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Supplement Article

The circadian rhythm as therapeutic target in inflammatory bowel disease

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Abstract

The primary objectives of the management of patients with inflammatory bowel disease (IBD) are to prevent IBD flares, prevent/delay disease progression and improve patients' quality of life. To this end, one needs to identify risk factor(s) associated with flare-ups and disease progression. We posit that disruption of circadian rhythms is one of the key factors that is associated with risk of flare-up and disease progression. This hypothesis is based on published studies that show: (1) The circadian rhythm regulates many biological processes including multiple IBD-relevant biological processes that are critical in inflammatory/immune processes such as environment/microbe interaction, microbe/host interaction, intestinal barrier integrity and mucosal immunity—all central in the pathogenesis of IBD, and (2) Circadian machinery is the primary tool for the host to interact with the environment. Circadian misalignment results in a loss of preparedness of the host to respond and adjust to the environmental changes that could make the host more vulnerable to IBD flare-ups. In this review, we first provide an overview of circadian rhythms and its role in healthy and disease states. Then we present data to support our hypothesis that: (1) IBD patients have disrupted circadian rhythms ("social jet lag") and (2) circadian misalignment and associated disrupted sleep decreases the resiliency of IBD patients resulting in microbiota dysbiosis, more disrupted intestinal barrier integrity and a more aggressive disease phenotype. We also show that circadian-directed interventions have a potential to mitigate the deleterious impact of disrupted circadian and improve IBD disease course.

Keywords: inflammatory bowel disease; circadian rhythm; circadian misalignment; chronotherapy; chrononutrition

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory condition, including Crohn's disease (CD) and ulcerative colitis, which involves inflammation of the intestinal mucosa due to a dysregulated immune system.[1] The mainstay of treatment involves controlling the inflammatory response, preventing disease flare-ups, and improving quality of life. Yet, despite several biologics with potent anti-inflammatory properties, at least 40% of IBD patients continue to have inflammation, frequent flare-ups, and complications leading to hospitalization and even surgery in a subset of these patients. Thus, there is still an urgent unmet need to better understand the risk factors that decrease the resiliency of IBD patients to better control gut inflammation and immune dysregulation that is required to maintain long-lasting remission. We posit that disrupted circadian homeostasis is such a risk factor. This hypothesis is based on published studies that show: (1) The circadian rhythm regulates many biological processes that play an important role in the pathophysiology of IBD[2] and (2) circadian machinery is the primary tool for the host and its gut microbiome to interact with the environment.[3] Circadian misalignment results in loss of preparedness of the host to respond and adjust to the environmental changes.[4,5] This could make the host more vulnerable to IBD flare-ups. In this review, we will first provide an overview of circadian rhythms and their role in healthy and disease states. Then, we will (1) summarize evidence showing that a disrupted circadian rhythm could promote an aggressive IBD disease course/phenotype and evidence that shows that circadian misalignment could be one of the triggers for an IBD flare-up and (2) provide evidence that circadian hygiene and chronobiology are underappreciated but potentially important tools to optimize IBD management.

Circadian rhythms and triggers for circadian disruption

The very first description of the circadian rhythm dates back to 1729, when Jean-Jacques de Mairan described the daily rhythm of mimosa plant leaves opening and closing, which persisted when placed in darkness. We have since learned about the complexities of the circadian rhythm, including the central and peripheral circadian rhythms with their intrinsic clocks and the need for external stimuli/cues.[6] The

master pacemaker of the circadian rhythm is the suprachiasmatic nucleus (SCN), located in the hypothalamus.[6] When removed from its central location and examined ex vivo, it continues to show rhythmic expression of proteins for over a year,[7] demonstrating its intrinsic pacemaker capabilities. The primary function of the circadian machinery is to prepare the host to respond to environmental cues and to coordinate that response among the different organ systems. The circadian machinery is the essential "language" for the bidirectional crosstalk between the host and environment and among the host's different organs. This function is achieved through (1) ensuring circadian rhythmicity throughout the body by a bidirectional relationship between the master clock and peripheral clocks, in which the central clock regulates the peripheral clocks, and the peripheral clocks conversely influence the central clock, and (2) neuronal and endocrine systems, such as the hypothalamic-pituitary-adrenal axis.[8] It is thus not surprising that disruption of circadian homeostasis would compromise the host to respond to the environmental triggers and increase the risk of pathologies.[9]

How does circadian machinery achieve its daunting function? In brief, on a cellular level, circadian locomotor output cycles kaput (CLOCK) and neuronal PAS domain-containing protein 2 (NPAS2) form a heterodimer with aryl hydrocarbon receptor nuclear translocator-like protein 1 (ARNTL, also known as BMAL1).[10,11] During the natural daytime, this heterodimer functions as a transcription factor for period circadian homologues (PER1, PER2, and PER3) and cryptochromes (CRY1 and CRY2).[12] At night, a negative feedback process occurs in which PER and CRY form a heterodimer to suppress CLOCK and BMAL1 and break down PER and CRY proteins.[11] As PER and CRY proteins are being degraded, CLOCK and BMAL1 can again form heterodimers and start the process from the start as the daytime begins. Other proteins that play an important role in the clock mechanism and that will appear in this review are REV-ERBα, REV-ERBβ and RAR-related orphan receptors α, β and γ (RORα, RORβ, and RORγ).[13,14] They form complexes with ROR/REV-ERB-response elements (RORE), leading to antiphase oscillation between BMAL1 and PER2.[11] Remarkably, most of our organs and organ systems have circadian machinery. A study in male baboons demonstrated that over 80% of protein-coding genes are under circadian control.[15] In addition, epigenetic modifications, post-transcriptional, and post-translational processes are also involved in creating daily rhythms.[11,16]

Circadian disruption, or circadian dysrhythmia/misalignment, can occur when the body receives signals that promote a particular phase of the circadian rhythm at the wrong time, and is associated with numerous diseases, including gastrointestinal disease.[2,17] A disrupted circadian rhythm likely decreases resiliency to disease,[2] as evidenced by worsening of intestinal barrier disruption, endotoxemia and steatohepatitis in alcohol-fed mice when their circadian rhythm is disrupted.[4] Signals that can influence the circadian rhythm are called Zeitgebers, which is German for "time givers". Common zeitgebers are light (the primary cue for the central circadian clock), eating (the primary cue for intestinal and liver circadian rhythms), exercise, and temperature.[18] Activities that can lead to circadian disruption are shift work (activity when the body naturally rests), jet lag (travel across multiple time zones), social jet lag (variation in sleep/wake time on weekdays versus weekend days), late night eating (when the body is naturally fasting), bright street lights and use of light-emitting devices at night-time (when the body is naturally exposed to darkness).[2,17] Even a 1-h shift, as occurs with daylight savings time, has been associated with increased risk of disease and body function compromise, such as myocardial infarction and car accidents.[19,20] Bright light at the wrong time, such as at night when the sun is down, leads to altered levels of melatonin and cortisol[18] and can impair cognitive performance.[21] When food is ingested at the wrong time (wrong time eating, WTE), misalignment can occur between the peripheral clock and the central clock.[22] Disruption of the circadian rhythm also occurs when an individual's day and night rhythm does not align with their chronotype, which is their biological pattern for sleep and wake cycles. There are 3 main types, the early bird or early chronotype (tendency towards early wake time), the night owl or evening chronotype (tendency towards staying up late) and an intermediate type.[2]

