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Rewinding the gut clock: from chronodisruption to targeted therapies

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ABSTRACT

Circadian rhythms orchestrate daily oscillations in physiology and behaviour, enabling optimal alignment between internal biological processes and environmental cycles. A hierarchical system centred in the suprachiasmatic nucleus and supported by peripheral clocks across tissues ensures temporal alignment of metabolic, immune and GI functions. Within the GI tract, local clocks drive rhythmic programmes that regulate digestion, absorption, motility, hormone secretion, immune responses and interactions with the gut microbiota. Feeding-fasting cycles and microbial metabolites act as powerful zeitgebers for intestinal clocks, shaping rhythmic gene expression and intestinal metabolic oscillations. Chronodisruption—arising from misaligned light exposure, sleep disturbances or mistimed eating schedules—uncouples central and peripheral clocks. These disturbances, increasingly prevalent in shift workers, disrupt microbial rhythmicity and intestinal homeostasis. Chronodisruption contributes to metabolic disorders, including obesity, dyslipidaemia and type 2 diabetes, and increases the susceptibility to GI disorders such as IBD, IBS, GORD and colorectal cancer. Emerging therapeutic strategies aim to restore circadian alignment. Time-restricted feeding reinforces endogenous rhythmicity, improves metabolic health and restores GI rhythmic processes through entrainment of clock genes, nutrient-sensing pathways and microbial oscillations. Chronobiotics, including melatonin and phytochemicals, further offer non-invasive approaches to resynchronise disrupted clocks. Finally, chronotherapy and chronotype-tailored interventions further underscore the potential of personalised medicine based on circadian biology. Advances in research on rhythmic metabolites and interorgan metabolic coupling offer promising opportunities for understanding systemic circadian coordination. Overall, reinforcing circadian alignment holds potential for preventing and treating metabolic and GI diseases associated with modern lifestyle-induced chronodisruption.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Circadian clocks form a hierarchical, multi-organ oscillator system that aligns the chrono-exposome with organ-specific timing programmes.
- ⇒ Intestinal circadian clocks coordinate GI functions, including digestion and absorption, motility, appetite regulation, immunity and host-microbiota interactions.

WHAT THIS STUDY ADDS

- ⇒ Feeding-fasting cycles and gut microbial metabolites are key synchronisers of intestinal circadian rhythms.
- ⇒ Chronodisruption driven by a misalignment between internal clocks and environmental cues, such as the light-dark cycle and feeding-fasting rhythms, increases the risk of metabolic and GI disorders.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Aligning eating patterns via time-restricted eating and reinforcing circadian timing signals with chronobiotics offer therapeutic potential to restore circadian alignment.
- ⇒ Chronotherapy, by tailoring drug interventions with an individual's chronotype, can optimise treatment efficacy, minimise toxicity and advance precision medicine.

light, food or temperature and (3) it is temperature-compensated, maintaining a stable periodicity across physiologically relevant temperatures.¹

In mammals, circadian clocks govern diverse physiological and behavioural processes, including the sleep-wake cycle, body temperature regulation, hormone secretion, feeding-fasting rhythms and metabolic homeostasis. At the cellular level, circadian rhythms regulate the expression of a substantial fraction of the genome in a tissue-specific manner. For instance, in mice maintained under a 12-hour light-dark cycle, 43% of protein-coding genes showed rhythmicity in at least one of the 12 tested tissues.² In baboons, >80% of all protein-coding genes exhibit circadian rhythms in at least one of 64 tissues studied.³

The circadian system is hierarchically organised, with a central pacemaker in the suprachiasmatic nucleus (SCN) of the hypothalamus that synchronises peripheral clocks located in nearly all cells, including the gut.^{4,5} These

INTRODUCTION TO CIRCADIAN RHYTHMS

Life on Earth evolved under predictable daily cycles of light and darkness, and virtually all organisms have developed endogenous circadian clocks that align internal physiology with these rhythms. The term *circadian* derives from the Latin ‘circa diem’, meaning ‘about a day’, and refers to intrinsic oscillations with a period close to 24 hours. A biological rhythm is considered circadian when it meets three criteria: (1) it persists under constant environmental conditions, demonstrating an endogenous period; (2) it is entrainable by external cues such as



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oscillators are coordinated through neural, endocrine and behavioural pathways to ensure temporal alignment of organ-specific functions. When properly synchronised, this system promotes physiological efficiency and adaptability. Conversely, disturbances—collectively termed chronodisruption—can lead to misalignment between internal clocks and the external environment, or desynchronisation among internal oscillators.⁶ Chronodisruption is increasingly linked to metabolic syndrome, cardiovascular disease, GI disorders, cancer and mood disturbances.⁷

MOLECULAR ARCHITECTURE OF THE CIRCADIAN CLOCK

The mammalian circadian system is generated by several positive and negative interlocked transcription-translation feedback loops, which rely on the concerted co-expression of a set of clock genes that sustain rhythmic gene expression with a period of ~24 hours (figure 1). These oscillators are conserved across tissues and coordinate systemic physiological rhythms.⁸

The core feedback loop is driven by the CLOCK-BMAL1 heterodimer, which activates *Per* and *Cry* transcription through E-box elements. PER and CRY proteins subsequently accumulate, translocate into the nucleus and inhibit CLOCK-BMAL1 activity, thereby forming the core transcription-translation feedback loop. Another interlocked feedback loop, the RORE loop, further regulates *Bmal1* transcription, in which RORs activate while

REV-ERBs repress transcription through RORE elements. In parallel, DBP and NFIL3 regulate downstream transcription through D-box elements, thereby forming the D-box loop that strengthens the robustness and amplitude of circadian oscillations.

Beyond self-regulation, the clock drives the expression of thousands of clock-controlled genes implicated in metabolism, immune responses, DNA repair and endocrine function. Importantly, transcriptional outputs are tissue-specific.^{2,3}

Circadian timing is further modulated by post-translational modifications. Casein kinase 1 δ/ϵ phosphorylates PER proteins, regulating stability and nuclear entry. Of note, mutations in these pathways underlie familial sleep phase disorders resulting from a dramatic shortening of the circadian period. Other modifications, including acetylation, ubiquitination and O-GlcNAcylation, provide flexibility to adjust circadian period and amplitude in response to cellular and environmental signals.⁹

HIERARCHICAL ORGANISATION OF THE CIRCADIAN SYSTEM

Central pacemaker: the suprachiasmatic nucleus

In mammals, circadian organisation is hierarchical, with the SCN of the anterior hypothalamus functioning as the central pacemaker (figure 2). The SCN contains approximately 20 000 neurons, each functioning as a self-sustained oscillator. These

