces CYP2J2 transcription, lowering EET levels and elevating nocturnal blood pressure, thereby increasing the risk of cardiovascular events [98,105].

LOX-derived metabolites, including LTs like LTB_4 and LTC_4, also display circadian rhythms and contribute to inflammation and atherosclerosis in CVD. LTB_4 facilitates neutrophil recruitment and vascular inflammation, exacerbating atherosclerotic lesion development, while LTC_4 promotes vascular permeability and smooth muscle contraction, which can destabilize plaques [106,107]. LTB_4 levels rise during injury-prone times to recruit immune cells, while rhythmic suppression limits chronic inflammation and vascular damage [108]. Lipoxins, which play a critical role in terminating inflammation via anti-inflammation and resolution of inflammation, also exhibit circadian rhythmicity, particularly with increased production at night [40]. Lipoxin A4 (LXA_4) has been found to inhibit inflammatory responses in vascular endothelial cells by reducing pro-inflammatory cytokines and chemokines. It blocks the activation of NF-kB and reduces the expression of vascular adhesion molecules, preventing leukocyte recruitment to the vessel walls, and thus protects against atherosclerotic plaque formation [109]. Studies have shown that lipoxins can resolve inflammation in atherosclerosis by counter-regulating the pro-inflammatory actions of other eicosanoids such as PGs and LTs [110]. Pirault, J. and M. Bäck also reported that beyond their anti-inflammatory effects, lipoxins can reduce plaque formation by modulating the functions of vascular smooth muscle and endothelial cells, highlighting their therapeutic potential in cardiovascular protection [111]. The circadian production of lipoxins is associated with the timing of atherosclerosis progression and cardiovascular events, especially at night [40].

5.2. Metabolic Diseases

PUFAs and their metabolites are essential in regulating glucose and lipid metabolism, influencing inflammation, and modulating insulin signaling pathways in metabolic diseases, including obesity, type 2 diabetes (T2D), and non-alcoholic fatty liver disease (NAFLD) [112,113]. Importantly, these processes are influenced by circadian rhythms, which regulate the expression and activity of the enzymes mediating PUFAs metabolism, and their disruption in metabolic diseases amplifies pathological outcomes [56].

The rhythms of these PUFAs metabolism enzymes synchronize with metabolic demands, ensuring the proper timing of anti-inflammatory, lipid-modulating, and insulin-sensitizing effects [113]. Elevated COX-2 expression increases PGE_2 and PGD_2 production in obese individuals [114]. PGD_2 promotes adipocyte differentiation and fat storage, while PGE_2 promotes insulin resistance and chronic inflammation in adipose tissue, partly through its effects on inflammatory cytokines and adipose tissue. Specifically, PGE_2 enhances the release of TNF-α, IL-1β, and IL-6, all of which contribute to insulin resistance and metabolic inflammation [115]. PGE_2 can also suppress glucose-stimulated insulin secretion by disrupting pancreatic islet function. It modulates insulin release through EP3 receptor activation, inhibiting cAMP production and glucose metabolism in pancreatic β-cells [116]. In NAFLD, studies have demonstrated that PGE_2, secreted by macrophages, binds to the EP4 receptor in hepatic stellate cells (HSCs), promoting liver fibrosis, contributing to fibrogenesis and cirrhosis [117]. PGE_2 also activates the MAPK pathway in hepatocytes, promoting lipogenesis and exacerbating liver fat accumulation [118]. PGE_2 levels fluctuate throughout the day, with higher levels typically observed during nighttime and early morning, correlating with increased insulin resistance and inflammation. Studies have suggested that these fluctuations in PGE_2 levels contribute to diabetic complications, including vascular dysfunction and increased cardiovascular risk [119,120]. Methylation of BMAL1 in obesity increases COX-2 activity, leading to PGE2-mediated insulin resistance [62]. TXA_2 is another COX-derived metabolite that contributes to vascular dysfunction and platelet aggregation in metabolic diseases. Elevated TXA_2 is associated with thrombus formation and vascular constriction, leading to cardiovascular events such as stroke and heart attacks in diabetes and increase fibrosis and liver dysfunction in NAFLD [121,122]. It increases particularly in the early hours of the day, heightening the risk of cardiovascular events in diabetic individuals [123]. LOX metabolites derived from AA and LA, including pro-inflammatory eicosanoids LTB_4 and LTC_4, are often accumulated in both NAFLD and diabetes, contributing to meta-inflammation, a form of metabolic inflammation that plays a central role in the development of insulin resistance and liver dysfunction [124,125]. The combined effects of COX and LOX-mediated metabolites in NAFLD and diabetes show synergistic interactions that enhance inflammation and insulin resistance [126]. Additionally, 12-LOX and 15-LOX mediate the production of 12-HETE and 15-HETE, respectively, which drive macrophage activation and hepatic stellate cell (HSC) activation, the key steps in liver fibrosis progression [127]. LTB_4 and LTC_4 also follow a circadian fluctuation pattern, with peak production during night-time hours [128]. Circadian misalignment, such as in shift workers or those with sleep disorders, can exacerbate LTs-driven inflammation and increase cardiovascular event risk in these diseases [129].

Diabetes and NAFLD are often accompanied by lower EET levels, particularly EETs produced by CYP2J2. A reduction in EET production in diabetes may thus exacerbate endothelial dysfunction and vascular inflammation, contributing to diabetic complications such as nephropathy and retinopathy [130]. Elevated lipid accumulation and hepatic fibrosis in NAFLD are partly due to the dysregulation of EETs [131]. EETs have been shown to fluctuate across the day, with their levels peaking during the daytime, higher EET levels during daytime hours help maintain vascular health and improve glucose metabolism in healthy individuals [48]. Circadian misalignment, due to factors like irregular feeding schedules, sleep disturbances, or high-fat diets, disrupts the rhythmic production of PUFAs' metabolites, leading to chronic inflammation and insulin resistance in metabolic syndromes [36,132,133].

In addition, dietary supplementation of PUFAs, particularly omega-3 fatty acids like DHA and EPA, has shown protective effects against circadian disruption, supporting metabolic and inflammatory balance [134]. PUFAs regulate lipid metabolism by modulating the expression of PPARα and sterol regulatory element-binding proteins (SREBPs) at the gene level, which are crucial in controlling hepatic lipid synthesis and fatty acid oxidation [135].

5.3. Neurological Disorders

PUFAs are abundant in the central nervous system (CNS), where they are essential for maintaining neuronal membrane structure and supporting neural function [136]. PUFAs and their derivatives follow circadian rhythms, which are involved in critical neurological processes, including neuroinflammation, synaptic dysfunction,

neuronal apoptosis, and blood-brain barrier (BBB) disruption. They play significant roles in the pathology of neurological disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS).

Metabolites of PUFAs, particularly those from the COX and LOX pathways, promote neuroinflammation and contribute to the pathology of neurological disorders [137,138]. These metabolites play a pivotal role in neuroinflammation by activating microglia and astrocytes. Specifically, PGE_2 binds to EP2 and EP4 receptors on microglia, triggering the activation of NF-κB and the subsequent release of pro-inflammatory cytokines, including IL-1β, TNF-α, and IL-6 [139]. Concurrently, TXA_2 engages TP receptors on vascular endothelial cells, promoting vascular inflammation and BBB disruption, facilitating peripheral immune cell infiltration into the brain [140,141]. In addition to its role in neuroinflammation, PGE_2 compromises BBB integrity by upregulating matrix MMP-9 expression, leading to the degradation of endothelial tight junction proteins [142]. Studies reported that PGE_2 impairs synaptic transmission by modulating glutamatergic signaling, with EP2 and EP3 receptor activation increasing intracellular calcium levels and disrupting synaptic plasticity [143]. This disruption is associated with cognitive decline observed in AD and frontotemporal dementia (FTD) [144]. In microglial cells, COX-2 expression and the ability to release PGE_2 and TXA_2 fluctuate, with higher expression during the morning hours, potentially contributing to stroke and other cardiovascular complications commonly seen in neurological disorders [145]. The circadian pattern of PGE_2 and TXA_2 highlights its involvement in neurovascular events that are exacerbated during the early morning [123].

LOX-mediated metabolites, including LTB_4 and LTC_4, play roles similar to those of PGE_2 and TXA_2 in the pathogenesis of neurological disorders by activating BLT1 receptors, modulating neuroinflammation, and contributing to neurodegeneration [146]. Studies have also demonstrated that the COX and LOX pathways exhibit a synergistic role in neurodegenerative disorders. COX-mediated PGE_2 upregulates 5-LOX expression, thereby increasing LTB_4 production. In turn, LTB_4 enhances COX-2 activity, creating a self-perpetuating cycle of neuroinflammation [147,148]. This feedback loop has been consistently observed in Alzheimer's disease (AD), where amyloid-β (Aβ)-induced neuroinflammation is sustained by COX/LOX interactions [149]. Similarly, LTB_4 and LTC_4 show circadian fluctuations in both brain and immune cells, with peak production typically occurring during the nighttime [150]. The nighttime peak in these metabolites have been linked to impaired clearance of amyloid plaques, chronic inflammation and neuron damage in conditions like AD and PD [151]. These rhythmic changes in eicosanoid levels are being explored as potential targets for chronotherapy to reduce neuroinflammation and neurodegeneration [152].

CYP epoxygenases convert PUFAs into EETs and HETEs, which also play significant roles in neurological disorders. CYP-derived 20-HETE stimulates astrocytic activation, increasing the release of pro-inflammatory cytokines and promoting neuroinflammation [153]. Additionally, it enhances vascular tone and promotes BBB leakage, particularly in conditions such as MS and stroke [154]. Conversely, CYP2J2-derived EETs exhibit neuroprotective properties by modulating synaptic integrity by activating the PI3K/Akt signaling pathway in neurons and mitigating mitochondrial damage via NRF2 signaling activation [155,156]. Furthermore, chronic neuroinflammation disrupts EET regulation, leading to increased BBB permeability and enhanced infiltration of neurotoxic substances [157]. Disrupted LTB_4 and EET cycles compromise neurovascular integrity and promote oxidative damage, underlying the progression of stroke and vascular dementia [135,158].

In addition, DHA and its metabolites like neuroprotectin D1 (NPD1), promoted neuronal survival and mitigated oxidative stress [159]. BMAL1 and SIRT1 transcriptionally regulate DHA biosynthesis [160]. Disruptions in DHA rhythms impaired these protective mechanisms, contributing to cognitive decline and neurodegenerative diseases, such as AD [161]. Dietary supplementation with ω-3 PUFAs, particularly DHA, offered promise in reducing neuroinflammation and improving cognitive and emotional health [162,163].

5.4. Immune Disorders

PUFAs and their metabolites play a crucial role in immune regulation. Their production follows circadian rhythms, aligning immune responses with environmental cycles. Disruptions in these metabolic rhythms are linked to immune disorders such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD [164,165].

COX- and LOX-derived PUFAs metabolites influence the innate immune response by modulating macrophage, neutrophil, and dendritic cell activity [166,167], and regulate adaptive immunity via T-cell polarization and antibody production [168]. PGE_2 suppresses macrophage activation while enhancing Th2 cell differentiation via the EP2/EP4 receptors, promoting autoimmune pathogenesis [169]. Likewise, LTB_4 binds to BLT1 receptors on neutrophils, triggering ROS production and the release of TNF-α, IL-1β, and IL-6 [170]. LTB_4 enhances neutrophil infiltration in synovial joints, leading to cytokine production and thus aggravating joint swelling in RA [171]. Additionally, LOX/COX metabolites promote tissue damage by inducing fibrosis and matrix

remodeling. In diseases like RA and IBD, PGE_2 and LTB_4 activate fibroblast-like synoviocytes and myofibroblasts, causing excessive tissue fibrosis [172]. Pro-resolving mediators like lipoxins (LXA_4/LXB_4) and resolvins modulate immune responses by terminating inflammatory signaling [173]. LXA_4 binds to the ALX/FPR2 receptor on macrophages, inducing the clearance of apoptotic cells. DHA-derived protectin D1 (PD1) suppresses NF-κB signaling, reducing pro-inflammatory cytokine release [174].

CYP2J2 and CYP4A dysregulation contribute to immune-related pathologies by altering PUFAs metabolism and eicosanoid signaling [3]. Targeting CYP pathways with inhibitors like soluble epoxide hydrolase (sEH) inhibitors may provide therapeutic benefits in chronic immune disorders [175]. CYP-mediated PUFAs metabolites, like EETs and HETEs, influence immune system dynamics by modulating cytokine release, immune cell recruitment, and immunometabolism [176]. 20-HETE predominantly promotes pro-inflammatory immune responses in autoimmune diseases like RA, leading to synovial inflammation and joint destruction [177], while EETs counteract HETE-induced inflammation by binding to PPARs on macrophages [178]. Furthermore, studies have shown CYP-mediated PUFAs metabolites regulate immunometabolism by influencing macrophage polarization, with EETs shifting macrophages toward an M2 anti-inflammatory phenotype, while 20-HETE promotes an M1 pro-inflammatory phenotype [179].