Sleep, circadian, and IBD

Patients with IBD tend to have poor sleep quality, which is associated with worsening of disease activity and quality of life and increased risk of disease flares.[2,23–26] Healthy individuals who received the proinflammatory cytokine interleukin-6 (IL-6) parenterally developed significant fatigue, had suppression of their REM sleep, and demonstrated changes in their slow wave sleep.[27] Sleep deprivation can promote a proinflammatory state as evidenced by elevated IL-6 and white blood cell levels during daytime.[25,28,29] Conversely, the presence of intestinal inflammation can result in sleep disturbance, causing a vicious cycle for the patient.[25,30] It should be noted that even in the absence of overt inflammation, IBD patients tend to have impaired sleep quality.[31]

Disruption of the circadian rhythm has been associated with worse outcomes in IBD. Increased rest-activity fragmentation, suggestive of circadian disruption, in patients with IBD is associated with increased systemic inflammation and an increase in pro-inflammatory microbiome.[32] A genetic polymorphism in PER3, one of the clock genes, is associated with a more aggressive disease phenotype in CD.[33] In addition, IBD patients with an evening chronotype tend to have a more severe disease course requiring escalation to biological therapies[23,34] and CD patients with social jet lag or sleep deprivation tend to have a more aggressive disease phenotype and complications.[35,36]

In mice, sleep deprivation resulted in worse colitis after administration of dextran sodium sulfate (DSS), but not in the absence of DSS exposure.[37] In a similar study, shifting light/dark cycles in mice led to worse colitis after DSS exposure, but again these changes were not observed in the circadian disrupted mice without DSS.[5] In a mouse model with colon-specific genetic circadian disruption (BMAL1 knock out in colonic epithelial cells), administration of DSS led to worse colitis as compared to non-circadian disrupted mice.[38] These animal studies demonstrate that sleep deprivation and circadian disruption alone do not cause an inflammatory response, but rather increase the susceptibility to inflammation after exposure to a pro-inflammatory insult. In later studies, it was found that circadian disruption was associated with intestinal barrier dysfunction, likely predisposing mice to worsening inflammation.[4] Additionally, circadian disruption

was associated with decreased production of short-chain fatty acids, an essential energy source for the intestinal epithelial cells that tend to have protective effects on the intestinal barrier function.[38]

Circadian rhythmicity of the immune system

In patients with IBD, the immune system and its inflammatory response are in overdrive. The inflammatory response with its proinflammatory cytokines such as IL-6, tumour necrosis factor alpha (TNFα), and IL-17, as well as leukocyte recruitment and homing facilitated by chemokines are under control of the circadian clock.[39,40] BMAL1 was found to regulate the expression of chemokine CXCL5 regulating neutrophil trafficking, REV-ERBα regulates gene expression in macrophages to control inflammation, and RORγ is involved in the development and differentiation of IL-17 secreting T-helper cells.[41–43] Based on multiple studies in healthy individuals, it was discovered that the immune system is most active in the evening and early night.[44–47] Genetic disruption of the circadian mechanism leads to opposing effects on the immune system: mice with CLOCK knockout have lower levels of proinflammatory cytokines, whereas mice with CRY knockout have increased levels,[48,49] emphasizing the importance of an intact circadian machinery in control of the inflammatory response. Conversely, the presence of inflammation in itself can alter the expression of clock genes, potentially worsening the detrimental inflammatory process due to lack of regulation.[50] In a mouse model, exposure to DSS markedly reduced the basal expression of circadian genes within the colon.[51] In an in vitro study, TNFα and TGFβ both reduced the expression of cold inducible RNA-binding protein, which under normal circumstances promotes expression of clock genes.[52] Other cytokines including IL-1β, IL-6, IFNα, and IFNγ did not alter the expression in this study. Furthermore, TGFβ suppresses the negative circadian clock regulators Per1, Per2, Per3, Rev-erbα, RORα, and DBP.[52] Taken together, this suggests a bidirectional relationship between the circadian machinery and the immune system (Figure 1).

Circadian rhythm disruption and intestinal barrier function

The intestinal barrier protects the body from toxins and environmental factors that may trigger inflammation when encountering the immune system. When the barrier is dysfunctional, referred to as gut leak, proteins that are foreign to the body or bacterial products such as endotoxins can illicit or worsen an inflammatory response such as in IBD.[53] The robustness of the intestinal barrier has a circadian machinery.[54,55] Disruption of the circadian rhythm increases the susceptibility of the intestinal mucosa to injury,[4,5] as apical junctional complex proteins that form tight junctions within the intestinal barrier are under direct control by the circadian rhythm.[56] This was further demonstrated in a mouse model where circadian disruption resulted in gut leak and was further exacerbated by alcohol ingestion.[57] In chronically shifted mice, who displayed disrupted circadian rhythms, there was evidence of increased intestinal permeability with a loss of barrier function.[58] This is further demonstrated by an inverse relationship between the severity of gut leak and serum melatonin levels, a marker of circadian output.[59,60] A similar effect is seen in humans, where individuals who work night shifts have worse gut leak after drinking 1 glass of red wine for 7 days as compared to day shift workers.[61] In addition, higher rates of IBD are seen in shift workers when compared to non-shift workers.[62]

Circadian rhythm disruption and the microbiome

The microbiome plays an integral part in maintaining the intestinal barrier, digestion of food and the production of hormones.[3] Just as most of the cells in the body have a circadian rhythm, the composition of the gut microbiome and the production of metabolites (such as short chain fatty acids (SCFA)) changes throughout the day,[63,64] in turn, affecting the host's circadian rhythm.[65,66] In germ-free mice, small intestine epithelial cells have a loss of diurnal variation in gene expression,[67] thought to be due to loss of cyclical histone acetylation with a reduction in histone deacetylase 3 (HDAC3) recruitment, demonstrating the importance of the gut microbiome in circadian rhythm function. The host and microbial circadian rhythm processes appear to have a bidirectional relationship,[3] as the microbial circadian rhythm is in part regulated by the host core CLOCK mechanism, as evident by the loss of circadian variation when the host core CLOCK genes are genetically altered.[63] Disruption of the host circadian rhythm can affect the composition and function of the microbial community.[68–70] In mice with circadian disruption, their microbiome tends to have a higher abundance of proinflammatory bacteria and a decrease in health-promoting bacteria that produce SCFA and support the host immune system.[64,68,71] Circadian disruption increases the vulnerability of dysfunction. Light/dark disrupted mice on a regular diet had no alteration of their microbiome, but when fed a high-fat high sugar diet or alcohol-containing diet, their microbiome changed significantly.[68] In addition, WTE was associated with a decreased abundance of SCFA-producing bacteria and increased gut leak.[72] The importance of the microbiome is further evidenced by its protective mechanism in an alcohol-fed mouse model: an SCFA promoting prebiotic normalized the microbiota community and SCFA production, and slowed down colon carcinogenesis in alcohol-fed, WTE mice.[73] In addition to gut microbiome variations, the oral microbiome also shows diurnal variations, which were affected by food timing.[74,75] In addition, circadian rhythm has been shown to impact the oral microbiome in humans due to its influence on salivary flow, tooth function, and oral homeostasis.[76]

Circadian rhythm hygiene as a therapeutic target in the management of IBD

As demonstrated throughout this review, it is biologically imperative to have an appropriately functioning circadian rhythm. While the central circadian clock drives the peripheral circadian clocks, the peripheral circadian clocks can conversely affect the timing of the central circadian clock. The circadian rhythm, both centrally and peripherally, is influenced by external cues, such as light, food, and other bodily exposures (Figure 1). The strongest cue determines the flow of the rhythm. For example, the timing of food consumption can in fact overrule influential signals coming from the SCN.[77] Changing the external cues that impact the circadian