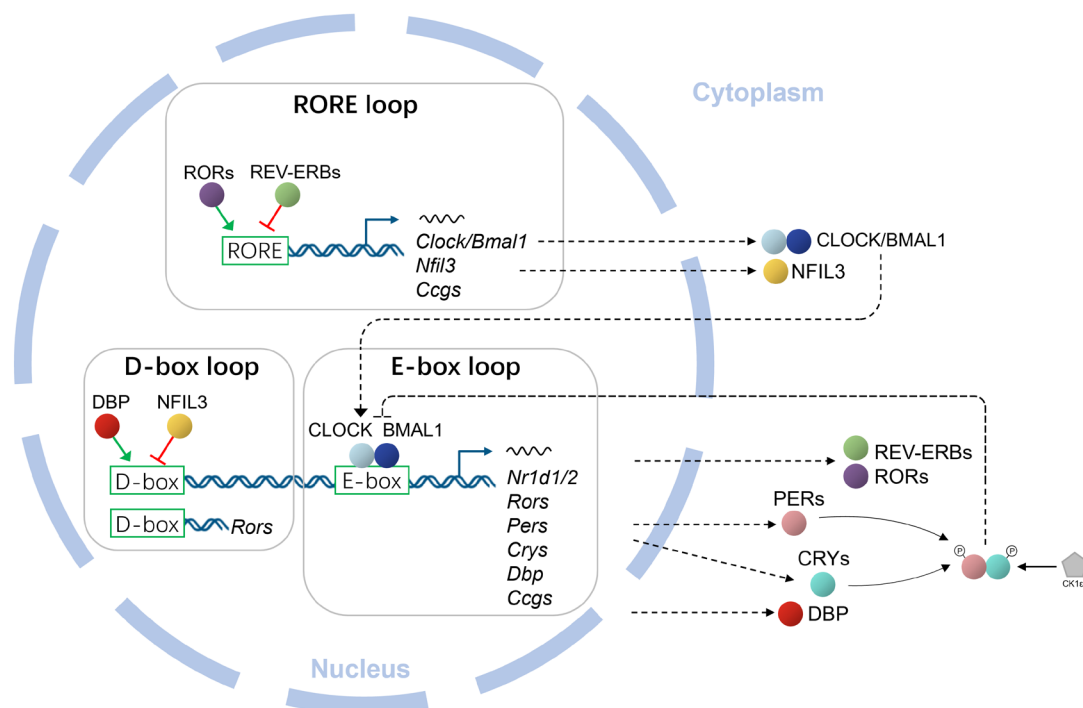


Figure 1 Molecular network of the mammalian circadian clock. This timekeeping system is driven by three interlocked transcription-translation feedback loops that sustain 24-hour rhythmic gene expression. *E-box loop*: CLOCK-BMAL1 heterodimer binds to the E-box elements present in the promoter region of several clock genes. PERs and CRY proteins form heterodimers in the cytoplasm and subsequently translocate into the nucleus, inhibiting CLOCK-BMAL1 activity, thereby forming the core transcription-translation feedback loop. *RORE loop*: REV-ERBs compete with RORs to bind to RORE elements, present in the promoter of *Bmal1* and *Nfil3*, to repress or stimulate their transcription, respectively. *D-box loop*: DBP and NFIL3 bind to D-box elements to regulate transcription of *Rors*, *Nr1d1/2* and *Ccgs* and other target genes. BMAL1, basic helix-loop-helix ARNT-like protein 1; CCG, clock-controlled genes; CLOCK, circadian locomotor output cycles kaput; CRY, cryptochrome circadian regulator; DBP, D-box binding PARb ZIP transcription factor; NFIL3, nuclear factor interleukin 3 regulated; PER, period circadian regulator; REV-ERBs, encoded by nuclear receptor subfamily 1 group D member 1 (NR1D1) and 2 (NR1D2); RORs, RAR-related orphan receptors.

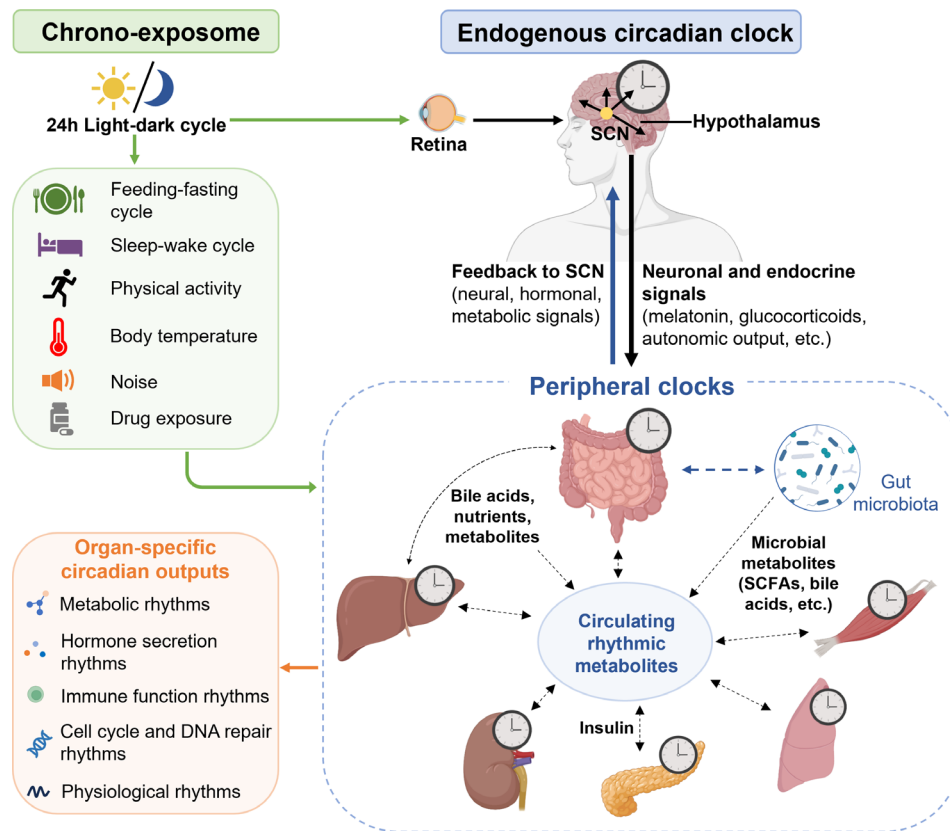


Figure 2 The hierarchical organisation of the circadian system. Photic information entrains the central clock in the SCN via the retina through the retinohypothalamic tract. The central clock conveys the temporal information to synchronise the peripheral circadian clocks via neuronal and endocrine signals. In turn, the signals from peripheral clocks feedback to affect the clock fluctuation in the SCN. In addition, peripheral clocks are entrained by external zeitgebers from the chrono-exposome including the feeding-fasting cycle, sleep-wake cycle, physical activity, noise, drugs and body temperature, thereby regulating the rhythmicity of metabolic pathways, hormone secretion, cellular functions and gene expression in several organs. SCFA, short-chain fatty acid; SCN, suprachiasmatic nucleus.

neurons are interconnected through neurotransmitters and gap junctions, enabling robust and synchronised rhythms at the tissue level. Lesion studies in rodents demonstrated that SCN destruction abolished circadian rhythmicity in locomotor activity and drinking behaviour, common markers of circadian clock function.¹⁰