The immune system operates under circadian control, governed by clock genes such as CLOCK and BMAL1 [180]. These genes regulate the temporal synthesis of PUFAs-derived metabolites, aligning inflammatory and anti-inflammatory responses with daily cycles. RA is a chronic autoimmune disorder characterized by symptoms such as joint stiffness, increased joint pain, and inflammation, which peak in the early morning due to circadian-driven increases in pro-inflammatory eicosanoids, including PGE_2, TXA_2, and LTB_4 [181,182]. Studies suggest that circadian fluctuations in PUFAs metabolism coincide with RA symptom severity, with BMAL1/REV-ERBα transcriptionally regulating the expression of COX-2 and 5-LOX [183]. The circadian rhythm of COX-2 peaking in the early morning promotes PGE_2 and TXA_2 production and increasing morning stiffness and joint swelling in RA patients [184]. 5-LOX activity peaks at night, leading to increased LTB_4 levels before symptom onset, exacerbating inflammation [184]. Furthermore, a nocturnal deficiency in anti-inflammatory PUFAs metabolites likely contributes to morning RA symptoms [185]. In healthy individuals, lipoxins (LXA_4, LXB_4) and resolvins (RvD1, RvE1) peak in the late evening to counteract inflammation [186]. However, circadian disruption in RA is believed to suppress specialized pro-resolving mediator (SPM) production, allowing inflammation to persist overnight [7]. While studies indicate that REV-ERBα deficiency in RA patients reduces 15-LOX expression, leading to chronic inflammation [183], direct clinical studies confirming this pathway in RA are still required. Circadian clock misalignment in RA skews the balance between pro- and anti-inflammatory PUFAs metabolites, driving morning symptom flares [187]. Studies suggest that circadian-controlled immune cells regulate PUFAs metabolism and contribute to rhythmic inflammatory cycles in RA [188]. Macrophage polarization (M1 and M2) follows a 24-h cycle, influencing pro- and anti-inflammatory lipid mediator production [189]. Monocyte infiltration peaks at night [190], but instead of resolving inflammation, RA synovial macrophages remain in a pro-inflammatory M1 state due to chrono-disruption, thereby sustaining joint inflammation [191]. However, while circadian control of macrophage metabolism is well established, its specific role in RA synovial inflammation still requires further targeted investigation. Glucocorticoid oscillations normally suppress 5-LOX at night [151,192], but this regulation appears to be impaired in RA [193], increasing overnight leukotriene synthesis. While circadian regulation of glucocorticoids affects immune function, and disruption of this rhythm contributes to sustained inflammation, direct evidence specifically linking glucocorticoid oscillations to 5-LOX suppression in RA remains limited and warrants further exploration.

6. Clinical Applications to Public Health

6.1. Chrononutrition: Dietary and Nutritional Strategies Based on Rhythmic Modulation

Chrononutrition is an emerging field that examines the interactions between meal timing and the circadian clock to achieve optimal health outcomes. By aligning nutrient intake with the body's natural biological rhythms, chrononutrition aims to enhance nutrient benefits, including PUFAs, whose metabolism follows a distinct circadian pattern [45,194]. Studies indicate that the timing of PUFAs intake significantly affects their metabolic pathways and the bioactivity of their metabolites (Table 2).

Furthermore, personalized health management encourages lifestyle recommendations based on an individual's circadian rhythms and metabolic profiles to maintain the metabolic hemostasis of PUFAs. For the general population and those at high risk of disease, personalized lifestyle modifications can effectively prevent and manage related conditions. First, it is important to maintain a regular schedule for preserving the metabolic rhythm of PUFAs. Irregular routines, such as night shifts or frequent time zone changes, may disrupt the circadian

clock, impacting the expression of the enzymes that mediate the metabolism of PUFAs and the onsite levels of their metabolites [195]. Thus, it is recommended to adhere to regular sleep and meal schedules to help sustain normal metabolic rhythms. Second, a balanced dietary structure is key to conserve PUFAs' metabolic equilibrium. Reducing ω-6 fatty acid intake while increasing ω-3 fatty acid consumption may help keeping the production balance between pro- and anti-inflammatory metabolites [196]. For individuals at higher risk of chronic diseases, customized dietary and pharmacological plans can be developed to prevent or slow disease progression, with regular monitoring of diurnal variations in PUFAs metabolites [197].

6.2. Therapeutic Strategies: Optimizing Therapeutic Effects through PUFAs Metabolic Rhythmicity

Understanding the circadian rhythmicity of PUFAs metabolism is essential for optimizing therapeutic interventions. The progression of many diseases, such as cardiovascular dysfunction, inflammatory conditions, and neurodegenerative disorders, are associated with the irregular production of PUFAs metabolites [173]. Leveraging the natural rhythmicity of PUFAs metabolism can enhance drug efficacy and reduce side effects. For example, patients with cardiovascular conditions often experience more cardiac events at night, likely due to elevated nighttime production of PUFAs metabolites such as thromboxane and prostaglandins [198]. To mitigate this risk, antiplatelet agents like aspirin can be administered at night to inhibit COX enzyme activity and reduce thromboxane production, thereby lowering the incidence of nighttime cardiac events [199]. This rhythm-based drug administration strategy has been shown to significantly improve prognosis in cardiovascular patients. In treating neurological disorders like Alzheimer's disease, the rhythmic nature of PUFAs metabolism also offers new therapeutic insights. Studies suggest that high levels of PUFAs metabolites like PGE_2 in the brain at night may exacerbate neuroinflammatory responses [146]. Consequently, nighttime use of anti-inflammatory medications or supplements that modulate lipid metabolism could help slow neurodegenerative disease progression [147].

ω-3 fatty acids (EPA/DHA) are known to reduce inflammation, improve lipid profiles, and stabilize atherosclerotic plaques. A landmark trial showed that morning 4g EPA intake helps reduce cardiovascular events [200]. Additionally, restricting ω-3 intake in the evening may prevent nighttime inflammatory surges associated with chronic diseases, including cardiovascular disease [194]. A randomized controlled trial published in *Diabetes Care* (2018) demonstrated that daily supplementation with 800–1500 mg of ω-3 fatty acids in the morning is beneficial for individuals with diabetes, as it enhances insulin sensitivity [201]. Moreover, minimizing ω-6 intake after 6:00 PM has been found to prevent glucose fluctuations [202,203]. Nighttime DHA supplementation (300–500 mg) has been shown to support neuronal repair and improve cognitive function [204,205], while morning ω-3 intake (EPA/DHA 1000 mg) contributes to memory enhancement [206]. Collectively, these findings highlight the importance of precise timing in PUFAs consumption to optimize metabolic and cognitive health.

6.3. Potential Challenges of PUFAs-Based Chronotherapy

The regulation of PUFAs metabolism by circadian rhythms represents a promising avenue in disease prevention and treatment. However, several challenges impede its clinical application. PUFAs metabolism relies on multiple enzymatic pathways (COXs, LOXs, CYPs), which are governed by circadian genes such as BMAL1, CLOCK, and REV-ERBα. BMAL1 and CLOCK orchestrate PUFAs metabolism by regulating lipid-processing enzymes, but their rhythmic activity is highly responsive to external cues such as feeding time and light exposure [45]. Modern lifestyle factors, including shift work, irregular eating patterns, and artificial light exposure, disrupt circadian lipid metabolism, thereby diminishing the efficacy of PUFAs-based interventions [207]. For instance, nighttime light exposure suppresses melatonin secretion, which in turn reduces BMAL1-driven DHA metabolism, further complicating metabolic regulation [208].

Personalized medicine requires accounting for individual differences in various factors, including age, gender, race, and medical history. As individuals age, the circadian regulation of PUFAs metabolism becomes increasingly desynchronized [209]. The suprachiasmatic nucleus (SCN) weakens with age, reducing sensitivity to light cues, which leads to phase delays and fragmented sleep-wake cycles. This disruption is largely driven by alterations in the circadian clock, including decreased BMAL1 and PER2 expression, resulting in a dampened circadian amplitude [210]. For instance, epigenetic age acceleration influences clock gene expression, modifying circadian-driven metabolic and immune processes [211]. Older adults may experience a reduced DHA-to-NPD1 conversion rate, which compromises the synthesis of key anti-inflammatory lipid mediators such as Resolvin D1 and LXA_4, ultimately diminishing neuroprotection in conditions like Alzheimer's disease [212]. Age-related circadian desynchronization further complicates PUFAs metabolism, making it difficult to determine optimal treatment windows for chronotherapy. DHA incorporation into phospholipids peaks during sleep cycles,

supporting membrane repair and neuroprotection. However, older adults exhibit lower DHA conversion efficiency, necessitating direct supplementation at night to optimize absorption and therapeutic efficacy [213].

Females and males exhibit distinct patterns of PUFAs metabolism, largely influenced by hormonal cycles, particularly estrogen and testosterone. Estrogen enhances omega-3 fatty acid conversion, whereas testosterone appears to exert an opposing effect [214]. Notably, women with RA may experience circadian shifts in PGE_2 production due to estrogen fluctuations, which can influence symptom severity [215]. Additionally, estrogen plays a role in enhancing BMAL1 and CLOCK expression, thereby strengthening circadian oscillations in women [216]. In contrast, testosterone suppresses circadian clock function, leading to weaker rhythm stability in males [217]. These gender-based variations in PUFAs metabolism and circadian regulation suggest that chronotherapy interventions may have differential efficacy depending on the sex of the patient. Furthermore, hormonal fluctuations in women, such as those occurring during the menstrual cycle or menopause, may alter PUFAs-based effectiveness, which should be taken into consideration.

Genetic polymorphisms in key regulatory genes such as FADS1/2, CLOCK, and BMAL1 vary across populations, influencing PUFAs metabolism efficiency [218,219]. Studies highlighted that ethnicity plays a significant role in circadian susceptibility to metabolic disorders due to complex gene-environment interactions. For instance, African and South Asian populations exhibit lower FADS1/2 activity, resulting in reduced omega-3 conversion efficiency [219]. Consequently, individuals with FADS polymorphisms may require higher direct DHA intake rather than relying on ALA conversion to meet their physiological needs. These racial differences in PUFAs metabolism efficiency underscore the necessity for personalized dosing strategies to optimize therapeutic outcomes.

Metabolic conditions such as diabetes and obesity impair PUFAs metabolism, resulting in inefficient EPA/DHA incorporation [220]. Notably, nighttime DHA supplementation has been shown to enhance glucose control in diabetic patients [221,222]. Additionally, chronic diseases, including diabetes and cardiovascular disease, further disrupt BMAL1-REV-ERBα regulation, leading to weakened metabolic cycles [223]. Studies reported that obstructive sleep apnea (OSA) suppresses PER2 oscillations, contributing to daytime fatigue and insulin resistance [224]. These medical conditions complicate the synchronization of PUFAs metabolism with the circadian clock, thereby limiting the effectiveness of chronotherapy. For instance, individuals with cardiovascular diseases may require tailored omega-3 supplementation strategies to compensate for impaired EET production and maintain metabolic balance [225].

Furthermore, most studies on circadian PUFAs metabolism are conducted in rodent models, which may not fully reflect human physiology. Rodents have nocturnal activity cycles, whereas humans are diurnal, leading to differences in lipid metabolism timing, making it difficult to translate animal research findings to humans. Additionally, standardizing PUFAs-based interventions requires individualized chronobiological assessments, which are not widely available in clinical practice, making it difficult to establish clinical time-based interventions.

Table 1. Metabolic changes and rhythmicity of PUFAs in diseases.