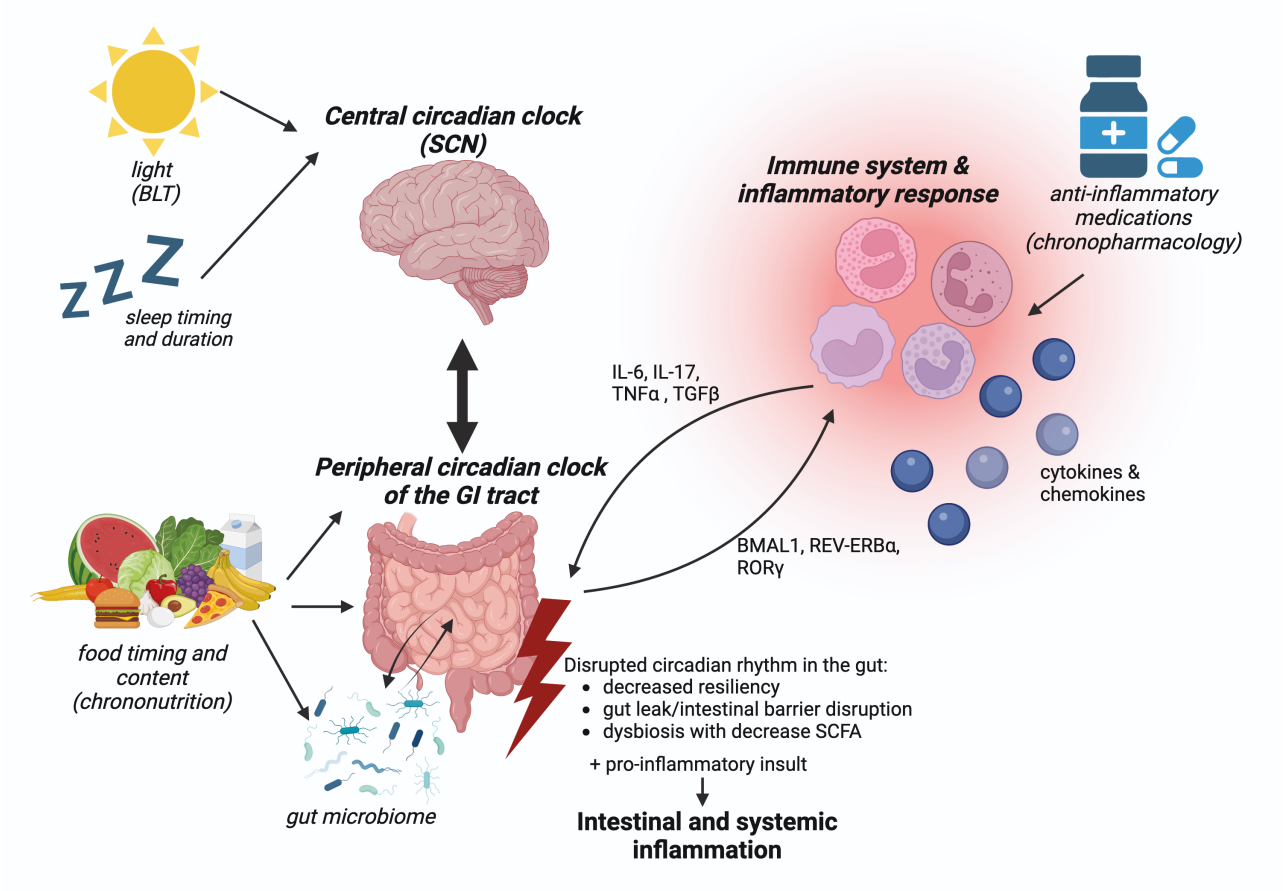

Figure 1. Schematic overview of the circadian rhythm with external and internal cues influencing its rhythm. There is a bidirectional relationship between the central and peripheral circadian rhythms, as well as a bidirectional relationship between circadian disruption (specifically within the gastrointestinal tract as discussed here) and the inflammatory response. BLT = bright light therapy; GI = gastrointestinal; IL = interleukin; SCFA = short chain fatty acids; SCN = suprachiasmatic nucleus; TGF = transforming growth factor; TNF = tumour necrosis factor. Created with BioRender.com.

rhythm can have a positive impact on the disease state in IBD as we will be showing in the following paragraphs.

Phototherapy in IBD

Bright light therapy (BLT), or phototherapy, refers to the non-invasive practice of exposing the human body to broad-spectrum bright light of 2000-10 000 lux during daytime when light exposure naturally occurs.[11] Its benefit is well known in the field of neuropsychiatry, where it helps patients with sleep disorders, seasonal affective/depressive disorders (by directly stimulating areas of the brain that regulate mood), attention deficit hyperactivity disorder, autism spectrum disorder, and delirium.[78–81] All these disorders are associated with disruption of the circadian rhythm,[82] and BLT is now studied in additional chronic diseases associated with circadian misalignment. For example, in animal models with myocardial infarction, BLT attenuated the size of the myocardial infarct through increased PER2 levels.[83] Translated to humans, ensuring appropriate light–dark patterns in the intensive care units is associated with better health outcomes.[78] In a randomized controlled trial looking at individuals with depression and diabetes, BLT improved both their mood and their insulin sensitivity.[84] Furthermore, exposure to blue light specifically during daytime hours promotes the nighttime circadian function of melatonin and was found to inhibit the growth of various cancer cell types.[85–87] More recently, studies have shown that "timed" BLT can either delay shift (when it is given in the evening before bedtime) or forward shift (when it is given in the morning at wake up time) and restore the disrupted circadian rhythms, such as those caused by jet lag, social jet lag or shift work.[88,89] The beneficial effects of phototherapy are even seen in individuals that are blind, if the pathway from the retinal ganglion cells to the SCN, known as the retinohypothalamic tract (RHT), and the rest of the brain are intact.[90,91] The effects of BLT in IBD remain unknown to date, but the prospect of its beneficial impact is intriguing since patients with IBD have known circadian misalignment with social jetlag and poor sleep.[23,24]

In addition to bright light therapy that focuses on light exposure at the *right time* during the day, efforts should be undertaken to minimize or eliminate light exposure at the *wrong time*, ie, nighttime. While studies on the effect of nighttime light exposure in IBD are lacking, studies have shown that even dim light exposure at night increases inflammatory responses.[92–94] Policies on light pollution and other environmental exposure to light would benefit not only IBD patients but also the general population.

Chrononutrition in IBD

Coordinating the time of food consumption with the circadian rhythm is referred to as chrononutrition.[2] Many processes related to the processing of food are under the

control of the circadian clock, including the uptake, synthesis, and digestion of nutrients.[95] By means of a bidirectional relationship, food intake and the activation of nutrient signalling pathways impacts CLOCK and CLOCK-controlled genes and downstream metabolic processes. One example of circadian disruption is wrong-time eating (WTE), which affects the peripheral circadian rhythm within the gastrointestinal tract and liver. In studies looking at obesity and metabolic syndrome in humans, consuming most calories earlier in the day can result in greater weight loss compared to later in the day, despite equal food intake.[96,97] The importance of meal timing is further demonstrated by the observation that consuming breakfast was associated with a normal oscillation pattern of CLOCK genes, whereas skipping breakfast adversely affected the expression of CLOCK and CLOCK-controlled genes in individuals with diabetes as well as healthy controls.[98,99] In addition, food timing influences the composition and daily rhythms of salivary microbiota within 1 week, and eating later in the day is associated with the pro-inflammatory composition of the oral microbiota.[75] Similar results were seen in an animal model, where it was demonstrated that WTE was associated with a higher abundance of pro-inflammatory microbiota and loss of normal circadian oscillation of SCFA-producing, anti-inflammatory bacteria.[65]