Circadian rhythms are modulated by zeitgebers, external cues that synchronise the internal clock with the environment. Light is the primary zeitgeber for the SCN, aligning the free-running period to conform to the exact 24-hour period of the environment. Light cues are transmitted from the eyes through the retinohypothalamic tract to the SCN via melanopsin-expressing intrinsically photosensitive retinal ganglion cells.¹¹

The intensity and timing of light exposure determine its phase-shifting effects. Morning light advances the circadian phase, while evening light delays it. Artificial light at night, particularly blue light from electronic devices, can significantly disrupt circadian timing, reduce melatonin secretion and impair sleep quality.^{11 12}

Peripheral clocks

Peripheral clocks are present in most extra-SCN tissues and regulate tissue-specific physiology (figure 2). In mPer2-luciferase knock-in mice, SCN lesions did not eliminate circadian rhythms in peripheral tissues but caused phase desynchrony among the

tissues of individual animals and between animals.⁴ This shows that peripheral tissues sustain autonomous oscillations and likely rely on organ-specific synchronisers. Thus, the SCN primarily coordinates phase relationships among tissues rather than generating their rhythms. In addition, peripheral clocks can influence SCN function, establishing bidirectional communication critical for circadian homeostasis.⁵

Although peripheral oscillators generate self-sustained rhythms, they dampen in vitro without input from the central pacemaker.¹³ Apart from the light-dark cycle, synchrony of peripheral clocks is also shaped by the human chrono-exposome, including feeding-fasting cycles, sleep-wake patterns, physical activity, noise, drug administration and body temperature (figure 2). This chrono-exposome, defined as the sum of all time-related cues that shapes an individual's circadian rhythm, can be modulated by our lifestyle and reinforce or alter the functions of central and peripheral clocks, with implications for chronic disease development.¹⁴

Since this review explores the interplay between circadian clocks and GI function, we provide a concise overview of key GI processes that display rhythmicity. Importantly, whether many of these diurnal fluctuations in the gut represent true circadian rhythms driven by a biological clock remains uncertain. In addition, caution is warranted when extrapolating mechanistic evidence for circadian regulation from rodents (nocturnal) to

humans (diurnal), as the SCN reaches peak activity at the same astronomical times in both mammals, yet their behavioural output is opposite.¹⁵ Therefore, findings should be interpreted relative to the species' active versus rest phase, rather than assuming alignment with human clock time.

Peripheral clocks in the gut

A recent transcriptomic study showed that about 18.3% of the transcripts in the intestinal mucosa of mice showed diurnal rhythmicity when food intake was restricted to the dark phase.¹⁶ Clock genes in the jejunal mucosa peaked into three temporal intervals that segregated different rhythmic biological functions. Genes involved in cell organisation peaked during feeding, whereas metabolic genes peaked during transitions between fed and fasted states.¹⁶

Digestion and absorption

Digestion and absorption are tightly regulated by circadian rhythms to optimise nutrient utilisation in anticipation of feeding-fasting cycles. The digestive process begins in the oral cavity, where salivary flow rate and composition exhibit diurnal fluctuations in humans.¹⁷ In mice, clock gene expression is rhythmic in submandibular glands, and diurnal aquaporin 5 expression was abolished in *Cry1*^{-/-} and *Cry2*^{-/-} mice.¹⁸

In the stomach, gastric acid secretion displays a robust diurnal pattern in humans, increasing throughout the day and peaking in the late evening and early morning, whereas gastrin does not.¹⁹ In humans, pepsin activity peaks after the evening meal, while in rats pepsin efflux peaks when gastric acid secretion is minimal.^{20,21}

The small intestine is a major site of circadian coordination between digestion and absorption. Brush border disaccharidase activity and pancreatic digestive enzymes exhibit diurnal patterns in both rodents and humans, whereas rhythmic pancreatic lipase expression was dampened in *Clock*^{-/-} mice.⁵ Nutrient transporters involved in glucose (SGLT1, GLUT2, GLUT5), protein (PEPT1, NHE3) and lipid (ABCA1) transport showed diurnal oscillations that were disrupted in circadian clock deficient models.⁵ Once taken up, nutrients are further metabolised in the intestine. Several genes involved in ketogenesis and lipid metabolism displayed diurnal fluctuations in the mouse small intestinal mucosa that were either lost or phase-shifted by chronic jetlag but prevented by time-restricted feeding (TRF).¹⁶ For example, lipid droplet abundance in intestinal sections peaked during the active phase, but chronic jetlag advanced this rhythm by 11.7 hours, an effect prevented by TRF. Rhythmic neutral lipid accumulation was also confirmed in intestinal organoids and lost in *Bmal1*^{-/-} mouse organoids.¹⁶ Yu *et al* showed that DGAT2, which channels triglycerides into lipid droplets, was transactivated by *Bmal1* and promoted fat absorption in the mouse intestine during high-fat diet feeding.²²

Motility

Diurnal variations in GI motility have been observed throughout the GI tract in humans.²³ In healthy volunteers, oesophageal motor activity was low during the night (rest phase) and increased with wakefulness (onset of active phase) and food intake.²⁴ Similarly, gastric emptying was slower in the evening compared with the morning, and individuals with polymorphisms in their clock components, *CLOCK* and *PER3*, were associated with impaired morning gastric motility.^{25,26} In the small intestine of healthy volunteers, pigs and sheep, the propagation velocity of the mammalian fasting motility pattern, the migrating

motor complex, was almost twice as high during the active phase as during the rest phase.²⁷ In the colon, pressure activity was low during the rest phase, rising after waking and meals in healthy humans.²⁸ Similarly, rectal motor complexes were observed during the active phase but not during sleep.²⁹

Animal studies provided mechanistic support for circadian regulation of GI motility. Clock genes show rhythmic expression in vagal afferent cell bodies of the mouse nodose ganglion.³⁰ This rhythmicity may drive diurnal variations in gastric vagal afferent mechanosensitivity, which is highest during the rest phase and inversely associated with the elevated food intake and gastric emptying observed during the active phase.^{26,30} In the colon, circadian clock gene oscillations have been demonstrated across epithelial cells, smooth muscle and the myenteric plexus in rodents and humans.^{31–33} Persistence of these rhythms in mice maintained under constant darkness and in primary colonic crypt cultures supports the presence of an intrinsic colonic clock.^{31,33} In mice, several clock-controlled genes involved in motility, including neuronal nitric oxide synthase, exhibited circadian oscillations.²³ Measures of colonic motility such as intracolonic pressure changes and stool output displayed robust diurnal rhythms peaking at the onset of the active phase, consistent with observations in humans. These rhythms were abolished in *Per1/2*^{-/-} mice.²³ Additionally, short-chain fatty acids (SCFAs) inhibited neural contractions in colonic smooth muscle strips in a diurnal pattern that paralleled rhythms in faecal SCFA levels and *Ffar2/3* messenger RNA expression. These rhythms peaked in the resting phase and were absent in *Bmal1*^{-/-} mice.³⁴

Collectively, rodent and human data indicate that gastric and colonic motility peak during their active phase. Data from circadian clock-deficient mice suggest that the colonic clock may drive the increase in colonic activity following awakening and in response to microbial metabolites, whereas postprandial increases in colonic motility may primarily reflect the gastrocolic reflex triggered by food intake.