Disease	Changes of Key PUFAs and Metabolites	Circadian Rhythmicity	Pathophysiological Impact	Reference
Cardiovascular Disease	↓PGI_2 ↑TXA_2 ↑PGE_2	PGE_2 and PGI_2 peak during active phase, TXA_2 peaks at rest elevate the risk of thrombotic events and myocardial infarction during nighttime or early morning	↓PGI_2 → reduced vasodilation, endothelial dysfunction, increased clot risk ↑TXA_2 → increased vasoconstriction, platelet aggregation, thrombus formation ↑PGE_2 → vasodilation (EP2, EP4 activation), vasoconstriction (EP1, EP3 activation), plaques instability, increased inflammation	[84,86,90]
	↓EETs	peak during daytime	↓EETs → impaired vasodilation, increased vascular resistance, reduced myocardial protection, reduced anti-inflammation	[99]
	↑LTB_4, LTC_4 ↑LXA_4	LTB_4 and LTC_4 peak during the night LXA_4 peaks during the night	↑LTB_4, LTC_4 →increased neutrophil recruitment and vascular inflammation, atherosclerosis ↑LXA_4 → anti-inflammation, resolution of inflammation	[106,107,109]

Table 1. *Cont.*

Disease	Changes of Key PUFAs and Metabolites	Circadian Rhythmicity	Pathophysiological Impact	Reference
Metabolic Diseases	↑PGE_2, PGD_2 ↑TXA_2	PGE_2 and PGD_2 peak during nighttime and early morning TXA_2 peaks in the morning	↑PGE_2, TXA_2 → exacerbated insulin resistance, hepatic inflammation and fibrosis ↑PGD_2 → fat accumulation	[114,115,117]
	↑LTB_4, LTC_4, 12-HETE,15-HETE	peak during nighttime	↑LTB_4, LTC_4, 12-HETE → exacerbated insulin resistance, hepatic inflammation and fibrosis	[124,125]
	↓EETs	peak during the daytime	↓ EETs → increased insulin resistance, hepatic inflammation, impaired glucose metabolism, vascular dysfunction	[130,131]
Neurological Disorders	↑PGE_2 ↑TXA_2	peak during the morning hours	↑PGE_2 → increased neuronal damage, cognitive decline, demyelination ↑TXA_2 → neurovascular dysfunction, thrombus formation	[139,140]
	↑LTB_4, LTC_4 ↑LXA_4	LTB_4 and LTC_4 peak during the night LXA_4 peaks during the night	↑LTB_4, LTC_4 → microglial activation, increased neuroinflammation, neurodegeneration ↑LXA_4 → resolution of inflammation	[146,148]
	↓EETs ↑20-HETE	EETs peak during daytime 20-HETE peaks during nighttime	↓EETs → increased neuroinflammation, BBB integrity disruption, dysregulated immune responses (activation of T-cells and microglia), amyloid plaque deposition ↑20-HETE → increased Neuroinflammation, BBB leakage	[153,155]
	↓DHA	disrupted in Neurological diseases	↓DHA → reduced neuronal repair, increased neuroinflammation	[159]
Immune Disorders	↑PGE_2 ↑TXA_2	peak during nighttime and early morning	↑PGE_2 → increased immune cell recruitment and pro-inflammatory cytokine release ↑TXA_2 → promoted gut permeability	[166,169]
	↑LTB_4, LTC_4 ↑LXA_4	peak during the nighttime or early morning	↑LTB_4, LTC_4 → increased neutrophil recruitment and inflammatory cell infiltration	[170]
	↓EETs ↑20-HETE	EETs peak during daytime 20-HETE peaks during nighttime	↓EETs → increased inflammation, dysregulated immune responses (T cells and macrophages), vascular damage ↑20-HETE → increased neuroinflammation	[176,177]

Table 2. Time-based recommendation of PUFAs Intake.

Time of Day	Recommended PUFAs Intake	Rationale	Reference
Morning (6:00–9:00 AM)	High-dose ω-3 fatty acids (EPA/DHA) from fish, flaxseed, or algae supplements	Enhances the production of anti-inflammatory resolvins and lipoxins; supports cognitive function and cardiovascular health.	[200,201,226]
Midday (12:00–2:00 PM)	Moderate ω-3 intake (fatty fish, walnuts, chia seeds)	Supports lipid metabolism stabilization and glucose homeostasis	[220,227,228]
Afternoon (3:00–5:00 PM)	Low ω-6 intake (avoid processed foods high in vegetable oils)	Reduces pro-inflammatory prostaglandin synthesis	[229–231]
Evening (6:00–8:00 PM)	Minimal ω-6 fatty acid intake; balance with small amounts of ω-3	Avoids excessive pro-inflammatory leukotrienes that peak at night.	[64,203,231]
Night (9:00–11:00 PM)	DHA supplementation (300–500 mg) from marine sources	Supports neuronal protection and circadian regulation; beneficial for neurodegeneration prevention	[204,232]

7. Conclusions

PUFAs metabolism follows a circadian rhythm, playing a vital role in chronic diseases like cardiovascular, metabolic, neurological, and immune disorders. Key enzymes such as COXs, LOXs, and CYPs regulate PUFAs metabolism, influencing cognition, inflammatory responses, and vascular function. Disruptions in these pathways contribute to disease progression, highlighting the importance of circadian regulation in health and disease. Understanding the circadian control of PUFAs metabolism opens new possibilities for time-based treatments.

Aligning nutritional and pharmacological interventions with these rhythms could improve treatment effectiveness and reduce side effects. Future research should further explore how PUFAs metabolism interacts with circadian biology to develop personalized, time-optimized therapies.

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Abbreviation

PUFAs: Polyunsaturated Fatty Acids; PGs: Prostaglandins; LTs: Leukotrienes EETs: Epoxyeicosatrienoic Acids; HETEs: Hydroxyeicosatrienoic Acids; COXs: Cyclooxygenases; LOXs: Lipoxygenases; CYPs: Cytochrome P450s; SPMs: Specialized Pro: resolving Mediators; ALA: α-Linolenic Acid; EPA: Eicosapentaenoic Acid; DHA: Docosahexaenoic Acid; LA: Linoleic Acid; GLA: γ-Linolenic Acid; AA: Arachidonic Acid; TXs: Thromboxanes; RvD1: Resolvin D1; LXA4: Lipoxin A4; NPD1: Neuroprotectin D1; EP1/EP2/EP3/EP4: Prostaglandin E2 Receptor subtypes; TP: Thromboxane Receptor; BLT1: Leukotriene B4 Receptor; ALX/FPR2: Lipoxin A4 Receptor/Formyl Peptide Receptor 2; CVD: Cardiovascular Disease; ACS: Acute Coronary Syndrome; T2D: Type 2 Diabetes NAFLD: Non-Alcoholic Fatty Liver Disease; AD: Alzheimer's Disease; PD: Parkinson's Disease; MS: Multiple Sclerosis; FTD: Frontotemporal Dementia; RA: Rheumatoid Arthritis; IBD: Inflammatory Bowel Disease; sEH: Soluble Epoxide Hydrolase; PPARs: Peroxisome Proliferator-Activated Receptors; FADS: Fatty Acid Desaturase; OSA: Obstructive Sleep Apnea; PER: Period Circadian Regulator; CRY: Cryptochrome; BMAL1: Brain and Muscle ARNT-Like 1; CLOCK: Circadian Locomotor Output Cycles Kaput; REV-ERBα: Nuclear Receptor Subfamily 1 Group D Member 1; RORα: Retinoic Acid Receptor-Related Orphan Receptor Alpha; RORE: Retinoic Acid Receptor-Related Orphan Receptor Response Element; HDACs: Histone Deacetylases; HAT: Histone Acetyltransferase; miRNAs: MicroRNAs; RISC: RNA-Induced Silencing Complex.

References

1. Simopoulos, A.P. The importance of the ratio of omega-6/omega-3 essential fatty acids. *Biomed. Pharmacother.* **2002**, *56*, 365–379. https://doi.org/10.1016/s0753-3322(02)00253-6.
2. Calder, P.C. Polyunsaturated fatty acids and inflammation. *Prostaglandins Leukot. Essent. Fat. Acids* **2006**, *75*, 197–202.
3. Meng, Y.W.; Liu, J.Y. Pathological and pharmacological functions of the metabolites of polyunsaturated sfatty acids mediated by cyclooxygenases, lipoxygenases, and cytochrome P450s in cancers. *Pharmacol. Ther.* **2024**, *256*, 108612. https://doi.org/10.1016/j.pharmthera.2024.108612.
4. Wang, B.; Wu, L.; Chen, J.; Dong, L.; Chen, C.; Wen, Z.; Hu, J.; Fleming, I.; Wang, D.W. Metabolism pathways of arachidonic acids: mechanisms and potential therapeutic targets. *Signal Transduct. Target. Ther.* **2021**, *6*, 94. https://doi.org/10.1038/s41392-020-00443-w.
5. Iñiguez, M.A.; Cacheiro-Llaguno, C.; Cuesta, N.; Díaz-Muñoz, M.D.; Fresno, M. Prostanoid function and cardiovascular disease. *Arch. Physiol. Biochem.* **2008**, *114*, 201–209. https://doi.org/10.1080/13813450802180882.
6. McLennan, P.L.; Owen, A.J.; Slee, E.L.; Theiss, M.L. Myocardial function, ischaemia and n-3 polyunsaturated fatty acids: A membrane basis. *J. Cardiovasc. Med.* **2007**, *8*, S15–S18. https://doi.org/10.2459/01.JCM.0000289272.87803.ce.
7. Serhan, C.N.; Brain, S.D.; Buckley, C.D.; Gilroy, D.W.; Haslett, C.; O'Neill, L.A.; Perretti, M.; Rossi, A.G.; Wallace, J.L. Resolution of inflammation: State of the art, definitions and terms. *Faseb J.* **2007**, *21*, 325–332. https://doi.org/10.1096/fj.06-7227rev.
8. Patterson, E.; Wall, R.; Fitzgerald, G.F.; Ross, R.P.; Stanton, C. Health implications of high dietary omega-6 polyunsaturated Fatty acids. *J. Nutr. Metab.* **2012**, *2012*, 539426. https://doi.org/10.1155/2012/539426.
9. Lian, M.; Luo, W.; Sui, Y.; Li, Z.; Hua, J. Dietary n-3 PUFA Protects Mice from Con A Induced Liver Injury by Modulating Regulatory T Cells and PPAR-γ Expression. *PLoS ONE* **2015**, *10*, e0132741. https://doi.org/10.1371/journal.pone.0132741.
10. Panda, S. Circadian physiology of metabolism. *Science* **2016**, *354*, 1008–1015. https://doi.org/10.1126/science.aah4967.
11. Panda, S.; Hogenesch, J.B.; Kay, S.A. Circadian rhythms from flies to human. *Nature* **2002**, *417*, 329–335. https://doi.org/10.1038/417329a.

12. Patke, A.; Young, M.W.; Axelrod, S. Molecular mechanisms and physiological importance of circadian rhythms. *Nat. Rev. Mol. Cell Biol.* **2019**, *21*, 67–84. https://doi.org/10.1038/s41580-019-0179-2.
13. Mills, J.N.; Minors, D.S.; Waterhouse, J.M. The circadian rhythms of human subjects without timepieces or indication of the alternation of day and night. *J. Physiol.* **1974**, *240*, 567–594. https://doi.org/10.1113/jphysiol.1974.sp010623.
14. Guan, D.; Lazar, M.A. Interconnections between circadian clocks and metabolism. *J. Clin. Investig.* **2021**, *131*. https://doi.org/10.1172/jci148278.
15. Gnocchi, D.; Pedrelli, M.; Hurt-Camejo, E.; Parini, P. Lipids around the Clock: Focus on Circadian Rhythms and Lipid Metabolism. *Biology* **2015**, *4*, 104–132. https://doi.org/10.3390/biology4010104.
16. Vatier, C.; Christin-Maitre, S. Epigenetic/circadian clocks and PCOS. *Hum. Reprod.* **2024**, *39*, 1167–1175. https://doi.org/10.1093/humrep/deae066.
17. Arble, D.M.; Ramsey, K.M.; Bass, J.; Turek, F.W. Circadian disruption and metabolic disease: Findings from animal models. *Best. Pract. Res. Clin. Endocrinol. Metab.* **2010**, *24*, 785–800. https://doi.org/10.1016/j.beem.2010.08.003.
18. Gabryelska, A.; Turkiewicz, S.; Karuga, F.F.; Sochal, M.; Strzelecki, D.; Białasiewicz, P. Disruption of Circadian Rhythm Genes in Obstructive Sleep Apnea Patients-Possible Mechanisms Involved and Clinical Implication. *Int. J. Mol. Sci.* **2022**, *23*, 709. https://doi.org/10.3390/ijms23020709.
19. Martemucci, G.; Khalil, M.; Di Luca, A.; Abdallah, H.; D'Alessandro, A.G. Comprehensive Strategies for Metabolic Syndrome: How Nutrition, Dietary Polyphenols, Physical Activity, and Lifestyle Modifications Address Diabesity, Cardiovascular Diseases, and Neurodegenerative Conditions. *Metabolites* **2024**, *14*, 327. https://doi.org/10.3390/metabo14060327.
20. Simopoulos, A.P. The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. *Exp. Biol. Med.* **2008**, *233*, 674–688. https://doi.org/10.3181/0711-mr-311.
21. Gupta, R.; Lakshmy, R.; Abraham, R.A.; Reddy, K.S.; Jeemon, P.; Prabhakaran, D. Serum Omega-6/Omega-3 Ratio and Risk Markers for Cardiovascular Disease in an Industrial Population of Delhi. *Food Nutr. Sci.* **2013**, *4*, 94–97. https://doi.org/10.4236/fns.2013.49A1015.
22. Robinson, L.E.; Buchholz, A.C.; Mazurak, V.C. Inflammation, obesity, and fatty acid metabolism: Influence of n-3 polyunsaturated fatty acids on factors contributing to metabolic syndrome. *Appl. Physiol. Nutr. Metab.* **2007**, *32*, 1008–1024. https://doi.org/10.1139/h07-087.
23. Negi, P.C.; Sharma, C.K.; Nihjawan, R.; Sharma, R.; Asotra, S. Role of omega 3 and omega 6 poly unsaturated fatty acids (PUFA) and vitamin D deficiency as risk determinants of metabolic syndrome in obesity: Worksite based case-control observational study. *Diabetes Metab. Syndr.* **2022**, *16*, 102467. https://doi.org/10.1016/j.dsx.2022.102467.
24. Khalili, L.; Valdes-Ramos, R.; Harbige, L.S. Effect of n-3 (Omega-3) Polyunsaturated Fatty Acid Supplementation on Metabolic and Inflammatory Biomarkers and Body Weight in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of RCTs. *Metabolites* **2021**, *11*, 742. https://doi.org/10.3390/metabo11110742.
25. Farooqui, A.A.; Farooqui, T.; Panza, F.; Frisardi, V. Metabolic syndrome as a risk factor for neurological disorders. *Cell Mol. Life Sci.* **2012**, *69*, 741–762. https://doi.org/10.1007/s00018-011-0840-1.
26. Rojas-Gutierrez, E.; Muñoz-Arenas, G.; Treviño, S.; Espinosa, B.; Chavez, R.; Rojas, K.; Flores, G.; Díaz, A.; Guevara, J. Alzheimer's disease and metabolic syndrome: A link from oxidative stress and inflammation to neurodegeneration. *Synapse* **2017**, *71*, e21990. https://doi.org/10.1002/syn.21990.
27. Lubrano, V.; Ndreu, R.; Balzan, S. Classes of Lipid Mediators and Their Effects on Vascular Inflammation in Atherosclerosis. *Int. J. Mol. Sci.* **2023**, *24*, 1637. https://doi.org/10.3390/ijms24021637.
28. Panezai, J.; Van Dyke, T.E. Resolution of inflammation: Intervention strategies and future applications. *Toxicol. Appl. Pharmacol.* **2022**, *449*, 116089. https://doi.org/10.1016/j.taap.2022.116089.
29. Margină, D.; Ungurianu, A.; Purdel, C.; Nițulescu, G.M.; Tsoukalas, D.; Sarandi, E.; Thanasoula, M.; Burykina, T.I.; Tekos, F.; Buha, A.; et al. Analysis of the intricate effects of polyunsaturated fatty acids and polyphenols on inflammatory pathways in health and disease. *Food Chem. Toxicol.* **2020**, *143*, 111558. https://doi.org/10.1016/j.fct.2020.111558.
30. Tucker, K.L. Assessment of usual dietary intake in population studies of gene-diet interaction. *Nutr. Metab. Cardiovasc. Dis.* **2007**, *17*, 74–81. https://doi.org/10.1016/j.numecd.2006.07.010.
31. Bass, J.; Takahashi, J.S. Circadian integration of metabolism and energetics. *Science* **2010**, *330*, 1349–1354. https://doi.org/10.1126/science.1195027.
32. Kulesza, A.; Paczek, L.; Burdzinska, A. The Role of COX-2 and PGE2 in the Regulation of Immunomodulation and Other Functions of Mesenchymal Stromal Cells. *Biomedicines* **2023**, *11*, 445. https://doi.org/10.3390/biomedicines11020445.
33. Ribas-Latre, A.; Eckel-Mahan, K. Nutrients and the Circadian Clock: A Partnership Controlling Adipose Tissue Function and Health. *Nutrients* **2022**, *14*, 2084. https://doi.org/10.3390/nu14102084.