In addition to the time of the day, the duration of time during which food is consumed is of importance. Time-restricted feeding (TRF), in which food is consumed within a 6-8 h time frame during the active phase (daytime in humans, dark period in rodents), improves the internal circadian clock function and has beneficial health effects in metabolic disorders, including improvement in beta-cell function and insulin sensitivity,[100,101] and in oncologic diseases, by improving antitumour immune responses, inhibiting tumour growth, and increasing sensitivity to cancer treatment.[102] Similar to the timing of the day, TRF has a positive effect on gut microbiome composition.[95] TRF can increase microbial diversity and restore the disrupted circadian rhythm of the microbiome caused by inappropriate dietary habits (WTE and/or high-fat diet) in animal models.[103–105] These benefits are maintained when alternating between 5 days of TRF and 2 days of ad libitum consumption in mice, reflecting the human lifestyle of workdays and weekend days.[100] In addition, TRF restores the peripheral circadian rhythm within the gastrointestinal tract and the liver, and normalized body weight and glucose metabolism in mice with Bmal1 knockout in the hypothalamic suprachiasmatic nucleus living in complete darkness.[106] Chrononutrition might also be beneficial in IBD. For example, TRF ameliorated intestinal inflammation induced by DSS in mice,[107] suggesting that timed eating promotes intestinal healing in the setting of inflammation. However, the benefits of TRF are not well described in humans and its benefits in IBD need to be explored further.

Chronopharmacology

Many studies have demonstrated that drug targets, in fact, have varying levels of expression throughout the day and night, commonly referred to as target cycling.[15,108,109] This observed phenomenon suggests that chronotherapy, the practice of administering medications at a specific time, could optimize the efficacy and maximize therapeutic benefits of a variety of drugs.[110] Determining the optimal time of drug administration is complex, as drugs are affected by absorption, distribution, metabolism, and excretion, which in turn are also regulated by circadian rhythms.[95] For example, expression of small intestine drug uptake transporters oscillates throughout the day, and gastric pH and gastrointestinal motility were also found to have circadian variations.[111,112] It has, therefore, been suggested that drugs with the following characteristics would be suitable for chronotherapy: cycling target, cycling physiology, short half-life, and cycling non-specific target (eg, target associated with side effects).[95,108] As discussed, the immune system and inflammatory cascade also exhibit a circadian rhythm, with their active phase being in the evening and early night.[44–47] Various studies demonstrated that anti-inflammatory medications, including nonsteroidal anti-inflammatory drugs, glucocorticosteroids and disease-modifying anti-rheumatic drugs (DMARD) have better efficacy when administered at nighttime,[113,114] likely as they influence the inflammatory response at its peak.[44–47,115]

Chronotherapy in IBD is a relatively new field of study, as evidenced by the very limited published data. The known circadian rhythm of the immune system with variations in its function suggests that the administration of immunogenic drugs at inappropriate times could result in suboptimal efficacy and a higher risk of side effects and anti-drug antibody development.[116] The only published clinical study looking at chronotherapy in IBD was done by Swanson et al, in which they looked at the timing of thiopurines and how it affects metabolite profiles.[117] Based on a cross-over trial with 26 patients, morning dosing of thiopurines led to more optimal drug levels. Interestingly, patients with more optimal drug levels when taking the drug in the morning also had an earlier chronotype, suggesting that a patient's chronotype can help define the optimal time for drug administration. It should be noted, however, that while patients in this study were asked to keep food timing and content the same, this was not monitored throughout the study and could have confounded the study results as individuals may have changed food timing behaviours based on medication administration timing.

Sulfasalazine, a DMARD used in IBD, acts on the drug transporter ABCG2, which is under the control of activating transcription factor 4, one of the CLOCK mechanism components.[118] ABCG2 was found to have circadian oscillations in mice, which could lead to variations in bioavailability of sulfasalazine. Berberine, a plant-derived chemical, is a REV-ERBα agonist and showed a time-dependent efficacy in improving inflammation in a colitis mouse model,[119] either due to diurnal variation in REV-ERBα expression or time-dependent changes in colitis severity. While no data exists on chronotherapy for biologics in IBD, it is reasonable to hypothesize that intravenous infliximab, with immediate systemic drug exposure, would be best administered shortly before the rise in inflammatory activity. Preliminary analysis from our group demonstrates that intravenous infliximab administered earlier in the day in patients hospitalized for IBD flare-up leads to better outcomes (data not published). On the other hand, we can hypothesize that the efficacy of subcutaneous administration of biologics, with slow absorption and lower peak concentrations,[120] may not be affected by circadian variation in the inflammatory response. Newer therapies for IBD include Janus Kinase inhibitors (JAKi) and sphingosine 1-phosphate (S1P) receptor modulators, both taken orally daily. In animal models, worsening of colitis in circadian disrupted mice after DSS is in part mediated through the JAK

pathway.[38] Baricitinib, a JAKi approved for rheumatoid arthritis, was more effective in terms of clinical disease activity scores, histopathology and bone destruction markers when administered during lights-on (rest) period in mice.[121] S1P is upregulated at the beginning of the light period in humans, with peak levels around 08:00 AM.[122,123] This suggests that JAKi and S1P use in IBD could have optimal administration times based on the time of day.

Conclusion

The circadian rhythm machinery is crucial for maintaining gut health. The circadian rhythm and the environment are constantly communicating, and when this interaction is misaligned, the body's resiliency to detrimental triggers decreases. Circadian misalignment is extremely common in our modern societies due to light polluted environments, social obligations leading to shift work, jet lags and social jet lags and high-fat/sugar-containing food eaten during nighttime, ie, WTE. This circadian rhythm disruption and associated poor sleep quality combined with other disrupters such as stress in genetically susceptible individuals promote intestinal and systemic inflammation leading to worsening of the IBD disease course. Conversely, the inflammatory response further disrupts the circadian rhythm leading to a vicious cycle. Thus, circadian-directed interventions, such as BLT targeting the central circadian clock or timing of eating and chronotherapy targeting the peripheral circadian clocks, may be essential in the management of IBD.

Supplementary material

Supplementary material is available at Journal of the *Canadian Association of Gastroenterology* online.

Author contributions

Zoë Post and Netanel F. Zilberstein wrote the first draft of the manuscript. Zoë Post, Netanel F. Zilberstein, and Ali Keshavarzian all worked on revising the manuscript. All authors approved the final version.

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Conflicts of interest

The authors declare no conflicts of interest.

In addition to this COI statement, ICMJE disclosure forms have been collected for all co-authors and can be accessed as supplementary material.

Data availability

There are no data associated with this manuscript.