From a clinical perspective, diurnal variations in gastric motility can bias assessments of gastric emptying rates, highlighting the need for time-stamped GI motility measurements to adjust for the internal biological clock (see 'Challenges and future directions in circadian research' section). These observations also support chronotherapeutic approaches, such as additional bedtime dosing of prokinetics (see 'Challenges and future directions in circadian research' section).

Gastrointestinal hormones

Appetite-regulating gut hormones show circadian regulation in addition to feeding-related fluctuations. Plasma levels of the hunger hormone ghrelin peak during the rest phase while levels of the satiety hormones glucagon-like peptide-1 (GLP-1) and peptide YY peak during the active phase in humans and rodents.^{5,35}

In mice, gastric ghrelin expression showed diurnal rhythms that were lost in *Bmal1*^{-/-} and *Per1/2*^{-/-} mice.^{35,36} In a ghrelinoma cell line, rhythmic ghrelin secretion in response to feeding cues occurred independently of the central clock, and exogenous ghrelin restored hepatic clock disruption in steatotic mice.^{35,37}

The rhythmic release of GLP-1 in response to secretagogues was disrupted in whole-body *Bmal1*^{-/-} mice as well as in primary intestinal cultures generated from these animals.³⁸ L-cell-specific knockout of *Bmal1* confirmed that clock genes are essential for rhythmic GLP-1 release, producing a blunted glucose-stimulated GLP-1 response without altering 24-hour food intake.³⁹ GLP-1 mimetics enhanced rhythmic *Per2* expression in pancreatic

β -cells, indicating that satiety hormones may modulate peripheral clocks and contribute to metabolic circadian alignment.⁴⁰

Immunity

The circadian clockwork plays a key role in innate and adaptive immune responses.⁴¹ Susceptibility to bacterial, viral and parasitic infections varies with the diurnal cycle. For example, animals are most sensitive to an acute inflammatory insult such as lipopolysaccharide at the beginning of the active phase.⁴¹ Genetic deficiencies in various circadian clock components have been linked to an increased susceptibility to IBD.⁴² In mice, intestinal epithelial *Bmal1* deletion disrupted immune homeostasis, abolished rhythmic immune recruitment and worsened colitis.⁴³ Specific immune cell populations also depend on circadian timing. Group 3 innate lymphoid cells (ILC3s) displayed light-entrained oscillations critical for gut barrier integrity and loss of *Bmal1* within ILC3s disturbed microbial balance, impaired lipid metabolism and heightened infection susceptibility.⁴⁴

Microbiota

Recent studies in animals and in humans revealed that the gut microbiome exhibits rhythmic oscillations in abundance, composition and function.⁴⁵ Total bacterial load peaks during the feeding phase and declines during fasting, preceded by metagenomic signs of proliferation. Taxonomic composition also oscillates daily: Bacillota peak near the end of feeding, while Bacteroidota peak during fasting.⁴⁵ Microbial functions such as mucus degradation, and metabolites like SCFAs and bile acids also display diurnal patterns in gut and plasma.^{32,34} Importantly, these oscillations are shaped by feeding rhythms and by the host intestinal epithelial clock, which regulates a substantial proportion of microbial rhythmicity.⁴⁶ Emerging evidence further suggests that certain bacteria may possess intrinsic circadian-like timing mechanisms. Light-sensitive cyanobacteria, for example, possess circadian clocks that coordinate daily bacterial functions via defined molecular mechanisms.⁴⁷ Although gut bacteria are not exposed to light-dark cues, similar circadian mechanisms may have evolved to anticipate and coordinate rhythmic changes in the gut environment, thereby promoting the adaptive evolution of human symbionts. Key evidence for the intrinsic nature of circadian rhythms in the gut comes from studies showing sustained 24-hour oscillations of distinct bacterial taxa from infant faecal samples cultured ex vivo.⁴⁸ Nevertheless, confirmation of endogenous circadian systems in gut bacteria and their entrainment mechanisms requires further investigation. The interactions between microbes and host factors that regulate circadian rhythms are complex and will be discussed in 'Microbiota and their metabolites as circadian cues' section.

Communication between central and peripheral clocks

The SCN coordinates peripheral clocks through neural, hormonal and behavioural mechanisms. Autonomic nervous system projections regulate organs such as the adrenal gland and liver, while hormonal signals, notably melatonin and glucocorticoids, act as systemic synchronisers via widely distributed receptors.

Glucocorticoid secretion is regulated through the hypothalamus/pituitary/adrenal axis, in which rhythmic release of corticotropin-releasing hormone drives circadian adrenocorticotropin secretion from the pituitary, resulting in a daily rhythm of adrenal corticosterone secretion.⁴⁹ In parallel, SCN-derived neuronal signals reach the adrenal cortex via the autonomic nervous system and further modulate circadian glucocorticoid output.⁴⁹

Melatonin transmits temporal signals from the SCN to peripheral clocks, particularly during the dark phase, and modulates a wide range of physiological functions.⁵⁰ Nevertheless, its direct role in entraining peripheral clocks remains debated.⁵¹ Instead, the synchronisation of these clocks appears to depend primarily on feeding schedules, glucocorticoids and tissue-specific metabolic signals.

Behavioural rhythms, such as sleep-wake, activity-rest and feeding-fasting cycles, provide additional feedback from the SCN to peripheral tissues. For instance, sleep deprivation altered circadian gene expression in the brain and liver, while in arrhythmic SCN-lesioned mice PER2 levels only increased in the liver.⁵² Vice versa, peripheral clocks can also influence brain rhythms. Intestinal *Bmal1*, for example, regulated glutamine absorption through rhythmic SLC6A19 expression during the active phase, and promoted wakefulness through hypothalamic glutamatergic circuits.⁵³ Physical activity further contributes to entrainment by elevating core body temperature and cortisol release, two gatekeepers of circadian clocks.⁵⁴

Together, these mechanisms maintain internal coherence of circadian rhythms throughout the organism. Disruption or misalignment between the central and peripheral clocks, or among different peripheral clocks, has been associated with diverse pathologies.⁷

IMPACT OF FEEDING-FASTING CYCLES AND MICROBIOTA ON THE GI CIRCADIAN SYSTEM

The alignment of feeding-fasting cycles with the circadian system is increasingly recognised as a key determinant of metabolic and systemic health. As the gut is the first organ exposed to changes in dietary timing and composition, feeding-fasting cycles serve as major entrainment cues for the intestine and its associated organs such as the liver.

In parallel, the gut microbiota and its metabolites exhibit strong diurnal oscillations that signal to the host clock in a bidirectional manner. Thus, the coordination between dietary timing, nutrient composition and microbiota-derived signals constitutes a multilayered circadian entrainment network that shapes intestinal physiology and systemic metabolic homeostasis.