34. Curtis, A.M.; Cheng, Y.; Kapoor, S.; Reilly, D.; Price, T.S.; Fitzgerald, G.A. Circadian variation of blood pressure and the vascular response to asynchronous stress. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 3450–3455. https://doi.org/10.1073/pnas.0611680104.
35. Hayashi, M.; Shimba, S.; Tezuka, M. Characterization of the molecular clock in mouse peritoneal macrophages. *Biol. Pharm. Bull.* **2007**, *30*, 621–626. https://doi.org/10.1248/bpb.30.621.
36. Prasai, M.J.; Mughal, R.S.; Wheatcroft, S.B.; Kearney, M.T.; Grant, P.J.; Scott, E.M. Diurnal variation in vascular and metabolic function in diet-induced obesity: Divergence of insulin resistance and loss of clock rhythm. *Diabetes* **2013**, *62*, 1981–1989. https://doi.org/10.2337/db11-1740.
37. Olufunmilayo, E.O.; Gerke-Duncan, M.B.; Holsinger, R.M.D. Oxidative Stress and Antioxidants in Neurodegenerative Disorders. *Antioxidants* **2023**, *12,* 517. https://doi.org/10.3390/antiox12020517.
38. Ingle, K.A.; Kain, V.; Goel, M.; Prabhu, S.D.; Young, M.E.; Halade, G.V. Cardiomyocyte-specific Bmal1 deletion in mice triggers diastolic dysfunction, extracellular matrix response, and impaired resolution of inflammation. *Am. J. Physiol. Heart Circ. Physiol.* **2015**, *309*, H1827–H1836. https://doi.org/10.1152/ajpheart.00608.2015.
39. Keller, M.; Mazuch, J.; Abraham, U.; Eom, G.D.; Herzog, E.D.; Volk, H.D.; Kramer, A.; Maier, B. A circadian clock in macrophages controls inflammatory immune responses. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 21407–21412. https://doi.org/10.1073/pnas.0906361106.
40. Reina-Couto, M.; Vale, L.; Carvalho, J.; Bettencourt, P.; Albino-Teixeira, A.; Sousa, T. Resolving Inflammation in Heart Failure: Novel Protective Lipid Mediators. *Curr. Drug Targets* **2016**, *17*, 1206–1223. https://doi.org/10.2174/1389450117666160101121135.
41. Cutolo, M. SP0040 The Immune/Inflammatory Response Follows Circadian Rhythms. *Ann. Rheum. Dis.* **2014**, *73*, 11–11.
42. Zielinski, M.R.; Gibbons, A.J. Neuroinflammation, sleep, and circadian rhythms. *Front. Cell. Infect. Microbiol.* **2022**, *12*, 853096.
43. Spies, C.M.; Cutolo, M.; Straub, R.H.; Burmester, G.-R.; Buttgereit, F. More night than day—circadian rhythms in polymyalgia rheumatica and ankylosing spondylitis. *J. Rheumatol.* **2010**, *37*, 894–899.
44. Shirato, K.; Sato, S. Macrophage meets the circadian clock: Implication of the circadian clock in the role of macrophages in acute lower respiratory tract infection. *Front. Cell. Infect. Microbiol.* **2022**, *12*, 826738.
45. Gooley, J.J. Circadian regulation of lipid metabolism. *Proc. Nutr. Soc.* **2016**, *75*, 440–450. https://doi.org/10.1017/s0029665116000288.
46. Okyar, A.; Ozturk Civelek, D.; Akyel, Y.K.; Surme, S.; Pala Kara, Z.; Kavakli, I.H. The role of the circadian timing system on drug metabolism and detoxification: An update. *Expert. Opin. Drug Metab. Toxicol.* **2024**, *20*, 503–517. https://doi.org/10.1080/17425255.2024.2356167.
47. Skowronek, R.; Czekaj, P.; Suszka-Świtek, A.; Czech, E.; Wiaderkiewicz, A.; Plewka, D.; Bryzek, A. Expression of cytochrome P450 2C and 3A in female rat liver after long-term administration of gonadoliberin analogs. *Int. J. Occup. Med. Environ. Health* **2016**, *29*, 293–314. https://doi.org/10.13075/ijomeh.1896.00528.
48. Carver, K.A.; Lourim, D.; Tryba, A.K.; Harder, D.R. Rhythmic expression of cytochrome P450 epoxygenases CYP4x1 and CYP2c11 in the rat brain and vasculature. *Am. J. Physiol. Cell Physiol.* **2014**, *307*, C989–C998. https://doi.org/10.1152/ajpcell.00401.2013.
49. Zhu, X.; Hou, Q.; Zhang, L.; Wang, D.; Tian, Z.; Liu, Y.; Wang, Y.; Li, Y.; Jiang, H. Isorhynchophylline improves lipid metabolism disorder by mediating a circadian rhythm gene Bmal1 in spontaneously hypertensive rat. *Phytother. Res.* **2023**, *37*, 5991–6005. https://doi.org/10.1002/ptr.8015.
50. Zardoya, R.; Diez, A.; Serradilla, M.C.; Madrid, J.A.; Bautista, J.M.; Garrido-Pertierra, A. Lipogenic activities in rat liver are subjected to circadian rhythms. *Rev. Esp. Fisiol.* **1994**, *50*, 239–244.
51. Ma, D.; Liu, T.; Chang, L.; Rui, C.; Xiao, Y.; Li, S.; Hogenesch, J.B.; Chen, Y.E.; Lin, J.D. The Liver Clock Controls Cholesterol Homeostasis through Trib1 Protein-mediated Regulation of PCSK9/Low Density Lipoprotein Receptor (LDLR) Axis. *J. Biol. Chem.* **2015**, *290*, 31003–31012. https://doi.org/10.1074/jbc.M115.685982.
52. Hussain, M.M.; Pan, X. Circadian regulators of intestinal lipid absorption. *J. Lipid Res.* **2015**, *56*, 761–770. https://doi.org/10.1194/jlr.R051573.
53. Poggiogalle, E.; Jamshed, H.; Peterson, C.M. Circadian regulation of glucose, lipid, and energy metabolism in humans. *Metabolism* **2018**, *84*, 11–27. https://doi.org/10.1016/j.metabol.2017.11.017.
54. Das, U.N. "Cell Membrane Theory of Senescence" and the Role of Bioactive Lipids in Aging, and Aging Associated Diseases and Their Therapeutic Implications. *Biomolecules* **2021**, *11*, 241. https://doi.org/10.3390/biom11020241.
55. Fagiani, F.; Di Marino, D.; Romagnoli, A.; Travelli, C.; Voltan, D.; Di Cesare Mannelli, L.; Racchi, M.; Govoni, S.; Lanni, C. Molecular regulations of circadian rhythm and implications for physiology and diseases. *Signal Transduct. Target. Ther.* **2022**, *7*, 41. https://doi.org/10.1038/s41392-022-00899-y.