References

1. Zhang YZ, Li YY. Inflammatory bowel disease: pathogenesis. *World J Gastroenterol*. 2014;20(1):91–99. https://doi.org/10.3748/wjg.v20.i1.91
2. Voigt RM, Forsyth CB, Keshavarzian A. Circadian rhythms: a regulator of gastrointestinal health and dysfunction. *Expert Rev Gastroenterol Hepatol*. 2019;13(5):411–424. https://doi.org/10.1080/17474124.2019.1595588
3. Bishehsari F, Keshavarzian A. Microbes help to track time. *Science*. 2019;365(6460):1379–1380. https://doi.org/10.1126/science.aaz0224
4. Summa KC, Voigt RM, Forsyth CB, et al. Disruption of the circadian clock in mice increases intestinal permeability and promotes alcohol-induced hepatic pathology and inflammation. *PLoS One*. 2013;8(6):e67102. https://doi.org/10.1371/journal.pone.0067102
5. Preuss F, Tang Y, Laposky AD, Arble D, Keshavarzian A, Turek FW. Adverse effects of chronic circadian desynchronization in animals in a "challenging" environment. *Am J Physiol Regul Integr Comp Physiol*. 2008;295(6):R2034–R2040. https://doi.org/10.1152/ajpregu.00118.2008
6. Takahashi JS. Transcriptional architecture of the mammalian circadian clock. *Nat Rev Genet*. 2017;18(3):164–179. https://doi.org/10.1038/nrg.2016.150
7. Yamazaki S, Takahashi JS. Real-time luminescence reporting of circadian gene expression in mammals. *Methods Enzymol*. 2005;393:288–301. https://doi.org/10.1016/S0076-6879(05)93012-7
8. Liu AC, Lewis WG, Kay SA. Mammalian circadian signaling networks and therapeutic targets. *Nat Chem Biol*. 2007;3(10):630–639. https://doi.org/10.1038/nchembio.2007.37
9. Allada R, Bass J. Circadian mechanisms in medicine. *N Engl J Med*. 2021;384(6):550–561. https://doi.org/10.1056/NEJMra1802337
10. Vitaterna MH, King DP, Chang AM, et al. Mutagenesis and mapping of a mouse gene, clock, essential for circadian behavior. *Science*. 1994;264(5159):719–725. https://doi.org/10.1126/science.8171325
11. Ruan W, Yuan X, Eltzschig HK. Circadian rhythm as a therapeutic target. *Nat Rev Drug Discov*. 2021;20(4):287–307. https://doi.org/10.1038/s41573-020-00109-w
12. Ko CH, Takahashi JS. Molecular components of the mammalian circadian clock. *Hum Mol Genet*. 2006;15(Spec No 2):R271–R277. https://doi.org/10.1093/hmg/ddl207
13. Preitner N, Damiola F, Lopez-Molina L, et al. The orphan nuclear receptor REV-ERBalpha controls circadian transcription within the positive limb of the mammalian circadian oscillator. *Cell*. 2002;110(2):251–260. https://doi.org/10.1016/s0092-8674(02)00825-5
14. Ueda HR, Chen W, Adachi A, et al. A transcription factor response element for gene expression during circadian night. *Nature*. 2002;418(6897):534–539. https://doi.org/10.1038/nature00906
15. Mure LS, Le HD, Benegiamo G, et al. Diurnal transcriptome atlas of a primate across major neural and peripheral tissues. *Science*. 2018;359(6381):eaao0318. https://doi.org/10.1126/science.aao0318
16. Gallego M, Virshup DM. Post-translational modifications regulate the ticking of the circadian clock. *Nat Rev Mol Cell Biol*. 2007;8(2):139–148. https://doi.org/10.1038/nrm2106
17. Bishehsari F, Voigt RM, Keshavarzian A. Circadian rhythms and the gut microbiota: from the metabolic syndrome to cancer. *Nat Rev Endocrinol*. 2020;16(12):731–739. https://doi.org/10.1038/s41574-020-00427-4
18. Schroeder AM, Colwell CS. How to fix a broken clock. *Trends Pharmacol Sci*. 2013;34(11):605–619. https://doi.org/10.1016/j.tips.2013.09.002
19. Manfredini R, Fabbian F, Cappadona R, et al. Daylight saving time and acute myocardial infarction: a meta-analysis. *J Clin Med*. 2019;8(3):404. https://doi.org/10.3390/jcm8030404