Timing of food intake as a circadian cue: time-restricted feeding

Feeding patterns are orchestrated by the light-entrainable SCN clock with food-sensitive oscillators in the hypothalamus and brainstem. SCN lesions abolished rhythmic feeding behaviour without altering meal quantity, demonstrating its role in temporal regulation rather than energy intake.⁵⁵

Restricted-feeding paradigms highlight the strong entraining power of food timing. In SCN-lesioned rodents, daily TRF restored pineal melatonin rhythms and robustly entrained hepatic clock gene rhythms.^{56,57} Similarly, night-time TRF in chronodisrupted jet-lagged mice realigned disturbances in hypothalamic and intestinal core clock gene oscillations and in the intestinal metabolomic transcriptome.^{16,58} In a gastric ghrelinoma cell line, feeding and fasting cues directly imposed rhythmic ghrelin release, a pattern paralleled by rhythmic GLP-1 secretion in L-cells in vitro.^{35,59} Meal timing also shapes microbial rhythmicity. TRF, especially when aligned with the host's active phase, reinforces microbial rhythmicity, even in genetically or environmentally chronodisrupted mice.⁶⁰

Conversely, mistimed feeding can uncouple peripheral from central rhythms. For example, daytime feeding in nocturnal rodents shifted the phase of hepatic clock gene expression by

up to 12 hours while leaving the SCN unaffected.⁶¹ Of note, mice given a high-fat diet only during the 12-hour light phase gained significantly more weight over 6 weeks than those fed only during the 12-hour dark phase, underscoring the metabolic risks of misaligned eating patterns as is frequently observed in night-shift workers.⁶²

These findings highlight food timing as a critical regulator of systemic circadian alignment, with therapeutic potential in circadian disruption (see 'Time-restricted feeding/eating' section).

Nutrient composition as a circadian cue

Beyond timing, dietary composition directly modulates circadian oscillations. In mice, a high-fat diet disrupted diurnal feeding patterns and dampened diurnal rhythms in locomotor activity and circadian clock gene expression across tissues.⁶³

A high-fat diet also blunted rhythmicity of the ileal microbiome composition and transcriptome, effects that were partially restored during TRF.⁶⁴ Additionally, a high-fat western diet perturbed the rhythmic production of microbiota-dependent metabolites reaching the liver, impairing hepatic clock-controlled networks. Notably, SCFAs but not H₂S directly modulated circadian clock gene expression within hepatocytes.⁶⁵

In the liver, a high-fat diet reprogrammed the circadian transcriptome by suppressing existing rhythms while generating *de novo* oscillations via impaired CLOCK:BMAL1 chromatin recruitment and circadian accumulation of peroxisome proliferator-activated receptor (PPAR) γ in the nucleus and on chromatin, respectively.⁶⁶ Diet-induced obesity further amplified hepatic circadian rhythms of metabolic transcriptional regulators such as SREBP and PPAR α , linking fatty acid synthesis and oxidation.⁶⁷ Notably, lipid-lowering drugs were most effective at the peak of PPAR α expression, emphasising the therapeutic relevance of chronotherapy.

Non-canonical clock regulators were shown to bridge the connection between nutritional challenges and genetic variants to regulate >80% of rhythmic hepatic transcripts that contribute to liver-related metabolic traits.⁶⁸

Finally, ketogenic diets reprogrammed the peripheral clocks in the liver and intestine through the activation of distinct transcription factors in a diurnal manner. It altered the amplitude of *Bmal1* chromatin recruitment and of clock-controlled genes in the liver, while inducing robust rhythmicity of PPAR α in the gut. These changes coincided with oscillations in serum and intestinal β -hydroxybutyrate levels and paralleled gut-specific cycling of histone H3 acetylation.⁶⁹

Collectively, dietary composition powerfully shapes circadian physiology independent of timing.

Microbiota and their metabolites as circadian cues

The gut microbiota and the circadian system interact bidirectionally. The gut microbiota exhibits rhythmic fluctuations that are mainly driven by the intestinal circadian clock and feeding rhythms.⁴⁵ Indeed, faecal microbial rhythms in mice persisted in constant darkness and were dampened in intestinal epithelial *Bmal1*-deficient mice and in mice with chronic jetlag.^{46 60}

Conversely, microbiota and their metabolites influence host circadian regulation by modulating clock gene expression and chromatin architecture. The elimination of the microbiome, whether in germ-free or antibiotic-treated mice, reduced the number of rhythmic genes in the intestine and liver and induced *de novo* rhythmicity.^{70 71} In addition, microbiota ablation reprogrammed the circadian chromatin dynamics in intestinal epithelial cells, disrupting histone deacetylase 3-dependent oscillation

in metabolic gene acetylation that governs nutrient absorption and lipid metabolism in germ-free mice.^{70 72}

Microbial rhythmicity is essential for host physiology. Transferring microbiota from intestinal clock-deficient mice to germ-free mice altered intestinal gene expression, increased lymphoid organ weights and suppressed immune cell recruitment.⁴⁶ Similarly, faecal transplantation from jet-lagged mice/humans to germ-free mice modulated the rhythmicity of peripheral clock genes, induced glucose intolerance and increased body weight.⁶⁰

Several microbiota-derived metabolites act as key mediators of host circadian regulation. SCFAs, generated through fermentation of polysaccharides, are key metabolites that support proper oscillations of clock genes in the liver, kidney and gut.^{33 34 65 73} Bile acids likewise contribute to the regulation of intestinal clock gene expression.⁷⁴ Indeed, chronic jetlag in mice abolished serum bile acid rhythms, triggering transcriptional reprogramming in colonic smooth muscle that affected secondary bile-acid-induced contractility.³² In addition, absence of microbiota abolished oscillations in serum amino acids and polyamines. Studies in mice fed a polyamine-deficient diet confirmed their causal role in hepatic circadian transcriptome regulation.⁷⁰

In conclusion, several findings underscore the critical role of gut microbiota and its metabolites in linking the intestinal clock to host homeostasis.

CHRONODISRUPTION AND ITS IMPACT ON HEALTH

Chronodisruption refers to a state of disturbed biological rhythms caused by misalignment between internal circadian clocks across tissues or between internal clocks and the external environment, leading to adverse health effects.⁶ It can arise from internal clock gene mutations or alterations in chrono-exposome patterns including irregular light exposure, sleep disruption and mistimed feeding cycles (figure 3). Well-known examples include shift work, chronic jetlag, social jetlag and high-fat diets. Chronodisruption has been linked to diverse pathologies, but this review focuses on metabolic and GI disorders.⁷ Studies are summarised in table 1.

Metabolic disorders

Human and animal models demonstrate that circadian misalignment promotes weight gain, dyslipidaemia, impaired glucose homeostasis and increased risk of type 2 diabetes and cardiovascular disease. It also disrupts gut microbiota rhythmicity, and faecal transplantation studies in germ-free mice suggest that these alterations contribute causally to obesity and metabolic dysfunction.