56. Xu, H.; Li, H.; Woo, S.L.; Kim, S.M.; Shende, V.R.; Neuendorff, N.; Guo, X.; Guo, T.; Qi, T.; Pei, Y.; et al. Myeloid cell-specific disruption of Period1 and Period2 exacerbates diet-induced inflammation and insulin resistance. *J. Biol. Chem.* **2014**, *289*, 16374–16388. https://doi.org/10.1074/jbc.M113.539601.
57. Downton, P.; Sanna, F.; Maidstone, R.; Poolman, T.M.; Hayter, E.A.; Dickson, S.H.; Ciccone, N.A.; Early, J.O.; Adamson, A.; Spiller, D.G.; et al. Chronic inflammatory arthritis drives systemic changes in circadian energy metabolism. *Proc. Natl. Acad. Sci. USA* **2022**, *119*, e2112781119. https://doi.org/10.1073/pnas.2112781119.
58. Bellet, M.M.; Masri, S.; Astarita, G.; Sassone-Corsi, P.; Della Fazia, M.A.; Servillo, G. Histone Deacetylase SIRT1 Controls Proliferation, Circadian Rhythm, and Lipid Metabolism during Liver Regeneration in Mice. *J. Biol. Chem.* **2016**, *291*, 23318–23329. https://doi.org/10.1074/jbc.M116.737114.
59. Shen, W.; Wang, C.; Xia, L.; Fan, C.; Dong, H.; Deckelbaum, R.J.; Qi, K. Epigenetic modification of the leptin promoter in diet-induced obese mice and the effects of N-3 polyunsaturated fatty acids. *Sci. Rep.* **2014**, *4*, 5282. https://doi.org/10.1038/srep05282.
60. Zhao, X.; Zhu, X.; Cheng, S.; Xie, Y.; Wang, Z.; Liu, Y.; Jiang, Z.; Xiao, J.; Guo, H.; Wang, Y. MiR-29a/b/c regulate human circadian gene hPER1 expression by targeting its 3'UTR. *Acta Biochim. Biophys. Sin.* **2014**, *46*, 313–317. https://doi.org/10.1093/abbs/gmu007.
61. Shende, V.R.; Goldrick, M.M.; Ramani, S.; Earnest, D.J. Expression and rhythmic modulation of circulating microRNAs targeting the clock gene Bmal1 in mice. *PLoS ONE* **2011**, *6*, e22586. https://doi.org/10.1371/journal.pone.0022586.
62. Milagro, F.I.; Gómez-Abellán, P.; Campión, J.; Martínez, J.A.; Ordovás, J.M.; Garaulet, M. CLOCK, PER2 and BMAL1 DNA methylation: Association with obesity and metabolic syndrome characteristics and monounsaturated fat intake. *Chronobiol. Int.* **2012**, *29*, 1180–1194. https://doi.org/10.3109/07420528.2012.719967.
63. Shende, V.R.; Neuendorff, N.; Earnest, D.J. Role of miR-142-3p in the post-transcriptional regulation of the clock gene Bmal1 in the mouse SCN. *PLoS ONE* **2013**, *8*, e65300. https://doi.org/10.1371/journal.pone.0065300.
64. Garaulet, M.; Lee, Y.-C.; Shen, J.; Parnell, L.D.; Arnett, D.K.; Tsai, M.Y.; Lai, C.-Q.; Ordovas, J.M. CLOCK genetic variation and metabolic syndrome risk: Modulation by monounsaturated fatty acids. *Am. J. Clin. Nutr.* **2009**, *90*, 1466–1475.
65. Kissling, C.; Retz, W.; Wiemann, S.; Coogan, A.N.; Clement, R.M.; Hünnerkopf, R.; Conner, A.C.; Freitag, C.M.; Rösler, M.; Thome, J. A polymorphism at the 3'-untranslated region of the CLOCK gene is associated with adult attention-deficit hyperactivity disorder. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **2008**, *147*, 333–338. https://doi.org/10.1002/ajmg.b.30602.
66. Camblor Murube, M.; Borregon-Rivilla, E.; Colmenarejo, G.; Aguilar-Aguilar, E.; Martínez, J.A.; Ramírez De Molina, A.; Reglero, G.; Loria-Kohen, V. Polymorphism of CLOCK Gene rs3749474 as a Modulator of the Circadian Evening Carbohydrate Intake Impact on Nutritional Status in an Adult Sample. *Nutrients* **2020**, *12*, 1142. https://doi.org/10.3390/nu12041142.
67. Maury, E.; Hong, H.K.; Bass, J. Circadian disruption in the pathogenesis of metabolic syndrome. *Diabetes Metab.* **2014**, *40*, 338–346. https://doi.org/10.1016/j.diabet.2013.12.005.
68. Leu, H.B.; Chung, C.M.; Lin, S.J.; Chiang, K.M.; Yang, H.C.; Ho, H.Y.; Ting, C.T.; Lin, T.H.; Sheu, S.H.; Tsai, W.C.; et al. Association of circadian genes with diurnal blood pressure changes and non-dipper essential hypertension: a genetic association with young-onset hypertension. *Hypertens. Res.* **2015**, *38*, 155–162. https://doi.org/10.1038/hr.2014.152.
69. Yamaguchi, M.; Uemura, H.; Arisawa, K.; Katsuura-Kamano, S.; Hamajima, N.; Hishida, A.; Suma, S.; Oze, I.; Nakamura, K.; Takashima, N.; et al. Association between brain-muscle-ARNT-like protein-2 (BMAL2) gene polymorphism and type 2 diabetes mellitus in obese Japanese individuals: A cross-sectional analysis of the Japan Multi-institutional Collaborative Cohort Study. *Diabetes Res. Clin. Pract.* **2015**, *110*, 301–308. https://doi.org/10.1016/j.diabres.2015.10.009.
70. Nascimento Ferreira, M.V.; Goumidi, L.; Carvalho, H.B.; De Moraes, A.C.F.; Santaliestra-Pasías, A.M.; Kafatos, A.; Molnar, D.; Lambrinou, C.P.; De Henauw, S.; Gutierrez, A.; et al. Associations between REV-ERBα, sleep duration and body mass index in European adolescents. *Sleep. Med.* **2018**, *46*, 56–60. https://doi.org/10.1016/j.sleep.2018.01.014.
71. Lin, Y.; He, L.; Cai, Y.; Wang, X.; Wang, S.; Li, F. The role of circadian clock in regulating cell functions: Implications for diseases. *MedComm* **2024**, *5*, e504. https://doi.org/10.1002/mco2.504.
72. D'Angelo, S.; Motti, M.L.; Meccariello, R. ω-3 and ω-6 Polyunsaturated Fatty Acids, Obesity and Cancer. *Nutrients* **2020**, *12*, 2751. https://doi.org/10.3390/nu12092751.
73. Namgyal, D.; Chandan, K.; Sultan, A.; Aftab, M.; Ali, S.; Mehta, R.; El-Serehy, H.A.; Al-Misned, F.A.; Sarwat, M. Dim Light at Night Induced Neurodegeneration and Ameliorative Effect of Curcumin. *Cells* **2020**, *9*, 2093. https://doi.org/10.3390/cells9092093.
74. Mora, I.; Arola, L.; Caimari, A.; Escoté, X.; Puiggròs, F. Structured Long-Chain Omega-3 Fatty Acids for Improvement of Cognitive Function during Aging. *Int. J. Mol. Sci.* **2022**, *23*, 3472. https://doi.org/10.3390/ijms23073472.

75. Checa-Ros, A.; D'Marco, L. Role of Omega-3 Fatty Acids as Non-Photic Zeitgebers and Circadian Clock Synchronizers. *Int. J. Mol. Sci.* **2022**, *23*, 12162. https://doi.org/10.3390/ijms232012162.
76. Tsuchiya, Y.; Minami, I.; Kadotani, H.; Nishida, E. Resetting of peripheral circadian clock by prostaglandin E2. *EMBO Rep.* **2005**, *6*, 256–261. https://doi.org/10.1038/sj.embor.7400356.
77. Chen, S.; Fuller, K.K.; Dunlap, J.C.; Loros, J.J. A Pro- and Anti-inflammatory Axis Modulates the Macrophage Circadian Clock. *Front. Immunol.* **2020**, *11*, 867. https://doi.org/10.3389/fimmu.2020.00867.
78. Baumann, A.; Gönnenwein, S.; Bischoff, S.C.; Sherman, H.; Chapnik, N.; Froy, O.; Lorentz, A. The circadian clock is functional in eosinophils and mast cells. *Immunology* **2013**, *140*, 465–474. https://doi.org/10.1111/imm.12157.
79. Wang, Y.; Pati, P.; Xu, Y.; Chen, F.; Stepp, D.W.; Huo, Y.; Rudic, R.D.; Fulton, D.J. Endotoxin Disrupts Circadian Rhythms in Macrophages via Reactive Oxygen Species. *PLoS ONE* **2016**, *11*, e0155075. https://doi.org/10.1371/journal.pone.0155075.
80. Baxter, M.; Ray, D.W. Circadian rhythms in innate immunity and stress responses. *Immunology* **2020**, *161*, 261–267. https://doi.org/10.1111/imm.13166.
81. Wang, Q.; Maillard, M.; Schibler, U.; Burnier, M.; Gachon, F. Cardiac hypertrophy, low blood pressure, and low aldosterone levels in mice devoid of the three circadian PAR bZip transcription factors DBP, HLF, and TEF. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2010**, *299*, R1013–R1019. https://doi.org/10.1152/ajpregu.00241.2010.
82. Man, A.W.C.; Li, H.; Xia, N. Circadian Rhythm: Potential Therapeutic Target for Atherosclerosis and Thrombosis. *Int. J. Mol. Sci.* **2021**, *22*, 676. https://doi.org/10.3390/ijms22020676.
83. Naito, Y.; Tsujino, T.; Kawasaki, D.; Okumura, T.; Morimoto, S.; Masai, M.; Sakoda, T.; Fujioka, Y.; Ohyanagi, M.; Iwasaki, T. Circadian gene expression of clock genes and plasminogen activator inhibitor-1 in heart and aorta of spontaneously hypertensive and Wistar-Kyoto rats. *J. Hypertens.* **2003**, *21*, 1107–1115. https://doi.org/10.1097/00004872-200306000-00010.
84. Smyth, E.M. Thromboxane and the thromboxane receptor in cardiovascular disease. *Clin. Lipidol.* **2010**, *5*, 209.
85. Félétou, M.; Huang, Y.; Vanhoutte, P.M. Endothelium-mediated control of vascular tone: COX-1 and COX-2 products. *Br. J. Pharmacol.* **2011**, *164*, 894–912.
86. Liu, D.; Ji, L.; Wang, Y.; Zheng, L. Cyclooxygenase-2 expression, prostacyclin production and endothelial protection of high-density lipoprotein. *Cardiovasc. Hematol. Disord. Drug Targets* **2012**, *12*, 98–105. https://doi.org/10.2174/1871529x11202020098.
87. Chen, H. Role of thromboxane A2 signaling in endothelium-dependent contractions of arteries. *Prostaglandins Other Lipid Mediat.* **2018**, *134*, 32–37.
88. Wong, M.S.-K.; Vanhoutte, P.M. COX-mediated endothelium-dependent contractions: From the past to recent discoveries. *Acta Pharmacol. Sin.* **2010**, *31*, 1095–1102.
89. Hristovska, A.-M.; Rasmussen, L.E.; Hansen, P.B.; Nielsen, S.S.; Nüsing, R.M.; Narumiya, S.; Vanhoutte, P.; Skøtt, O.; Jensen, B.L. Prostaglandin E2 induces vascular relaxation by E-prostanoid 4 receptor-mediated activation of endothelial nitric oxide synthase. *Hypertension* **2007**, *50*, 525–530.
90. Eskildsen, M.P.; Hansen, P.B.; Stubbe, J.; Toft, A.; Walter, S.; Marcussen, N.; Rasmussen, L.M.; Vanhoutte, P.M.; Jensen, B.L. Prostaglandin I2 and prostaglandin E2 modulate human intrarenal artery contractility through prostaglandin E2-EP4, prostacyclin-IP, and thromboxane A2-TP receptors. *Hypertension* **2014**, *64*, 551–556.
91. Lang, P.; Kempe, D.; Myssina, S.; Tanneur, V.; Birka, C.; Laufer, S.; Lang, F.; Wieder, T.; Huber, S. PGE2 in the regulation of programmed erythrocyte death. *Cell Death Differ.* **2005**, *12*, 415–428.
92. Cipollone, F.; Prontera, C.; Pini, B.; Marini, M.; Fazia, M.; De Cesare, D.; Iezzi, A.; Ucchino, S.; Boccoli, G.; Saba, V. Overexpression of functionally coupled cyclooxygenase-2 and prostaglandin E synthase in symptomatic atherosclerotic plaques as a basis of prostaglandin E2-dependent plaque instability. *Circulation* **2001**, *104*, 921–927.
93. Yang, G.; Chen, L. An update of microsomal prostaglandin E synthase-1 and PGE2 receptors in cardiovascular health and diseases. *Oxidative Med. Cell. Longev.* **2016**, *2016*, 5249086.
94. Caligiuri, S.P.B.; Aukema, H.M.; Ravandi, A.; Lavallée, R.; Guzman, R.; Pierce, G.N. Specific plasma oxylipins increase the odds of cardiovascular and cerebrovascular events in patients with peripheral artery disease. *Can. J. Physiol. Pharmacol.* **2017**, *95*, 961–968. https://doi.org/10.1139/cjpp-2016-0615.
95. Libby, P.; Ridker, P.M.; Hansson, G.K. Inflammation in atherosclerosis: From pathophysiology to practice. *J. Am. Coll. Cardiol.* **2009**, *54*, 2129–2138. https://doi.org/10.1016/j.jacc.2009.09.009.
96. Pignone, M.; Alberts, M.J.; Colwell, J.A.; Cushman, M.; Inzucchi, S.E.; Mukherjee, D.; Rosenson, R.S.; Williams, C.D.; Wilson, P.W.; Kirkman, M.S. Aspirin for primary prevention of cardiovascular events in people with diabetes. *J. Am. Coll. Cardiol.* **2010**, *55*, 2878–2886. https://doi.org/10.1016/j.jacc.2010.04.003.
97. Yang, J.; Xu, Z.F.; Su, J.; Fan, S.F.; Wang, J.Y.; Ji, L.D.; Chen, X.M. [Research progress on the circadian clock regulation in cardiovascular system and association between circadian clock regulation and cardiovascular diseases]. *Zhonghua Xin Xue Guan Bing Za Zhi* **2020**, *48*, 610–615. https://doi.org/10.3760/cma.j.cn112148-20190725-00430.