20. Martín-Olalla JM. Traffic accident increase attributed to daylight saving time doubled after energy policy act. *Curr Biol*. 2020;30(7):R298–R300. https://doi.org/10.1016/j.cub.2020.03.007
21. LeGates TA, Altimus CM, Wang H, et al. Aberrant light directly impairs mood and learning through melanopsin-expressing neurons. *Nature*. 2012;491(7425):594–598. https://doi.org/10.1038/nature11673
22. Izumo M, Pejchal M, Schook AC, et al. Differential effects of light and feeding on circadian organization of peripheral clocks in a forebrain Bmal1 mutant. *Elife*. 2014;3:e04617. https://doi.org/10.7554/eLife.04617
23. Swanson GR, Burgess HJ, Keshavarzian A. Sleep disturbances and inflammatory bowel disease: a potential trigger for disease flare? *Expert Rev Clin Immunol*. 2011;7(1):29–36. https://doi.org/10.1586/eci.10.83
24. Ananthakrishnan AN, Long MD, Martin CF, Sandler RS, Kappelman MD. Sleep disturbance and risk of active disease in patients with Crohn's disease and ulcerative colitis. *Clin Gastroenterol Hepatol*. 2013;11(8):965–971. https://doi.org/10.1016/j.cgh.2013.01.021
25. Ranjbaran Z, Keefer L, Stepanski E, Farhadi A, Keshavarzian A. The relevance of sleep abnormalities to chronic inflammatory conditions. *Inflamm Res*. 2007;56(2):51–57. https://doi.org/10.1007/s00011-006-6067-1
26. Hood MM, Wilson R, Gorenz A, et al. Sleep quality in ulcerative colitis: associations with inflammation, psychological distress, and quality of life. *Int J Behav Med*. 2018;25(5):517–525. https://doi.org/10.1007/s12529-018-9745-9
27. Späth-Schwalbe E, Hansen K, Schmidt F, et al. Acute effects of recombinant human interleukin-6 on endocrine and central nervous sleep functions in healthy men. *J Clin Endocrinol Metab*. 1998;83(5):1573–1579. https://doi.org/10.1210/jcem.83.5.4795
28. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Circadian interleukin-6 secretion and quantity and depth of sleep. *J Clin Endocrinol Metab*. 1999;84(8):2603–2607. https://doi.org/10.1210/jcem.84.8.5894
29. Born J, Lange T, Hansen K, Mölle M, Fehm HL. Effects of sleep and circadian rhythm on human circulating immune cells. *J Immunol*. 1997;158(9):4454–4464.
30. Ali T, Madhoun MF, Orr WC, Rubin DT. Assessment of the relationship between quality of sleep and disease activity in inflammatory bowel disease patients. *Inflamm Bowel Dis*. 2013;19(11):2440–2443. https://doi.org/10.1097/MIB.0b013e3182a0ea54
31. Keefer L, Stepanski EJ, Ranjbaran Z, Benson LM, Keshavarzian A. An initial report of sleep disturbance in inactive inflammatory bowel disease. *J Clin Sleep Med*. 2006;2(4):409–416.
32. Swanson GR, Kochman N, Amin J, et al. Disrupted circadian rest-activity cycles in inflammatory bowel disease are associated with aggressive disease phenotype, subclinical inflammation, and Dysbiosis. *Front Med (Lausanne)*. 2022;8:770491. https://doi.org/10.3389/fmed.2021.770491
33. Mazzoccoli G, Palmieri O, Corritore G, et al. Association study of a polymorphism in clock gene PERIOD3 and risk of inflammatory bowel disease. *Chronobiol Int*. 2012;29(8):994–1003. https://doi.org/10.3109/07420528.2012.705935
34. Swanson GR, Burgess HJ. Sleep and circadian hygiene and inflammatory bowel disease. *Gastroenterol Clin North Am*. 2017;46(4):881–893. https://doi.org/10.1016/j.gtc.2017.08.014
35. Burgess HJ, Swanson GR, Keshavarzian A. Endogenous melatonin profiles in asymptomatic inflammatory bowel disease. *Scand J Gastroenterol*. 2010;45(6):759–761. https://doi.org/10.3109/00365521003749818
36. Chakradeo PS, Keshavarzian A, Singh S, et al. Chronotype, social jet lag, sleep debt and food timing in inflammatory bowel disease. *Sleep Med*. 2018;52:188–195. https://doi.org/10.1016/j.sleep.2018.08.002
37. Tang Y, Preuss F, Turek FW, Jakate S, Keshavarzian A. Sleep deprivation worsens inflammation and delays recovery in a mouse model of colitis. *Sleep Med*. 2009;10(6):597–603. https://doi.org/10.1016/j.sleep.2008.12.009
38. Jochum SB, Engen PA, Shaikh M, et al. Colonic epithelial circadian disruption worsens dextran sulfate sodium-induced colitis. *Inflamm Bowel Dis*. 2023;29(3):444–457. https://doi.org/10.1093/ibd/izac219
39. Man K, Loudon A, Chawla A. Immunity around the clock. *Science*. 2016;354(6315):999–1003. https://doi.org/10.1126/science.aah4966
40. Scheiermann C, Kunisaki Y, Lucas D, et al. Adrenergic nerves govern circadian leukocyte recruitment to tissues. *Immunity*. 2012;37(2):290–301. https://doi.org/10.1016/j.immuni.2012.05.021
41. Gibbs JE, Blaikley J, Beesley S, et al. The nuclear receptor REV-ERBα mediates circadian regulation of innate immunity through selective regulation of inflammatory cytokines. *Proc Natl Acad Sci U S A*. 2012;109(2):582–587. https://doi.org/10.1073/pnas.1106750109
42. Gibbs J, Ince L, Matthews L, et al. An epithelial circadian clock controls pulmonary inflammation and glucocorticoid action. *Nat Med*. 2014;20(8):919–926. https://doi.org/10.1038/nm.3599
43. Jetten AM. Retinoid-related orphan receptors (RORs): critical roles in development, immunity, circadian rhythm, and cellular metabolism. *Nucl Recept Signal*. 2009;7(1):e003. https://doi.org/10.1621/nrs.07003
44. Scheiermann C, Gibbs J, Ince L, Loudon A. Clocking in to immunity. *Nat Rev Immunol*. 2018;18(7):423–437. https://doi.org/10.1038/s41577-018-0008-4
45. Bourin P, Mansour I, Doinel C, Roué R, Rouger P, Levi F. Circadian rhythms of circulating NK cells in healthy and human immunodeficiency virus-infected men. *Chronobiol Int*. 1993;10(4):298–305. https://doi.org/10.1080/07420529309059712
46. Ackermann K, Revell VL, Lao O, Rombouts EJ, Skene DJ, Kayser M. Diurnal rhythms in blood cell populations and the effect of acute sleep deprivation in healthy young men. *Sleep*. 2012;35(7):933–940. https://doi.org/10.5665/sleep.1954
47. Petrovsky N, Harrison LC. The chronobiology of human cytokine production. *Int Rev Immunol*. 1998;16(5–6):635–649. https://doi.org/10.3109/08830189809043012
48. Narasimamurthy R, Hatori M, Nayak SK, Liu F, Panda S, Verma IM. Circadian clock protein cryptochrome regulates the expression of proinflammatory cytokines. *Proc Natl Acad Sci U S A*. 2012;109(31):12662–12667. https://doi.org/10.1073/pnas.1209965109
49. Bellet MM, Deriu E, Liu JZ, et al. Circadian clock regulates the host response to Salmonella. *Proc Natl Acad Sci U S A*. 2013;110(24):9897–9902. https://doi.org/10.1073/pnas.1120636110
50. Haas S, Straub RH. Disruption of rhythms of molecular clocks in primary synovial fibroblasts of patients with osteoarthritis and rheumatoid arthritis, role of IL-1β/TNF. *Arthritis Res Ther*. 2012;14(3):R122. https://doi.org/10.1186/ar3852
51. Liu X, Yu R, Zhu L, Hou X, Zou K. Bidirectional regulation of circadian disturbance and inflammation in inflammatory bowel disease. *Inflamm Bowel Dis*. 2017;23(10):1741–1751. https://doi.org/10.1097/MIB.0000000000001265
52. Lopez M, Meier D, Müller A, Franken P, Fujita J, Fontana A. Tumor necrosis factor and transforming growth factor β regulate clock genes by controlling the expression of the cold inducible RNA-binding protein (CIRBP). *J Biol Chem*. 2014;289(5):2736–2744. https://doi.org/10.1074/jbc.M113.508200
53. Farhadi A, Banan A, Fields J, Keshavarzian A. Intestinal barrier: an interface between health and disease. *J Gastroenterol Hepatol*. 2003;18(5):479–497. https://doi.org/10.1046/j.1440-1746.2003.03032.x
54. Voigt RM, Forsyth CB, Shaikh M, et al. Diurnal variations in intestinal barrier integrity and liver pathology in mice: implications for alcohol binge. *Am J Physiol Gastrointest Liver Physiol*. 2018;314(1):G131–G141. https://doi.org/10.1152/ajpgi.00103.2017
55. Kyoko O, Kono H, Ishimaru K, et al. Expressions of tight junction proteins Occludin and Claudin-1 are under the circadian control in the mouse large intestine: implications in intestinal permeability and susceptibility to colitis. *PLoS One*. 2014;9(5):e98016. https://doi.org/10.1371/journal.pone.0098016