Gastrointestinal disorders

Circadian disruption has been associated with IBS, IBD, GORD, peptic ulcer disease and colorectal cancer. Epidemiological studies indicate an increased risk of IBS, GORD and colorectal cancer among night-shift and rotating-shift workers, while experimental models demonstrate that clock gene dysfunction and circadian misalignment can worsen intestinal inflammation and promote tumourigenesis. Melatonin has shown therapeutic benefits in IBS and GORD, highlighting the potential of circadian-based interventions. However, further studies are needed to establish causal links between clock disruption and GI disease susceptibility.

Collectively, these findings identify circadian rhythms as key regulators of metabolic and GI health and represent potential targets for prevention and therapy.

MANAGEMENT OF CHRONODISRUPTION

The most promising strategies to restore circadian alignment include TRF/time-restricted eating (TRE) and the use of chronobiotics. Bright-light therapy is not discussed here, as only a protocol paper is available on the effect of morning light treatment for IBD.⁷⁵ In parallel, chronotherapy—tailoring medical treatments to circadian timing—offers an avenue for personalised interventions (figure 4).

Time-restricted feeding/eating

Restricting food intake to a daily window that aligns with circadian rhythms—typically 4–10 hours—is an effective strategy to counteract chronodisruption.⁷⁶ In animals, this is termed TRF, and in humans TRE. TRE is low-cost, accessible with minimal side effects and associated with mild to moderate weight loss and metabolic improvements in patients with obesity and T2D.⁷⁶ TRE may improve glucose metabolism in shift workers, although results remain inconclusive due to small sample sizes and study limitations.⁷⁷ In general, the number of randomised controlled trials is limited and heterogeneity in trial design and adherence complicates translation. Recent recommendations aim to optimise future TRE study designs.⁷⁸

Mechanistically, intermittent fasting promotes metabolic flexibility through increased utilisation of alternative fuel sources (free fatty acids, glycerol and ketones) to maintain energy homeostasis and glycaemia, thereby breaking the vicious cycle of meta-inflammation and restoring metabolic control.⁷⁹

In rodents, TRF also stabilised metabolic outputs by preventing phase shifts in glucose rhythms, appetite-regulating hormones and microbial metabolites, while reducing weight gain and attenuating metabolic diseases arising from a variety of obesogenic diets.^{58 80} A study in a mouse model of chronic jetlag further showed that TRF restored rhythmic gene expression in the small intestine, particularly genes involved in nutrient transport, lipid metabolism, ketogenesis and cellular organisation.¹⁶

A first pilot randomised controlled trial in patients with Crohn's disease showed that TRE reduced body mass index

(BMI), visceral adiposity, systemic inflammation and clinical disease activity. The effects on BMI were independent of caloric restriction and diet quality.⁸¹ Night-time TRF improved intestinal clock functions including immune cell recruitment and microbial rhythmicity in an IBD-relevant mouse model.⁴³

Finally, emerging preclinical evidence suggests that circadian-aligned feeding/fasting regimens may also promote healthy ageing and longevity. A study in male C57BL/6 mice, separating the effects of calories, fasting duration and circadian timing found that beyond calorie reduction, at least 12 hours of daily fasting with food restricted to the active phase, extended life span by 35%. This delayed many of the age-related shifts in immune, inflammatory and metabolic gene expression.⁸²

Collectively, these findings suggest that restricting feeding to consistent daily intervals improves systemic metabolism and stabilises GI rhythms. This pattern may also support healthy ageing, offering therapeutic potential for shift workers suffering from several disorders.

Mechanistic insights into TRF/TRE

The feeding-fasting cycle strongly influences circadian organisation at multiple levels. TRF/TRE acts through at least three overlapping pathways (online supplemental table S1): (i) many benefits depend on an intact circadian system, including the intestinal epithelial clock; (ii) feeding-fasting cycles can also generate metabolic rhythms independently of the molecular clock through nutrient-sensing pathways, such as mechanistic target of rapamycin signalling and (iii) finally, TRF promotes rhythmic fluctuations in the gut microbiota and its metabolites, which may contribute to systemic circadian regulation. The relative contributions of host and microbiota intrinsic clocks in microbial rhythmicity remain unclear.

Chronobiotics

Adherence to TRE is often challenged by cultural and religious practices (eg, Ramadan), hedonic food cues and unrestricted

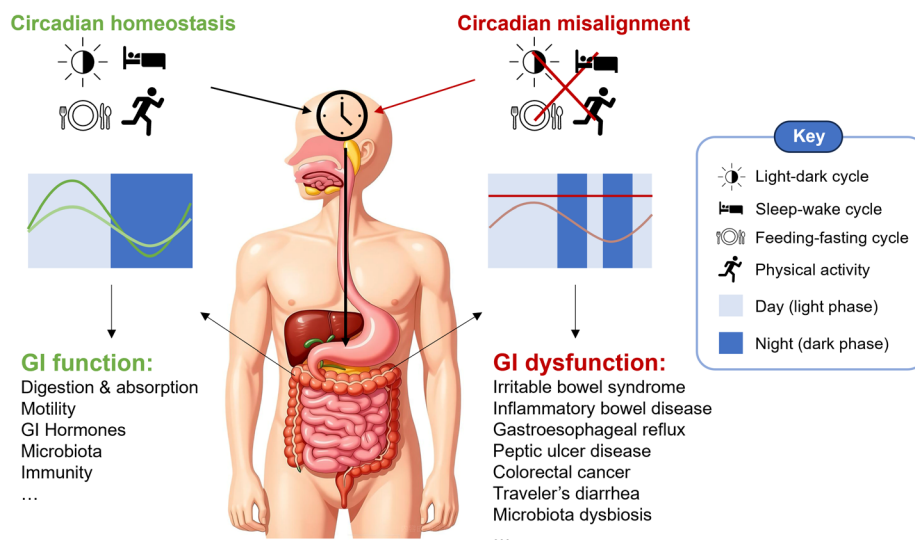


Figure 3 Pathological GI conditions associated with disruption of the intestinal clock. Elements of the human chrono-exposome will under normal conditions reinforce the function of central and peripheral clocks. During chronodisruption, loss of rhythmicity of clock-controlled genes will alter intestinal physiology and result in symptom generation or increase susceptibility to GI disease.