98. Zhang, J.; Sun, R.; Jiang, T.; Yang, G.; Chen, L. Circadian Blood Pressure Rhythm in Cardiovascular and Renal Health and Disease. *Biomolecules* **2021**, *11*, 868. https://doi.org/10.3390/biom11060868.
99. Aliwarga, T.; Evangelista, E.A.; Sotoodehnia, N.; Lemaitre, R.N.; Totah, R.A. Regulation of CYP2J2 and EET levels in cardiac disease and diabetes. *Int. J. Mol. Sci.* **2018**, *19*, 1916.
100. Bhatnagar, A. Beating ischemia: A new feat of EETs? *Am. Heart Assoc.* **2004**, *95*, 443–445.
101. Imig, J.D. Epoxides and soluble epoxide hydrolase in cardiovascular physiology. *Physiol. Rev.* **2012**, *92*, 101–130.
102. Thosar, S.S.; Berman, A.M.; Herzig, M.X.; McHill, A.W.; Bowles, N.P.; Swanson, C.M.; Clemons, N.A.; Butler, M.P.; Clemons, A.A.; Emens, J.S. Circadian rhythm of vascular function in midlife adults. *Arterioscler. Thromb. Vasc. Biol.* **2019**, *39*, 1203–1211.
103. Kezeli, T.; Gongadze, N.; Sukoyan, G.; Shikhashvili, M.; Chapichadze, Z.; Okujava, M.; Dolidze, N. Circadian variation in vasoconstriction and vasodilation mediators and baroreflex sensitivity in hypertensive rats. *J. Circadian Rhythm.* **2019**, *17*, 10.
104. Gross, G.J.; Hsu, A.; Falck, J.R.; Nithipatikom, K. Mechanisms by which epoxyeicosatrienoic acids (EETs) elicit cardioprotection in rat hearts. *J. Mol. Cell Cardiol.* **2007**, *42*, 687–691. https://doi.org/10.1016/j.yjmcc.2006.11.020.
105. Xie, Z.; Su, W.; Liu, S.; Zhao, G.; Esser, K.; Schroder, E.A.; Lefta, M.; Stauss, H.M.; Guo, Z.; Gong, M.C. Smooth-muscle BMAL1 participates in blood pressure circadian rhythm regulation. *J. Clin. Investig.* **2015**, *125*, 324–336.
106. Gianazza, E.; Brioschi, M.; Fernandez, A.M.; Banfi, C. Lipoxidation in cardiovascular diseases. *Redox Biol.* **2019**, *23*, 101119.
107. Sonnweber, T.; Pizzini, A.; Nairz, M.; Weiss, G.; Tancevski, I. Arachidonic acid metabolites in cardiovascular and metabolic diseases. *Int. J. Mol. Sci.* **2018**, *19*, 3285.
108. Bäck, M. Inflammatory signaling through leukotriene receptors in atherosclerosis. *Curr. Atheroscler. Rep.* **2008**, *10*, 244–251. https://doi.org/10.1007/s11883-008-0038-7.
109. Baker, N.; O'Meara, S.J.; Scannell, M.; Maderna, P.; Godson, C. Lipoxin A4: Anti-inflammatory and anti-angiogenic impact on endothelial cells. *J. Immunol.* **2009**, *182*, 3819–3826.
110. Kotlyarov, S.; Kotlyarova, A. Molecular pharmacology of inflammation resolution in atherosclerosis. *Int. J. Mol. Sci.* **2022**, *23*, 4808.
111. Pirault, J.; Bäck, M. Lipoxin and Resolvin Receptors Transducing the Resolution of Inflammation in Cardiovascular Disease. *Front. Pharmacol.* **2018**, *9*, 1273. https://doi.org/10.3389/fphar.2018.01273.
112. Sun, R.; Huang, J.; Yang, N.; He, J.; Yu, X.; Feng, S.; Xie, Y.; Wang, G.; Ye, H.; Aa, J. Purine Catabolism Shows a Dampened Circadian Rhythmicity in a High-fat Diet-Induced Mouse Model of Obesity. *Molecules* **2019**, *24*, 4524. https://doi.org/10.3390/molecules24244524.
113. Guesnet, P.; Alessandri, J.M.; Vancassel, S.; Zamaria, N. Analysis of the 2nd symposium "Anomalies of fatty acids, ageing and degenerating pathologies". *Reprod. Nutr. Dev.* **2004**, *44*, 263–271. https://doi.org/10.1051/rnd:2004031.
114. Clarke, S.D.; Baillie, R.; Jump, D.B.; Nakamura, M.T. Fatty acid regulation of gene expression. Its role in fuel partitioning and insulin resistance. *Ann. N. Y Acad. Sci.* **1997**, *827*, 178–187. https://doi.org/10.1111/j.1749-6632.1997.tb51833.x.
115. Chan, P.C.; Liao, M.T.; Hsieh, P.S. The Dualistic Effect of COX-2-Mediated Signaling in Obesity and Insulin Resistance. *Int. J. Mol. Sci.* **2019**, *20*, 3115. https://doi.org/10.3390/ijms20133115.
116. Robertson, R.P. Dominance of cyclooxygenase-2 in the regulation of pancreatic islet prostaglandin synthesis. *Diabetes* **1998**, *47*, 1379–1383. https://doi.org/10.2337/diabetes.47.9.1379.
117. Cao, Y.; Mai, W.; Li, R.; Deng, S.; Li, L.; Zhou, Y.; Qin, Q.; Zhang, Y.; Zhou, X.; Han, M.; et al. Macrophages evoke autophagy of hepatic stellate cells to promote liver fibrosis in NAFLD mice via the PGE2/EP4 pathway. *Cell Mol. Life Sci.* **2022**, *79*, 303. https://doi.org/10.1007/s00018-022-04319-w.
118. Kaffe, E.; Tisi, A.; Magkrioti, C.; Aidinis, V.; Mehal, W.Z.; Flavell, R.A.; Maccarrone, M. Bioactive signalling lipids as drivers of chronic liver diseases. *J. Hepatol.* **2024**, *80*, 140–154. https://doi.org/10.1016/j.jhep.2023.08.029.
119. Nakao, T.; Yasumoto, A.; Tokuoka, S.; Kita, Y.; Kawahara, T.; Daimon, M.; Yatomi, Y. The impact of night-shift work on platelet function in healthy medical staff. *J. Occup. Health* **2018**, *60*, 324–332. https://doi.org/10.1539/joh.2018-0027-FS.
120. Radi, Z.A.; Khan, K.N. Cardio-renal safety of non-steroidal anti-inflammatory drugs. *J. Toxicol. Sci.* **2019**, *44*, 373–391. https://doi.org/10.2131/jts.44.373.
121. Gaiz, A.; Mosawy, S.; Colson, N.; Singh, I. Thrombotic and cardiovascular risks in type two diabetes; Role of platelet hyperactivity. *Biomed. Pharmacother.* **2017**, *94*, 679–686. https://doi.org/10.1016/j.biopha.2017.07.121.
122. Ma, K.; Jin, X.; Liang, X.; Zhao, Q.; Zhang, X. Inflammatory mediators involved in the progression of the metabolic syndrome. *Diabetes Metab. Res. Rev.* **2012**, *28*, 388–394. https://doi.org/10.1002/dmrr.2291.
123. Szczuko, M.; Kozioł, I.; Kotlęga, D.; Brodowski, J.; Drozd, A. The Role of Thromboxane in the Course and Treatment of Ischemic Stroke: Review. *Int. J. Mol. Sci.* **2021**, *22*, 11644. https://doi.org/10.3390/ijms222111644.

124. Dahik, V.D.; Frisdal, E.; Le Goff, W. Rewiring of Lipid Metabolism in Adipose Tissue Macrophages in Obesity: Impact on Insulin Resistance and Type 2 Diabetes. *Int. J. Mol. Sci.* **2020**, *21*, 5505. https://doi.org/10.3390/ijms21155505.
125. Khan, S.A.; Ali, A.; Khan, S.A.; Zahran, S.A.; Damanhouri, G.; Azhar, E.; Qadri, I. Unraveling the complex relationship triad between lipids, obesity, and inflammation. *Mediators Inflamm.* **2014**, *2014*, 502749. https://doi.org/10.1155/2014/502749.
126. Brennan, E.; Kantharidis, P.; Cooper, M.E.; Godson, C. Pro-resolving lipid mediators: Regulators of inflammation, metabolism and kidney function. *Nat. Rev. Nephrol.* **2021**, *17*, 725–739. https://doi.org/10.1038/s41581-021-00454-y.
127. Shi, D.; Chen, J.; Wang, J.; Yao, J.; Huang, Y.; Zhang, G.; Bao, Z. Circadian Clock Genes in the Metabolism of Non-alcoholic Fatty Liver Disease. *Front. Physiol.* **2019**, *10*, 423. https://doi.org/10.3389/fphys.2019.00423.
128. Chernyshev, O.Y.; McCarty, D.E.; Chesson, A.L. Inflammatory Mediators in Obstructive Sleep Apnea. In *Neuroinflammation*; Elsevier: Amsterdam, The Netherlands, 2018; pp. 449–491.
129. Drozd, A.; Kotlęga, D.; Nowacki, P.; Ciećwież, S.; Trochanowski, T.; Szczuko, M. Fatty Acid Levels and Their Inflammatory Metabolites Are Associated with the Nondipping Status and Risk of Obstructive Sleep Apnea Syndrome in Stroke Patients. *Biomedicines* **2022**, *10*, 2200. https://doi.org/10.3390/biomedicines10092200.
130. Xu, X.; Li, R.; Chen, G.; Hoopes, S.L.; Zeldin, D.C.; Wang, D.W. The Role of Cytochrome P450 Epoxygenases, Soluble Epoxide Hydrolase, and Epoxyeicosatrienoic Acids in Metabolic Diseases. *Adv. Nutr.* **2016**, *7*, 1122–1128. https://doi.org/10.3945/an.116.012245.
131. Misheva, M.; Johnson, J.; McCullagh, J. Role of Oxylipins in the Inflammatory-Related Diseases NAFLD, Obesity, and Type 2 Diabetes. *Metabolites* **2022**, *12*, 1238. https://doi.org/10.3390/metabo12121238.
132. Pivovarova, O.; Jürchott, K.; Rudovich, N.; Hornemann, S.; Ye, L.; Möckel, S.; Murahovschi, V.; Kessler, K.; Seltmann, A.C.; Maser-Gluth, C.; et al. Changes of Dietary Fat and Carbohydrate Content Alter Central and Peripheral Clock in Humans. *J. Clin. Endocrinol. Metab.* **2015**, *100*, 2291–2302. https://doi.org/10.1210/jc.2014-3868.
133. Qian, J.; Yeh, B.; Rakshit, K.; Colwell, C.S.; Matveyenko, A.V. Circadian Disruption and Diet-Induced Obesity Synergize to Promote Development of β-Cell Failure and Diabetes in Male Rats. *Endocrinology* **2015**, *156*, 4426–4436. https://doi.org/10.1210/en.2015-1516.
134. Froy, O. Metabolism and circadian rhythms--implications for obesity. *Endocr. Rev.* **2010**, *31*, 1–24. https://doi.org/10.1210/er.2009-0014.
135. Lefebvre, P.; Chinetti, G.; Fruchart, J.C.; Staels, B. Sorting out the roles of PPAR alpha in energy metabolism and vascular homeostasis. *J. Clin. Investig.* **2006**, *116*, 571–580. https://doi.org/10.1172/jci27989.
136. Salvati, S.; Attorri, L.; Di Benedetto, R.; Di Biase, A.; Leonardi, F. Polyunsaturated fatty acids and neurological diseases. *Mini Rev. Med. Chem.* **2006**, *6*, 1201–1211. https://doi.org/10.2174/138955706778742740.
137. Sheremeta, C.L.; Yarlagadda, S.; Smythe, M.L.; Noakes, P.G. Prostaglandins in the Inflamed Central Nervous System: Potential Therapeutic Targets. *Curr. Drug Targets* **2024**, *25*, 885–908. https://doi.org/10.2174/0113894501323980240815113851.
138. Vezzani, A.; Friedman, A.; Dingledine, R.J. The role of inflammation in epileptogenesis. *Neuropharmacology* **2013**, *69*, 16–24. https://doi.org/10.1016/j.neuropharm.2012.04.004.
139. Andreasson, K. Emerging roles of PGE2 receptors in models of neurological disease. *Prostaglandins Other Lipid Mediat.* **2010**, *91*, 104–112. https://doi.org/10.1016/j.prostaglandins.2009.04.003.
140. Gao, C.; Wang, H.; Wang, T.; Luo, C.; Wang, Z.; Zhang, M.; Chen, X.; Tao, L. Platelet regulates neuroinflammation and restores blood-brain barrier integrity in a mouse model of traumatic brain injury. *J. Neurochem.* **2020**, *154*, 190–204. https://doi.org/10.1111/jnc.14983.
141. Gorica, E.; Calderone, V. Arachidonic Acid Derivatives and Neuroinflammation. *CNS Neurol. Disord. Drug Targets* **2022**, *21*, 118–129. https://doi.org/10.2174/1871527320666210208130412.
142. Engblom, D.; Ek, M.; Saha, S.; Ericsson-Dahlstrand, A.; Jakobsson, P.J.; Blomqvist, A. Prostaglandins as inflammatory messengers across the blood-brain barrier. *J. Mol. Med.* **2002**, *80*, 5–15. https://doi.org/10.1007/s00109-001-0289-z.
143. Lu, J.; Xing, J.; Li, J. Prostaglandin E2 (PGE2) inhibits glutamatergic synaptic transmission in dorsolateral periaqueductal gray (dl-PAG). *Brain Res.* **2007**, *1162*, 38–47. https://doi.org/10.1016/j.brainres.2007.06.004.
144. Beura, S.K.; Dhapola, R.; Panigrahi, A.R.; Yadav, P.; Kumar, R.; Reddy, D.H.; Singh, S.K. Antiplatelet drugs: Potential therapeutic options for the management of neurodegenerative diseases. *Med. Res. Rev.* **2023**, *43*, 1835–1877. https://doi.org/10.1002/med.21965.
145. Murakami, M. Lipid mediators in life science. *Exp. Anim.* **2011**, *60*, 7–20. https://doi.org/10.1538/expanim.60.7.
146. Phillis, J.W.; Horrocks, L.A.; Farooqui, A.A. Cyclooxygenases, lipoxygenases, and epoxygenases in CNS: Their role and involvement in neurological disorders. *Brain Res. Rev.* **2006**, *52*, 201–243. https://doi.org/10.1016/j.brainresrev.2006.02.002.