56. Yamato M, Ito T, Iwatani H, Yamato M, Imai E, Rakugi H. E-cadherin and claudin-4 expression has circadian rhythm in adult rat kidney. *J Nephrol*. 2010;23(1):102–110.
57. Forsyth CB, Voigt RM, Burgess HJ, Swanson GR, Keshavarzian A. Circadian rhythms, alcohol and gut interactions. *Alcohol*. 2015;49(4):389–398. https://doi.org/10.1016/j.alcohol.2014.07.021
58. Tran L, Jochum SB, Shaikh M, et al. Circadian misalignment by environmental light/dark shifting causes circadian disruption in colon. *PLoS One*. 2021;16(6):e0251604. https://doi.org/10.1371/journal.pone.0251604
59. Swanson GR, Gorenz A, Shaikh M, et al. Decreased melatonin secretion is associated with increased intestinal permeability and marker of endotoxemia in alcoholics. *Am J Physiol Gastrointest Liver Physiol*. 2015;308(12):G1004–G1011. https://doi.org/10.1152/ajpgi.00002.2015
60. Swanson G, Gorenz A, Shaikh M, Forsyth CB, Burgess H, Keshavarzian A. Research Society on Alcoholism, 37th Annual Meeting. Bellevue, WA.: 2014. Area under the curve of plasma melatonin in alcoholics inversely related to increased intestinal permeability.
61. Swanson GR, Gorenz A, Shaikh M, et al. Night workers with circadian misalignment are susceptible to alcohol-induced intestinal hyperpermeability with social drinking. *Am J Physiol Gastrointest Liver Physiol*. 2016;311(1):G192–G201. https://doi.org/10.1152/ajpgi.00087.2016
62. Sonnenberg A. Occupational distribution of inflammatory bowel disease among German employees. *Gut*. 1990;31(9):1037–1040. https://doi.org/10.1136/gut.31.9.1037
63. Thaiss CA, Zeevi D, Levy M, et al. Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. *Cell*. 2014;159(3):514–529. https://doi.org/10.1016/j.cell.2014.09.048
64. Tahara Y, Yamazaki M, Sukigara H, et al. Gut microbiota-derived short chain fatty acids induce circadian clock entrainment in mouse peripheral tissue. *Sci Rep*. 2018;8(1):1395. https://doi.org/10.1038/s41598-018-19836-7
65. Leone V, Gibbons SM, Martinez K, et al. Effects of diurnal variation of gut microbes and high-fat feeding on host circadian clock function and metabolism. *Cell Host Microbe*. 2015;17(5):681–689. https://doi.org/10.1016/j.chom.2015.03.006
66. Thaiss CA, Levy M, Korem T, et al. Microbiota diurnal rhythmicity programs host transcriptome oscillations. *Cell*. 2016;167(6):1495–1510.e12. https://doi.org/10.1016/j.cell.2016.11.003
67. Kuang Z, Wang Y, Li Y, et al. The intestinal microbiota programs diurnal rhythms in host metabolism through histone deacetylase 3. *Science*. 2019;365(6460):1428–1434. https://doi.org/10.1126/science.aaw3134
68. Voigt RM, Forsyth CB, Green SJ, et al. Circadian disorganization alters intestinal microbiota. *PLoS One*. 2014;9(5):e97500. https://doi.org/10.1371/journal.pone.0097500
69. Forsyth CB, Farhadi A, Jakate SM, Tang Y, Shaikh M, Keshavarzian A. Lactobacillus GG treatment ameliorates alcohol-induced intestinal oxidative stress, gut leakiness, and liver injury in a rat model of alcoholic steatohepatitis. *Alcohol*. 2009;43(2):163–172. https://doi.org/10.1016/j.alcohol.2008.12.009
70. Mutlu E, Keshavarzian A, Engen P, Forsyth CB, Sikaroodi M, Gillevet P. Intestinal dysbiosis: a possible mechanism of alcohol-induced endotoxemia and alcoholic steatohepatitis in rats. *Alcohol Clin Exp Res*. 2009;33(10):1836–1846. https://doi.org/10.1111/j.1530-0277.2009.01022.x
71. Huang YJ, Pai YC, Yu LC. Host–microbiota interaction and intestinal epithelial functions under circadian control: implications in colitis and metabolic disorders. *Chin J Physiol*. 2018;61(6):325–340. https://doi.org/10.4077/CJP.2018.BAH641
72. Bishehsari F, Engen PA, Adnan D, et al. Abnormal food timing and predisposition to weight gain: Role of barrier dysfunction and microbiota. *Transl Res*. 2021;231:113–123. https://doi.org/10.1016/j.trsl.2020.11.007
73. Bishehsari F, Engen PA, Voigt RM, et al. Abnormal eating patterns cause circadian disruption and promote alcohol-associated colon carcinogenesis. *Cell Mol Gastroenterol Hepatol*. 2020;9(2):219–237. https://doi.org/10.1016/j.jcmgh.2019.10.011
74. Chellappa SL, Engen PA, Naqib A, et al. Proof-of-principle demonstration of endogenous circadian system and circadian misalignment effects on human oral microbiota. *FASEB J*. 2022;36(1):e22043. https://doi.org/10.1096/fj.202101153R
75. Collado MC, Engen PA, Bandín C, et al. Timing of food intake impacts daily rhythms of human salivary microbiota: a randomized, crossover study. *FASEB J*. 2018;32(4):2060–2072. https://doi.org/10.1096/fj.201700697RR
76. Feng G, Zhao J, Peng J, et al. Circadian clock: a promising scientific target in oral science. *Front Physiol*. 2022;13:1031519. https://doi.org/10.3389/fphys.2022.1031519
77. Konturek PC, Brzozowski T, Konturek SJ. Gut clock: implication of circadian rhythms in the gastrointestinal tract. *J Physiol Pharmacol*. 2011;62(2):139–150.
78. Oldham MA, Lee HB, Desan PH. Circadian rhythm disruption in the critically ill: an opportunity for improving outcomes. *Crit Care Med*. 2016;44(1):207–217. https://doi.org/10.1097/CCM.0000000000001282
79. Barion A, Zee PC. A clinical approach to circadian rhythm sleep disorders. *Sleep Med*. 2007;8(6):566–577. https://doi.org/10.1016/j.sleep.2006.11.017
80. LeGates TA, Fernandez DC, Hattar S. Light as a central modulator of circadian rhythms, sleep and affect. *Nat Rev Neurosci*. 2014;15(7):443–454. https://doi.org/10.1038/nrn3743
81. Vallée A, Lecarpentier Y, Guillevin R, Vallée JN. The influence of circadian rhythms and aerobic glycolysis in autism spectrum disorder. *Transl Psychiatry*. 2020;10(1):400. https://doi.org/10.1038/s41398-020-01086-9
82. Erren TC, Reiter RJ. Light hygiene: time to make preventive use of insights—old and new—into the nexus of the drug light, melatonin, clocks, chronodisruption and public health. *Med Hypotheses*. 2009;73(4):537–541. https://doi.org/10.1016/j.mehy.2009.06.003
83. Eckle T, Hartmann K, Bonney S, et al. Adora2b-elicited Per2 stabilization promotes a HIF-dependent metabolic switch crucial for myocardial adaptation to ischemia. *Nat Med*. 2012;18(5):774–782. https://doi.org/10.1038/nm.2728
84. Brouwer A, van Raalte DH, Nguyen HT, et al. Effects of light therapy on mood and insulin sensitivity in patients with type 2 diabetes and depression: results from a randomized placebo-controlled trial. *Diabetes Care*. 2019;42(4):529–538. https://doi.org/10.2337/dc18-1732
85. Mao L, Dauchy RT, Blask DE, et al. Circadian gating of epithelial-to-mesenchymal transition in breast cancer cells via melatonin-regulation of GSK3β [published correction appears in Mol Endocrinol. 2013 Jan;27(1):188]. *Mol Endocrinol*. 2012;26(11):1808–1820. https://doi.org/10.1210/me.2012-1071
86. Dauchy RT, Hoffman AE, Wren-Dail MA, et al. Daytime blue light enhances the nighttime circadian melatonin inhibition of human prostate cancer growth. *Comp Med*. 2015;65(6):473–485.
87. Dauchy RT, Wren-Dail MA, Dupepe LM, et al. Effect of daytime blue-enriched LED light on the nighttime circadian melatonin inhibition of hepatoma 7288CTC Warburg effect and progression. *Comp Med*. 2018;68(4):269–279. https://doi.org/10.30802/AALAS-CM-17-000107
88. Cuesta M, Boudreau P, Cermakian N, Boivin DB. Rapid resetting of human peripheral clocks by phototherapy during simulated night shift work. *Sci Rep*. 2017;7(1):16310. https://doi.org/10.1038/s41598-017-16429-8
89. Kervezee L, Cuesta M, Cermakian N, Boivin DB. The phase-shifting effect of bright light exposure on circadian rhythmicity in the human transcriptome. *J Biol Rhythms*. 2019;34(1):84–97. https://doi.org/10.1177/0748730418821776
90. Czeisler CA, Shanahan TL, Klerman EB, et al. Suppression of melatonin secretion in some blind patients by exposure to bright light. *N Engl J Med*. 1995;332(1):6–11. https://doi.org/10.1056/NEJM199501053320102