Table 1 Chronodisruption and its impact on health: both epidemiological and mechanistic studies indicate that maintaining circadian alignment is important for metabolic and GI health

Disease area	Model	Key findings	Relevance
Metabolic disorders	Epidemiological study in shift workers	Rotating night-shift work was associated with a higher risk of diabetes and greater weight gain with longer duration. ⁹²	Long-term chronodisruption may increase T2D risk.
	Controlled laboratory study in healthy volunteers	Sleep restriction (5.6-hour sleep/24 hours)+circadian misalignment (recurring 28-hour 'days') reduced metabolic rate and meal-induced insulin secretion, increasing glucose to prediabetic levels. ⁹³	Demonstrates direct metabolic consequences of chronodisruption in humans.
	Mouse model of chronic jetlag	Increased body weight, disrupted rhythms of glucose, appetite regulating hormones and intestinal lipid accumulation. ^{16 33}	Supports causal link between circadian disruption and metabolic disease.
	Circadian clock gene mutant mice	Different clock gene targeting approaches affect body weight, glucose and lipid homeostasis. ⁹⁴	Genetic models underscore the importance of circadian clocks in metabolic homeostasis.
	Circadian microbiome study in cohorts of patients with obesity and T2D	Patients with obesity and T2D showed loss of microbial rhythmicity; arrhythmic microbial signatures enabled classification and prediction of T2D. ⁹⁵	Connects human microbiome rhythms to metabolic health.
	Germ-free mice receiving faecal transplants	Transplanted microbiota from clock-deficient or chronic jet-lagged mice/humans induced obesity and glucose intolerance in germ-free mice. ⁶⁰	Demonstrates a causal role of disrupted microbiota rhythms in the induction of obesity.
IBS	Epidemiological studies in shift workers	Rotating and night-shift work is associated with increased IBS prevalence and symptoms. Findings on the role of sleep quality are inconsistent. ^{96–99}	Links circadian disruption to IBS.
	Patients with functional abdominal pain, including patients with IBS	Urinary 6-sulfatoxy melatonin and body temperature rhythms showed reduced amplitudes compared with healthy controls. ¹⁰⁰	Suggests impaired circadian melatonin regulation in IBS.
	RCTs with melatonin in patients with IBS	Melatonin improved abdominal pain without affecting sleep, anxiety, depression scores and bowel habits but probably by affecting visceral pain perception. ^{84–86}	Supports a potential therapeutic role for melatonin as a circadian-based therapy in patients with IBS.
IBD	Epidemiological studies in shift workers	Shift work is associated with higher CGRP levels and other inflammatory markers. ¹⁰¹	Links circadian disruption to increased inflammatory markers but increased risk of IBD has not been investigated.
	Patients with IBD	Circadian clock-gene expression was reduced in intestinal biopsies and peripheral blood mononuclear cells and negatively correlated with disease activity. ¹⁰²	Indicates circadian involvement in disease severity.
	Patients with IBD	<i>Per3</i> polymorphism is increased in patients with IBD and is associated with a more aggressive form of Crohn's disease. ¹⁰³	Suggests the clock gene machinery could be involved in the pathogenesis of IBD.
	Genetic IBD model of colitis (<i>IL10</i> ^{−/−} mice)	Dysfunctional colonic clock correlated with histological score and frequency of immune cells in lamina propria. ⁴³	Supports an association between clock dysfunction and the inflammatory phenotype.
	Light/Dark phase shift studies in mice with DSS/TNBS-induced acute colitis	Circadian disruption worsened DSS/TNBS colitis and increased inflammatory cytokines. ¹⁰²	Supports a causal relationship between clock disruption and intestinal inflammation.
	Conventional and intestinal epithelial <i>Bmal1</i> -deficient mice	Loss of <i>Bmal1</i> aggravated chemically (DSS) and genetically (<i>IL10</i> ^{−/−}) induced colitis and reduced survival. ^{43 104}	Demonstrates a protective role of the intestinal clock.
GORD	Epidemiological studies in shift workers	Higher GORD risk among shift workers, especially with long-term exposure. ^{105–108}	Epidemiological evidence linking chronodisruption and reflux disease.
	Rat model of reflux oesophagitis	Circadian variation of several clock genes was disrupted in the oesophagus and GI tract during the acute phase, despite unchanged melatonin levels. ¹⁰⁹	Disruption of clock genes is associated with oesophagitis.
	Patients with GORD	Melatonin levels were lower in patients with GORD than in healthy controls. ¹¹⁰	Suggests impaired circadian melatonin regulation in GORD.
	RCT with melatonin in patients with GORD	Sublingual melatonin+omeprazole improved symptoms and quality of life more than omeprazole alone. ⁸⁷	Supports circadian rhythm-based adjunctive therapy for GORD.

Continued

Table 1 Continued

Disease area	Model	Key findings	Relevance
Peptic ulcer disease	Epidemiological studies in shift workers	Increased prevalence of gastric and duodenal ulcers, particularly with <i>Helicobacter pylori</i> infection, although evidence is inconsistent. ^{111–114}	Association between shift work and ulcer occurrence needs further investigation.
	Patients with duodenal ulcer	Diurnal rhythm in intragastric acidity is higher in patients with duodenal ulcer than in controls, with largest differences in the early evening. ¹¹⁵	Suggests treatment strategies should be tailored according to time of day.
	Patients with perforated gastroduodenal ulcer	Ulcer perforations show a circadian pattern, occurring more frequently in the evening, particularly in duodenal/pyloric ulcers. ^{116,117}	Ulcer complications follow a circadian rhythm.
	Experimental model	<i>H. pylori</i> infection disrupted gastric clock-gene rhythmicity and increased BMAL1 expression in gastric epithelial cells. Chronodisruption aggravated the <i>H. pylori</i> -induced inflammatory response in vivo. ¹¹⁸	Mechanistic link between <i>H. pylori</i> infection, circadian disruption and inflammation.
Colon cancer	Working Group of the International Agency for Research on Cancer	Based on strong mechanistic evidence in experimental animals and limited evidence from epidemiological studies the workgroup concluded that 'night-shift work' is probably carcinogenic to humans (a group 2A carcinogen). ¹¹⁹	Indications that night-shift work is associated with increased risk of breast, prostate and colorectal cancer.
	Nurses' Health Study, 24 years of follow-up	Overall colorectal cancer risk was not increased, but rectal cancer risk was higher in women with >15 years of rotating night-shift work. ¹²⁰	Long-term rotating night-shift work may increase cancer risk.
	Patient samples and cancer cell lines	Altered expression of clock genes. ¹²¹	Potential role of clock genes in tumourigenesis.
	Mouse model of colorectal cancer (<i>Apc^{min}</i> strain)	Loss of <i>Bmal1</i> leads to aberrant regulation of stem cell signalling pathways and increased tumour initiation. ¹²²	Identifies clock genes as tumour suppressors.
	Colon cell lines and primary fibroblasts from patients	Disruption of <i>Bmal1</i> increases glycolytic activity and changes treatment response. ¹²³	The biological clock regulates cancer cell metabolism.
	Human colon cancer tissue and cell lines	<i>BMAL2</i> promoted 5-FU resistance by upregulating the ferroptosis regulator, <i>SLC7A11</i> . ¹²⁴	<i>BMAL2</i> as a potential biomarker for chemoresistance.

CGRP, calcitonin gene-related peptide; DSS, dextran sulfate sodium; 5-FU, 5-fluorouracil; RCT, randomised controlled trial; T2D, type 2 diabetes; TNBS, 2,4,6-trinitrobenzene sulfonic acid.