147. Razavi, S.M.; Khayatan, D.; Arab, Z.N.; Momtaz, S.; Zare, K.; Jafari, R.M.; Dehpour, A.R.; Abdolghaffari, A.H. Licofelone, a potent COX/5-LOX inhibitor and a novel option for treatment of neurological disorders. *Prostaglandins Other Lipid Mediat.* **2021**, *157*, 106587. https://doi.org/10.1016/j.prostaglandins.2021.106587.
148. Farooqui, A.A.; Farooqui, A.A. Metabolism and Roles of Eicosanoids in Brain. In *Lipid Mediators and Their Metabolism in the Brain*; Springer: New York, NY, USA, 2011; pp. 1–47.
149. Farooqui, A.A. Lipid mediators and their metabolism in the nucleus: Implications for Alzheimer's disease. *Journal of Alzheimer's Disease* **2012**, *30*, S163–S178.
150. Kabata, H.; Moro, K.; Koyasu, S. The group 2 innate lymphoid cell (ILC2) regulatory network and its underlying mechanisms. *Immunol. Rev.* **2018**, *286*, 37–52. https://doi.org/10.1111/imr.12706.
151. Manev, H.; Uz, T.; Sugaya, K.; Qu, T. Putative role of neuronal 5-lipoxygenase in an aging brain. *Faseb J.* **2000**, *14*, 1464–1469. https://doi.org/10.1096/fj.14.10.1464.
152. Castro-Lopez, N.; Campuzano, A.; Mdalel, E.; Vanegas, D.; Chaturvedi, A.; Nguyen, P.; Pulse, M.; Cardona, A.E.; Wormley, F.L., Jr. Inhibition of host 5-lipoxygenase reduces overexuberant inflammatory responses and mortality associated with Cryptococcus meningoencephalitis. *mBio* **2024**, *15*, e0148324. https://doi.org/10.1128/mbio.01483-24.
153. Gonzalez-Fernandez, E.; Staursky, D.; Lucas, K.; Nguyen, B.V.; Li, M.; Liu, Y.; Washington, C.; Coolen, L.M.; Fan, F.; Roman, R.J. 20-HETE Enzymes and Receptors in the Neurovascular Unit: Implications in Cerebrovascular Disease. *Front. Neurol.* **2020**, *11*, 983. https://doi.org/10.3389/fneur.2020.00983.
154. Gonzalez-Fernandez, E.; Liu, Y.; Auchus, A.P.; Fan, F.; Roman, R.J. Vascular contributions to cognitive impairment and dementia: The emerging role of 20-HETE. *Clin. Sci.* **2021**, *135*, 1929–1944. https://doi.org/10.1042/cs20201033.
155. Atone, J.; Wagner, K.; Hashimoto, K.; Hammock, B.D. Cytochrome P450 derived epoxidized fatty acids as a therapeutic tool against neuroinflammatory diseases. *Prostaglandins Other Lipid Mediat.* **2020**, *147*, 106385. https://doi.org/10.1016/j.prostaglandins.2019.106385.
156. Davis, C.M.; Liu, X.; Alkayed, N.J. Cytochrome P450 eicosanoids in cerebrovascular function and disease. *Pharmacol. Ther.* **2017**, *179*, 31–46. https://doi.org/10.1016/j.pharmthera.2017.05.004.
157. Yuan, W.Q.; Huang, W.P.; Jiang, Y.C.; Xu, H.; Duan, C.S.; Chen, N.H.; Liu, Y.J.; Fu, X.M. The function of astrocytes and their role in neurological diseases. *Eur. J. Neurosci.* **2023**, *58*, 3932–3961. https://doi.org/10.1111/ejn.16160.
158. Guo, C.; Sun, L.; Chen, X.; Zhang, D. Oxidative stress, mitochondrial damage and neurodegenerative diseases. *Neural Regen. Res.* **2013**, *8*, 2003–2014.
159. Zhang, M.; Wang, S.; Mao, L.; Leak, R.K.; Shi, Y.; Zhang, W.; Hu, X.; Sun, B.; Cao, G.; Gao, Y. Omega-3 fatty acids protect the brain against ischemic injury by activating Nrf2 and upregulating heme oxygenase 1. *J. Neurosci.* **2014**, *34*, 1903–1915.
160. Fan, R.; Peng, X.; Xie, L.; Dong, K.; Ma, D.; Xu, W.; Shi, X.; Zhang, S.; Chen, J.; Yu, X.; et al. Importance of Bmal1 in Alzheimer's disease and associated aging-related diseases: Mechanisms and interventions. *Aging Cell* **2022**, *21*, e13704. https://doi.org/10.1111/acel.13704.
161. Nakato, M.; Matsuo, M.; Kono, N.; Arita, M.; Arai, H.; Ogawa, J.; Kioka, N.; Ueda, K. Neurite outgrowth stimulation by n-3 and n-6 PUFAs of phospholipids in apoE-containing lipoproteins secreted from glial cells. *J. Lipid Res.* **2015**, *56*, 1880–1890.
162. Alessandri, J.-M.; Guesnet, P.; Vancassel, S.; Astorg, P.; Denis, I.; Langelier, B.; Aïd, S.; Poumès-Ballihaut, C.; Champeil-Potokar, G.; Lavialle, M. Polyunsaturated fatty acids in the central nervous system: Evolution of concepts and nutritional implications throughout life. *Reprod. Nutr. Dev.* **2004**, *44*, 509–538.
163. Lavialle, M.; Champeil-Potokar, G.; Alessandri, J.M.; Balasse, L.; Guesnet, P.; Papillon, C.; Pévet, P.; Vancassel, S.; Vivien-Roels, B.; Denis, I. An (n-3) Polyunsaturated Fatty Acid–Deficient Diet Disturbs Daily Locomotor Activity, Melatonin Rhythm, and Striatal Dopamine in Syrian Hamsters13. *J. Nutr.* **2008**, *138*, 1719–1724.
164. Ruggiero, C.; Lattanzio, F.; Lauretani, F.; Gasperini, B.; Andres-Lacueva, C.; Cherubini, A. Omega-3 polyunsaturated fatty acids and immune-mediated diseases: Inflammatory bowel disease and rheumatoid arthritis. *Curr. Pharm. Des.* **2009**, *15*, 4135–4148. https://doi.org/10.2174/138161209789909746.
165. Calder, P. PUFA, inflammatory processes and rheumatoid arthritis. *Proc. Nutr. Soc.* **2008**, *67*, 409–418.
166. Araújo, A.C.; Wheelock, C.E.; Haeggström, J.Z. The Eicosanoids, Redox-Regulated Lipid Mediators in Immunometabolic Disorders. *Antioxid. Redox Signal* **2018**, *29*, 275–296. https://doi.org/10.1089/ars.2017.7332.
167. Miyata, J.; Fukunaga, K.; Kawashima, Y.; Ohara, O.; Kawana, A.; Asano, K.; Arita, M. Dysregulated metabolism of polyunsaturated fatty acids in eosinophilic allergic diseases. *Prostaglandins Other Lipid Mediat.* **2020**, *150*, 106477. https://doi.org/10.1016/j.prostaglandins.2020.106477.
168. Kalinski, P. Regulation of immune responses by prostaglandin E2. *J. Immunol.* **2012**, *188*, 21–28. https://doi.org/10.4049/jimmunol.1101029.
169. Tsuge, K.; Inazumi, T.; Shimamoto, A.; Sugimoto, Y. Molecular mechanisms underlying prostaglandin E2-exacerbated inflammation and immune diseases. *Int. Immunol.* **2019**, *31*, 597–606. https://doi.org/10.1093/intimm/dxz021.

170. Henderson, W.R., Jr. The role of leukotrienes in inflammation. *Ann. Intern. Med.* **1994**, *121*, 684–697. https://doi.org/10.7326/0003-4819-121-9-199411010-00010.
171. Korotkova, M.; Jakobsson, P.J. Persisting eicosanoid pathways in rheumatic diseases. *Nat. Rev. Rheumatol.* **2014**, *10*, 229–241. https://doi.org/10.1038/nrrheum.2014.1.
172. Li, K.; Zhao, J.; Wang, M.; Niu, L.; Wang, Y.; Li, Y.; Zheng, Y. The roles of various prostaglandins in fibrosis: A review. *Biomolecules* **2021**, *11*, 789.
173. Serhan, C.N.; Petasis, N.A. Resolvins and protectins in inflammation resolution. *Chem. Rev.* **2011**, *111*, 5922–5943. https://doi.org/10.1021/cr100396c.
174. Lee, H.N.; Surh, Y.J. Therapeutic potential of resolvins in the prevention and treatment of inflammatory disorders. *Biochem. Pharmacol.* **2012**, *84*, 1340–1350. https://doi.org/10.1016/j.bcp.2012.08.004.
175. Morisseau, C.; Hammock, B.D. Impact of soluble epoxide hydrolase and epoxyeicosanoids on human health. *Annu. Rev. Pharmacol. Toxicol.* **2013**, *53*, 37–58. https://doi.org/10.1146/annurev-pharmtox-011112-140244.
176. Shoieb, S.M.; El-Ghiaty, M.A.; Alqahtani, M.A.; El-Kadi, A.O. Cytochrome P450-derived eicosanoids and inflammation in liver diseases. *Prostaglandins Other Lipid Mediat.* **2020**, *147*, 106400.
177. Hoxha, M.; Zappacosta, B. CYP-derived eicosanoids: Implications for rheumatoid arthritis. *Prostaglandins Other Lipid Mediat.* **2020**, *146*, 106405. https://doi.org/10.1016/j.prostaglandins.2019.106405.
178. Gilroy, D.W.; Bishop-Bailey, D. Lipid mediators in immune regulation and resolution. *Br. J. Pharmacol.* **2019**, *176*, 1009–1023. https://doi.org/10.1111/bph.14587.
179. Dai, M.; Wu, L.; He, Z.; Zhang, S.; Chen, C.; Xu, X.; Wang, P.; Gruzdev, A.; Zeldin, D.C.; Wang, D.W. Epoxyeicosatrienoic acids regulate macrophage polarization and prevent LPS-induced cardiac dysfunction. *J. Cell Physiol.* **2015**, *230*, 2108–2119. https://doi.org/10.1002/jcp.24939.
180. Man, K.; Loudon, A.; Chawla, A. Immunity around the clock. *Science* **2016**, *354*, 999–1003. https://doi.org/10.1126/science.aah4966.
181. Straub, R.H.; Cutolo, M. Circadian rhythms in rheumatoid arthritis: Implications for pathophysiology and therapeutic management. *Arthritis Rheum.* **2007**, *56*, 399–408. https://doi.org/10.1002/art.22368.
182. Cutolo, M.; Seriolo, B.; Craviotto, C.; Pizzorni, C.; Sulli, A. Circadian rhythms in RA. *Ann. Rheum. Dis.* **2003**, *62*, 593–596.
183. Hand, L.E.; Hopwood, T.W.; Dickson, S.H.; Walker, A.L.; Loudon, A.S.; Ray, D.W.; Bechtold, D.A.; Gibbs, J.E. The circadian clock regulates inflammatory arthritis. *Faseb J.* **2016**, *30*, 3759–3770. https://doi.org/10.1096/fj.201600353R.
184. Jahanban-Esfahlan, R.; Mehrzadi, S.; Reiter, R.J.; Seidi, K.; Majidinia, M.; Baghi, H.B.; Khatami, N.; Yousefi, B.; Sadeghpour, A. Melatonin in regulation of inflammatory pathways in rheumatoid arthritis and osteoarthritis: Involvement of circadian clock genes. *Br. J. Pharmacol.* **2018**, *175*, 3230–3238. https://doi.org/10.1111/bph.13898.
185. Norling, L.V.; Perretti, M. The role of omega-3 derived resolvins in arthritis. *Curr. Opin. Pharmacol.* **2013**, *13*, 476–481. https://doi.org/10.1016/j.coph.2013.02.003.
186. Cox, S.L.; O'Siorain, J.R.; Fagan, L.E.; Curtis, A.M.; Carroll, R.G. Intertwining roles of circadian and metabolic regulation of the innate immune response. *Semin. Immunopathol.* **2022**, *44*, 225–237. https://doi.org/10.1007/s00281-021-00905-5.
187. Kouri, V.P.; Olkkonen, J.; Kaivosoja, E.; Ainola, M.; Juhila, J.; Hovatta, I.; Konttinen, Y.T.; Mandelin, J. Circadian timekeeping is disturbed in rheumatoid arthritis at molecular level. *PLoS ONE* **2013**, *8*, e54049. https://doi.org/10.1371/journal.pone.0054049.
188. Gibbs, J.E.; Ray, D.W. The role of the circadian clock in rheumatoid arthritis. *Arthritis Res. Ther.* **2013**, *15*, 205. https://doi.org/10.1186/ar4146.
189. Dar, M.I.; Hussain, Y.; Pan, X. Roles of Circadian Clocks in Macrophage Metabolism and Cardiovascular Disease: Implications in Inflammation, and Metabolism of Lipids, Glucose, and Amino Acids. *Med. Pharmacol.* **2024**, *not peer.*
190. Curtis, A.M.; Fagundes, C.T.; Yang, G.; Palsson-McDermott, E.M.; Wochal, P.; McGettrick, A.F.; Foley, N.H.; Early, J.O.; Chen, L.; Zhang, H.; et al. Circadian control of innate immunity in macrophages by miR-155 targeting Bmal1. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 7231–7236. https://doi.org/10.1073/pnas.1501327112.
191. Laria, A.; Lurati, A.; Marrazza, M.; Mazzocchi, D.; Re, K.A.; Scarpellini, M. The macrophages in rheumatic diseases. *J. Inflamm. Res.* **2016**, *9*, 1–11. https://doi.org/10.2147/jir.S82320.
192. Schouten, M.; Bielefeld, P.; Garcia-Corzo, L.; Passchier, E.M.J.; Gradari, S.; Jungenitz, T.; Pons-Espinal, M.; Gebara, E.; Martín-Suárez, S.; Lucassen, P.J.; et al. Circadian glucocorticoid oscillations preserve a population of adult hippocampal neural stem cells in the aging brain. *Mol. Psychiatry* **2020**, *25*, 1382–1405. https://doi.org/10.1038/s41380-019-0440-2.
193. Hua, C.; Buttgereit, F.; Combe, B. Glucocorticoids in rheumatoid arthritis: Current status and future studies. *RMD Open* **2020**, *6*, e000536. https://doi.org/10.1136/rmdopen-2017-000536.