91. Koronowski KB, Sassone-Corsi P. Communicating clocks shape circadian homeostasis. *Science*. 2021;371(6530):eabd0951. https://doi.org/10.1126/science.abd0951
92. Walker WH, Bumgarner JR, Becker-Krail DD, May LE, Liu JA, Nelson RJ. Light at night disrupts biological clocks, calendars, and immune function. *Semin Immunopathol*. 2022;44(2):165–173. https://doi.org/10.1007/s00281-021-00899-0
93. Xu YX, Shen YT, Li J, et al. Real-ambient bedroom light at night increases systemic inflammation and disrupts circadian rhythm of inflammatory markers. *Ecotoxicol Environ Saf*. 2024. https://doi.org/10.1016/j.ecoenv.2024.116590
94. Fonken LK, Weil ZM, Nelson RJ. Mice exposed to dim light at night exaggerate inflammatory responses to lipopolysaccharide. *Brain Behav Immun*. 2013;34:159–163. https://doi.org/10.1016/j.bbi.2013.08.011
95. Lee Y, Field JM, Sehgal A. Circadian rhythms, disease and chronotherapy. *J Biol Rhythms*. 2021;36(6):503–531. https://doi.org/10.1177/07487304211044301
96. Jakubowicz D, Barnea M, Wainstein J, Froy O. High caloric intake at breakfast vs. dinner differentially influences weight loss of overweight and obese women. *Obesity (Silver Spring)*. 2013;21(12):2504–2512. https://doi.org/10.1002/oby.20460
97. Garaulet M, Gómez-Abellán P, Alburquerque-Béjar JJ, Lee YC, Ordovás JM, Scheer FAJL. Timing of food intake predicts weight loss effectiveness. *Int J Obes (Lond)*. 2013;37(4):604–611. https://doi.org/10.1038/ijo.2012.229
98. Jakubowicz D, Wainstein J, Landau Z, et al. Influences of breakfast on clock gene expression and postprandial glycemia in healthy individuals and individuals with diabetes: a randomized clinical trial. *Diabetes Care*. 2017;40(11):1573–1579. https://doi.org/10.2337/dc16-2753
99. Lévi FA, Okyar A, Hadadi E, Innominato PF, Ballesta A. Circadian regulation of drug responses: toward sex-specific and personalized chronotherapy. *Annu Rev Pharmacol Toxicol*. 2024;64:89–114. https://doi.org/10.1146/annurev-pharmtox-051920-095416
100. Chaix A, Zarrinpar A, Miu P, Panda S. Time-restricted feeding is a preventative and therapeutic intervention against diverse nutritional challenges. *Cell Metab*. 2014;20(6):991–1005. https://doi.org/10.1016/j.cmet.2014.11.001
101. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes. *Cell Metab*. 2018;27(6):1212–1221.e3. https://doi.org/10.1016/j.cmet.2018.04.010
102. Zhao X, Yang J, Huang R, Guo M, Zhou Y, Xu L. The role and its mechanism of intermittent fasting in tumors: friend or foe? *Cancer Biol Med*. 2021;18(1):63–73. https://doi.org/10.20892/j.issn.2095-3941.2020.0250
103. Zarrinpar A, Chaix A, Yooseph S, Panda S. Diet and feeding pattern affect the diurnal dynamics of the gut microbiome. *Cell Metab*. 2014;20(6):1006–1017. https://doi.org/10.1016/j.cmet.2014.11.008
104. Ye Y, Xu H, Xie Z, et al. Time-restricted feeding reduces the detrimental effects of a high-fat diet, possibly by modulating the circadian rhythm of hepatic lipid metabolism and gut microbiota. *Front Nutr*. 2020;7:596285. https://doi.org/10.3389/fnut.2020.596285
105. Zeb F, Wu X, Chen L, et al. Effect of time-restricted feeding on metabolic risk and circadian rhythm associated with gut microbiome in healthy males. *Br J Nutr*. 2020;123(11):1216–1226. https://doi.org/10.1017/S0007114519003428
106. Kolbe I, Leinweber B, Brandenburger M, Oster H. Circadian clock network desynchrony promotes weight gain and alters glucose homeostasis in mice. *Mol Metab*. 2019;30:140–151. https://doi.org/10.1016/j.molmet.2019.09.012
107. Song S, Chen L, Bai M, et al. Time-restricted feeding ameliorates dextran sulfate sodium-induced colitis via reducing intestinal inflammation. *Front Nutr*. 2022;9:1043783. https://doi.org/10.3389/fnut.2022.1043783
108. Zhang R, Lahens NF, Ballance HI, Hughes ME, Hogenesch JB. A circadian gene expression atlas in mammals: implications for biology and medicine. *Proc Natl Acad Sci U S A*. 2014;111(45):16219–16224. https://doi.org/10.1073/pnas.1408886111
109. Ruben MD, Smith DF, FitzGerald GA, Hogenesch JB. Dosing time matters. *Science*. 2019;365(6453):547–549. https://doi.org/10.1126/science.aax7621
110. Levi F, Schibler U. Circadian rhythms: mechanisms and therapeutic implications. *Annu Rev Pharmacol Toxicol*. 2007;47:593–628. https://doi.org/10.1146/annurev.pharmtox.47.120505.105208
111. Ohdo S. Chronotherapeutic strategy: rhythm monitoring, manipulation and disruption. *Adv Drug Deliv Rev*. 2010;62(9–10):859–875. https://doi.org/10.1016/j.addr.2010.01.006
112. Stearns AT, Balakrishnan A, Rhoads DB, Ashley SW, Tavakkolizadeh A. Diurnal rhythmicity in the transcription of jejunal drug transporters. *J Pharmacol Sci*. 2008;108(1):144–148. https://doi.org/10.1254/jphs.08100sc
113. Buttgereit F, Smolen JS, Coogan AN, Cajochen C. Clocking in: chronobiology in rheumatoid arthritis. *Nat Rev Rheumatol*. 2015;11(6):349–356. https://doi.org/10.1038/nrrheum.2015.31
114. Cutolo M. Circadian rhythms and rheumatoid arthritis. *Joint Bone Spine*. 2019;86(3):327–333. https://doi.org/10.1016/j.jbspin.2018.09.003
115. Dimitrov S, Benedict C, Heutling D, Westermann J, Born J, Lange T. Cortisol and epinephrine control opposing circadian rhythms in T cell subsets. *Blood*. 2009;113(21):5134–5143. https://doi.org/10.1182/blood-2008-11-190769
116. Cermakian N, Lange T, Golombek D, et al. Crosstalk between the circadian clock circuitry and the immune system. *Chronobiol Int*. 2013;30(7):870–888. https://doi.org/10.3109/07420528.2013.782315
117. Swanson GR, Biglin M, Raff H, et al. Impact of chronotherapy on 6-mercaptopurine metabolites in inflammatory bowel disease: a pilot crossover trial. *Clin Transl Gastroenterol*. 2023;14(2):e00549. https://doi.org/10.14309/ctg.0000000000000549
118. Hamdan AM, Koyanagi S, Wada E, et al. Intestinal expression of mouse Abcg2/breast cancer resistance protein (BCRP) gene is under control of circadian clock-activating transcription factor-4 pathway. *J Biol Chem*. 2012;287(21):17224–17231. https://doi.org/10.1074/jbc.M111.333377
119. Zhou Z, Lin Y, Gao L, Yang Z, Wang S, Wu B. Circadian pharmacological effects of berberine on chronic colitis in mice: role of the clock component Rev-erbα. *Biochem Pharmacol*. 2020;172:113773. https://doi.org/10.1016/j.bcp.2019.113773
120. Schreiber S, Ben-Horin S, Leszczyszyn J, et al. Randomized controlled trial: subcutaneous vs intravenous infliximab CT-P13 maintenance in inflammatory bowel disease. *Gastroenterology*. 2021;160(7):2340–2353. https://doi.org/10.1053/j.gastro.2021.02.068
121. Yaekura A, Yoshida K, Morii K, et al. Chronotherapy targeting cytokine secretion attenuates collagen-induced arthritis in mice. *Int Immunopharmacol*. 2020;84:106549. https://doi.org/10.1016/j.intimp.2020.106549
122. Brunkhorst R, Pfeilschifter W, Rajkovic N, et al. Diurnal regulation of sphingolipids in blood. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2019;1864(3):304–311. https://doi.org/10.1016/j.bbalip.2018.12.001
123. Budkowska M, Ostrycharz E, Wojtowicz A, et al. A Circadian rhythm in both complement cascade (ComC) activation and sphingosine-1-phosphate (S1P) levels in human peripheral blood supports a role for the ComC-S1P axis in circadian changes in the number of stem cells circulating in peripheral blood. *Stem Cell Rev Rep*. 2018;14(5):677–685. https://doi.org/10.1007/s12015-018-9836-7