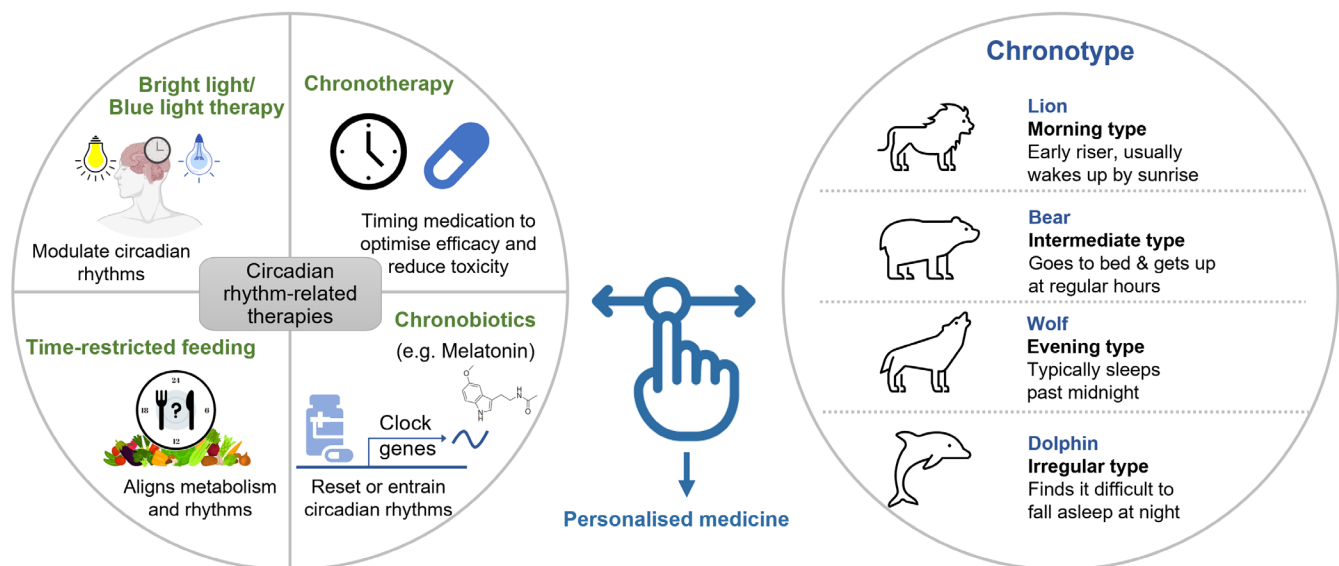


Figure 4 Circadian rhythm-based therapies. Light therapy, time-restricted feeding/eating, chronobiotics and chronotherapy are promising strategies for restoring and reinforcing endogenous circadian rhythms in the intestine. Tailoring these interventions to a person's chronotype helps align treatment with their internal biological clock, often resulting in better outcomes compared with standardised, 'one-size-fits-all' timing. Representative chronotypes, including morning, intermediate, evening and irregular chronotypes, are illustrated with corresponding behavioural and sleep characteristics to highlight the potential of personalised circadian medicine.

food availability. Chronobiotics may therefore serve as an alternative or complementary strategy for chronodisruption-related disorders. Chronobiotics are defined as substances (drug, natural compound, hormone or even an environmental cue like light) capable of shifting the phase, amplitude or period of the body's internal circadian rhythm.⁸³ This allows them to re-entrain or synchronise a desynchronised biological clock to the external environment.

Melatonin is the prototypical chronobiotic, acting through receptors in the brain and peripheral tissues to regulate the sleep-wake cycle and circadian physiology. It is widely used for circadian rhythm sleep disorders and jetlag and has shown benefits in improving symptoms in IBS and GORD, although its chronobiotic mechanism in these contexts remains unproven.^{50 84–87}

Beyond melatonin, several dietary and microbial compounds display chronobiotic properties. Phytochemicals such as caffeine, resveratrol and flavonoids can modulate clock function.⁸⁸ For example, resveratrol improved the metabolic status of high-fat diet-induced mice by attenuating lipogenesis and normalising rhythmic expression of plasma lipids via its effect on the hepatic clock machinery.⁸⁸ In a double-blind, placebo-controlled within-subject study, caffeine induced a 40 min phase delay in the circadian melatonin rhythm. In vitro data indicated that caffeine directly affected the circadian clock via adenosine A1 receptor/cyclic adenosine monophosphate signalling.⁸⁹ Microbial metabolites, including SCFAs, also act as circadian cues that entrain peripheral clocks across tissues including the gut.^{33 73} In general, several phytochemicals are promising candidates for IBD management because of their antioxidant and anti-inflammatory properties, involving clock-controlled genes such as *Sirt1* and *Nrf2*.⁹⁰

An ideal chronobiotic should restore rhythmicity without overcorrecting or undercorrecting, maintaining internal synchronisation while ensuring alignment with environmental cues. Although promising, most compounds require further testing in preclinical animal models and large-scale clinical settings. However, human circadian studies remain limited due to challenges of time-series sampling. Three-dimensional organoid systems recapitulate clock function and provide powerful tools to analyse clock-controlled processes in disease contexts, and to identify circadian drug targets.^{16 91}

CHALLENGES AND FUTURE DIRECTIONS IN CIRCADIAN RESEARCH

As the field of circadian biology continues to evolve, addressing current knowledge gaps and translating mechanistic insights into clinical practice represent major priorities. Relevant studies are summarised in online supplemental table S2.

Circadian metabolomics show that feeding and sleep-wake cycles drive oscillations in many metabolites, providing temporal signals that coordinate peripheral clocks and metabolism across tissues. Emerging evidence identifies the intestine as an important regulator of these rhythms, underscoring the need for multi-organ circadian metabolomic studies.

A major limitation in biomedical research is the widespread neglect of circadian timing. Variation in sampling time, sleep patterns, chronotype and circadian phase across experimental models can introduce significant bias and should be considered in study design and interpretation.

Circadian biology also has important clinical implications. Chronotherapy, which aligns treatment with biological rhythms, can improve efficacy while reducing toxicity in diseases including cancer, cardiovascular, respiratory and inflammatory disorders.

Individual chronotype—defined by natural preferences for morning or evening activity—further modulates circadian physiology, disease susceptibility and the effectiveness of timed therapies (figure 4). Its integration into clinical decision-making may advance precision medicine. Future developments in wearable monitoring and circadian biomarkers could enable assessment of patient's 'chrono-fitness' and support personalised medicine.

CONCLUSION

Research in circadian biology has highlighted that temporal regulation is fundamental to metabolic and GI health. Rhythmic metabolites coordinate interorgan communication, with intestinal clocks serving as key synchronisers of systemic circadian rhythms. Managing chronodisruption requires a multifaceted approach: TRE strengthens rhythmicity through feeding cues, chronobiotics help reset circadian organisation. Chronotherapy further extends these principles into precision medicine, optimising treatment timing according to circadian biology and individual chronotype.

Progress will depend on interdisciplinary strategies that integrate systems-level metabolomics, advanced in vitro models and patient-centred chronobiology to translate circadian science into effective preventive strategies.

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