194. Franzago, M.; Alessandrelli, E.; Notarangelo, S.; Stuppia, L.; Vitacolonna, E. Chrono-Nutrition: Circadian Rhythm and Personalized Nutrition. *Int. J. Mol. Sci.* **2023**, *24*, 2571. https://doi.org/10.3390/ijms24032571.
195. Roenneberg, T.; Allebrandt, K.V.; Merrow, M.; Vetter, C. Social jetlag and obesity. *Curr. Biol.* **2012**, *22*, 939–943. https://doi.org/10.1016/j.cub.2012.03.038.
196. Katsi, V.; Papakonstantinou, I.P.; Soulaidopoulos, S.; Katsiki, N.; Tsioufis, K. Chrononutrition in Cardiometabolic Health. *J. Clin. Med.* **2022**, *11*, 296. https://doi.org/10.3390/jcm11020296.
197. Calder, P.C. Omega-3 fatty acids and inflammatory processes. *Nutrients* **2010**, *2*, 355–374. https://doi.org/10.3390/nu2030355.
198. Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. *N. Engl. J. Med.* **1987**, *317*, 1736–1737.
199. Bonten, T.N.; Snoep, J.D.; Assendelft, W.J.; Zwaginga, J.J.; Eikenboom, J.; Huisman, M.V.; Rosendaal, F.R.; van der Bom, J.G. Time-dependent effects of aspirin on blood pressure and morning platelet reactivity: A randomized cross-over trial. *Hypertension* **2015**, *65*, 743–750. https://doi.org/10.1161/hypertensionaha.114.04980.
200. Bhatt, D.L.; Steg, P.G.; Miller, M.; Brinton, E.A.; Jacobson, T.A.; Ketchum, S.B.; Doyle, R.T., Jr.; Juliano, R.A.; Jiao, L.; Granowitz, C.; et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N. Engl. J. Med.* **2019**, *380*, 11–22. https://doi.org/10.1056/NEJMoa1812792.
201. Delpino, F.M.; Figueiredo, L.M.; da Silva, B.G.C.; da Silva, T.G.; Mintem, G.C.; Bielemann, R.M.; Gigante, D.P. Omega-3 supplementation and diabetes: A systematic review and meta-analysis. *Crit. Rev. Food Sci. Nutr.* **2022**, *62*, 4435–4448. https://doi.org/10.1080/10408398.2021.1875977.
202. Brown, T.J.; Brainard, J.; Song, F.; Wang, X.; Abdelhamid, A.; Hooper, L. Omega-3, omega-6, and total dietary polyunsaturated fat for prevention and treatment of type 2 diabetes mellitus: Systematic review and meta-analysis of randomised controlled trials. *BMJ* **2019**, *366*, l4697.
203. Dufoo-Hurtado, E.; Wall-Medrano, A.; Campos-Vega, R. Molecular mechanisms of chronobiotics as functional foods. *Mol. Mech. Funct. Food* **2022**, 57–86. https://doi.org/10.1002/9781119804055.ch3.
204. Neves, A.R.; Albuquerque, T.; Quintela, T.; Costa, D. Circadian rhythm and disease: Relationship, new insights, and future perspectives. *J. Cell Physiol.* **2022**, *237*, 3239–3256. https://doi.org/10.1002/jcp.30815.
205. Yurko-Mauro, K.; Alexander, D.D.; Van Elswyk, M.E. Docosahexaenoic acid and adult memory: A systematic review and meta-analysis. *PLoS ONE* **2015**, *10*, e0120391. https://doi.org/10.1371/journal.pone.0120391.
206. Chang, Y.Y.; Ting, B.; Chen, D.T.; Hsu, W.T.; Lin, S.C.; Kuo, C.Y.; Wang, M.F. Omega-3 Fatty Acids for Depression in the Elderly and Patients with Dementia: A Systematic Review and Meta-Analysis. *Healthcare* **2024**, *12*, 536. https://doi.org/10.3390/healthcare12050536.
207. Zhang, Z.; Xin, H.; Li, M.D. Circadian rhythm of lipid metabolism in health and disease. *Small Methods* **2020**, *4*, 1900601.
208. Gooley, J.J.; Chua, E.C. Diurnal regulation of lipid metabolism and applications of circadian lipidomics. *J. Genet. Genomics* **2014**, *41*, 231–250. https://doi.org/10.1016/j.jgg.2014.04.001.
209. Li, X.; Joehanes, R.; Hoeschele, I.; Rich, S.S.; Rotter, J.I.; Levy, D.; Liu, Y.; Redline, S.; Sofer, T. Association between sleep disordered breathing and epigenetic age acceleration: Evidence from the Multi-Ethnic Study of Atherosclerosis. *EBioMedicine* **2019**, *50*, 387–394. https://doi.org/10.1016/j.ebiom.2019.11.020.
210. Blacher, E.; Tsai, C.; Litichevskiy, L.; Shipony, Z.; Iweka, C.A.; Schneider, K.M.; Chuluun, B.; Heller, H.C.; Menon, V.; Thaiss, C.A.; et al. Aging disrupts circadian gene regulation and function in macrophages. *Nat. Immunol.* **2022**, *23*, 229–236. https://doi.org/10.1038/s41590-021-01083-0.
211. Colombini, B.; Dinu, M.; Murgo, E.; Lotti, S.; Tarquini, R.; Sofi, F.; Mazzoccoli, G. Ageing and Low-Level Chronic Inflammation: The Role of the Biological Clock. *Antioxidants* **2022**, *11*, 2228. https://doi.org/10.3390/antiox11112228.
212. Cutuli, D. Functional and Structural Benefits Induced by Omega-3 Polyunsaturated Fatty Acids During Aging. *Curr. Neuropharmacol.* **2017**, *15*, 534–542. https://doi.org/10.2174/1570159x14666160614091311.
213. Külzow, N.; Witte, A.V.; Kerti, L.; Grittner, U.; Schuchardt, J.P.; Hahn, A.; Flöel, A. Impact of Omega-3 Fatty Acid Supplementation on Memory Functions in Healthy Older Adults. *J. Alzheimers Dis.* **2016**, *51*, 713–725. https://doi.org/10.3233/jad-150886.
214. Childs, C.E.; Romeu-Nadal, M.; Burdge, G.C.; Calder, P.C. Gender differences in the n-3 fatty acid content of tissues. *Proc. Nutr. Soc.* **2008**, *67*, 19–27. https://doi.org/10.1017/s0029665108005983.
215. Cutolo, M.; Sulli, A.; Capellino, S.; Villaggio, B.; Montagna, P.; Seriolo, B.; Straub, R.H. Sex hormones influence on the immune system: Basic and clinical aspects in autoimmunity. *Lupus* **2004**, *13*, 635–638. https://doi.org/10.1191/0961203304lu1094oa.
216. Nakamura, T.J.; Sellix, M.T.; Menaker, M.; Block, G.D. Estrogen directly modulates circadian rhythms of PER2 expression in the uterus. *Am. J. Physiol. Endocrinol. Metab.* **2008**, *295*, E1025–E1031. https://doi.org/10.1152/ajpendo.90392.2008.

217. Bailey, M.; Silver, R. Sex differences in circadian timing systems: Implications for disease. *Front. Neuroendocrinol.* **2014**, *35*, 111–139. https://doi.org/10.1016/j.yfrne.2013.11.003.
218. Škrlec, I.; Talapko, J.; Džijan, S.; Cesar, V.; Lazić, N.; Lepeduš, H. The Association between Circadian Clock Gene Polymorphisms and Metabolic Syndrome: A Systematic Review and Meta-Analysis. *Biology* **2021**, *11*, 20. https://doi.org/10.3390/biology11010020.
219. Ameur, A.; Enroth, S.; Johansson, A.; Zaboli, G.; Igl, W.; Johansson, A.C.; Rivas, M.A.; Daly, M.J.; Schmitz, G.; Hicks, A.A.; et al. Genetic adaptation of fatty-acid metabolism: A human-specific haplotype increasing the biosynthesis of long-chain omega-3 and omega-6 fatty acids. *Am. J. Hum. Genet.* **2012**, *90*, 809–820. https://doi.org/10.1016/j.ajhg.2012.03.014.
220. Brenna, J.T.; Salem, N., Jr.; Sinclair, A.J.; Cunnane, S.C. alpha-Linolenic acid supplementation and conversion to n-3 long-chain polyunsaturated fatty acids in humans. *Prostaglandins Leukot. Essent. Fatty Acids* **2009**, *80*, 85–91. https://doi.org/10.1016/j.plefa.2009.01.004.
221. Serhiyenko, V.; Segin, V.; Serhiyenko, A. Effects of omega-3 polyunsaturated fatty acids on the circadian rhythm of heart rate variability parameters in patients with type 2 diabetes mellitus and cardiovascular autonomic neuropathy. *Российский Кардиологический журнал* **2018**, *5*, 56–60.
222. Mazaherioun, M.; Djalali, M.; Koohdani, F.; Javanbakht, M.H.; Zarei, M.; Beigy, M.; Ansari, S.; Rezvan, N.; Saedisomeolia, A. Beneficial Effects of n-3 Fatty Acids on Cardiometabolic and Inflammatory Markers in Type 2 Diabetes Mellitus: A Clinical Trial. *Med. Princ. Pract.* **2017**, *26*, 535–541. https://doi.org/10.1159/000484089.
223. Marcheva, B.; Ramsey, K.M.; Buhr, E.D.; Kobayashi, Y.; Su, H.; Ko, C.H.; Ivanova, G.; Omura, C.; Mo, S.; Vitaterna, M.H.; et al. Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinaemia and diabetes. *Nature* **2010**, *466*, 627–631. https://doi.org/10.1038/nature09253.
224. Arnardottir, E.S.; Mackiewicz, M.; Gislason, T.; Teff, K.L.; Pack, A.I. Molecular signatures of obstructive sleep apnea in adults: A review and perspective. *Sleep* **2009**, *32*, 447–470. https://doi.org/10.1093/sleep/32.4.447.
225. Jump, D.B.; Depner, C.M.; Tripathy, S. Omega-3 fatty acid supplementation and cardiovascular disease: Thematic review series: New lipid and lipoprotein targets for the treatment of cardiometabolic diseases. *J. Lipid Res.* **2012**, *53*, 2525–2545
226. Calder, P.C. Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. *Biochim. Biophys. Acta* **2015**, *1851*, 469–484. https://doi.org/10.1016/j.bbalip.2014.08.010.
227. Dashti, H.S.; Follis, J.L.; Smith, C.E.; Tanaka, T.; Garaulet, M.; Gottlieb, D.J.; Hruby, A.; Jacques, P.F.; Kiefte-de Jong, J.C.; Lamon-Fava, S.; et al. Gene-Environment Interactions of Circadian-Related Genes for Cardiometabolic Traits. *Diabetes Care* **2015**, *38*, 1456–1466. https://doi.org/10.2337/dc14-2709.
228. Abdelhamid, A.S.; Brown, T.J.; Brainard, J.S.; Biswas, P.; Thorpe, G.C.; Moore, H.J.; Deane, K.H.; Summerbell, C.D.; Worthington, H.V.; Song, F.; et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst. Rev.* **2020**, *3*, Cd003177. https://doi.org/10.1002/14651858.CD003177.pub5.
229. Maury, E. Off the clock: From circadian disruption to metabolic disease. *Int. J. Mol. Sci.* **2019**, *20*, 1597.
230. Simopoulos, A.P. An Increase in the Omega-6/Omega-3 Fatty Acid Ratio Increases the Risk for Obesity. *Nutrients* **2016**, *8*, 128. https://doi.org/10.3390/nu8030128.
231. Calder, P.C. Omega-3 fatty acids and inflammatory processes: From molecules to man. *Biochem. Soc. Trans.* **2017**, *45*, 1105–1115. https://doi.org/10.1042/bst20160474.
232. Lukiw, W.J.; Bazan, N.G. Docosahexaenoic acid and the aging brain. *J. Nutr.* **2008**, *138*, 2510–2514. https://doi.org/10.3945/jn.108.096016.