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Circadian rhythms: a regulator of gastrointestinal health and dysfunction

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Abstract

Introduction: Circadian rhythms regulate much of gastrointestinal physiology including cell proliferation, motility, digestion, absorption, and electrolyte balance. Disruption of circadian rhythms can have adverse consequences including the promotion of and/or exacerbation of a wide variety of gastrointestinal disorders and diseases.

Areas covered: In this review, we evaluate some of the many functions that are regulated by circadian rhythms and how dysregulation of these functions may contribute to disease. This review also discusses some common gastrointestinal disorders that are known to be influenced by circadian rhythms as well as speculation about the mechanisms by which circadian rhythm disruption promotes dysfunction and disease pathogenesis. We discuss how knowledge of circadian rhythms and the advent of chrono-nutrition, chrono-pharmacology, and chrono-therapeutics might influence clinical practice.

Expert opinion: As our knowledge of circadian biology increases, it may be possible to incorporate strategies that take advantage of circadian rhythms and chronotherapy to prevent and/or treat disease.

Keywords

Circadian rhythm; diurnal fluctuation; clock genes; shift work; circadian rhythm disruption; social jet lag; chronotype; intestine; gastrointestinal tract; gastrointestinal disease

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(1.0) INTRODUCTION

Have you ever wondered why you feel sleepy at the same time each night and why you feel hungry at the same time each day? Well, you can thank circadian rhythms. Sleep and hunger are just a few examples of the physical, mental, and behavioral changes that are governed by circadian rhythms. The term circadian is derived from Latin *circa* (meaning about) and *diem* (meaning day) and indeed circadian rhythms are approximately 24 hours in duration. Nearly all organisms from unicellular eukaryotes to mammals demonstrate circadian rhythms and have circadian clocks.

The 24 hour circadian rhythms are generated by the molecular circadian clock which is present in nearly every cell in the mammalian body. The molecular circadian clock is responsible for the generation of circadian rhythms and consists of a set of interlocking transcriptional-translational feedback loops that take approximately 24 hours to complete. Briefly, the circadian clock proteins circadian locomotor output cycles kaput (CLOCK) and aryl-hydrocarbon receptor nuclear translocator-like 1 (ARNT1, also called BMAL1/2) are transcription factors that dimerize and bind to cis-elements called E-boxes in the promoters of what are known as “clock controlled genes.” Two clock-controlled genes are *Period* (*Per1, Per2, Per3*) and *Cryptochrome* (*Cry1, Cry2*). The transcription and subsequent translation of two clock controlled genes known as *Period* (*Per1, Per2, Per3*) and *Cryptochrome* (*Cry1, Cry2*) results in these proteins accumulating in the cytosol and binding to each other to form a complex that translocates into the nucleus where it acts as a transcriptional repressor of further CLOCK-BMAL1-mediated transcription. In addition to this basic clock, there are several layers of complexity that exquisitely regulate the function of the molecular circadian clock. For example, the CLOCK-BMAL1 heterodimer promotes expression of the nuclear receptor retinoic acid-related orphan receptor (RORα) and reverse transcript of erythroblastosis gene (Rev-ERBα) that, respectively, activates and represses *Bmal1* expression. Further regulation of this molecular clock is achieved by post-translational modifications (e.g., phosphorylation, acetylation, SUMOylation) of CLOCK, BMAL1, CRY, and PER proteins that influence their stability and half-lives [1]. Many studies use genetic manipulation of the molecular circadian clock to manipulate circadian rhythms and the essential components of the molecular clock are depicted in Figure 1.

The molecular circadian clock is self-sustained, meaning it can function in the absence of external cues but it is often aligned (i.e., entrained) with environmental factors that are known as *zeitgebers* (German word for time giver) (Figure 2). Most humans have an endogenous circadian rhythm that is slightly longer than 24 hours (on average 24.2 hours); thus, humans are required to adjust their internal clocks daily to remain in synchrony (i.e., entrained) to the external 24 hour day [2]. Light is the primary factor that entrains the central circadian clock (also known as the master clock) located in the suprachiasmatic nucleus (SCN) in the brain. The central clock acts as a musical conductor, coordinating the rhythms of molecular clocks throughout the body using a variety of different mechanisms including hormone production and temperature fluctuations, just to name a few [1]. Circadian clocks

outside of the SCN are referred to as peripheral clocks. Peripheral clocks are directed by the central circadian clock; however, clocks in the periphery can also be entrained by tissue-specific zeitgebers. For example, circadian rhythms in the intestine are robustly entrained by the time of food consumption which can override the direction coming from the SCN [3].

Circadian rhythms are critically important to optimize biological functions to match regular and predictable changes in the environment. For example, the GI tract functions very differently during the day when food is consumed compared to the night when sleep occurs. These functions include motility, secretion, digestion, absorption/metabolism of nutrients, cell proliferation, and tissue repair [4] (Figure 3). Alterations in the regulator patterns of zeitgebers such as sleep and time of eating can disrupt circadian rhythms and result in a mismatch between circadian rhythms in the body and the external environment, called circadian misalignment. Circadian rhythm disruption (or misalignment) induces changes in the molecular circadian clock including changes in the characteristics of clock gene expression including blunting of the amplitude of the rhythm or shifting the time of peak gene expression. Night shift work or traveling across multiple time zones (i.e., jet lag) are obvious conditions that disrupt circadian rhythms; however, circadian disruption is much more pervasive in our 24/7 society than it might seem at first glance. More subtle lifestyle factors that induce circadian rhythm disruption include social jet lag (a phenomenon where schedules on non-work days are different from work day schedules including sleep and eating schedules), light exposure at night (including the use of electronic devices, watching television, or light pollution), and eating late at night or eating at irregular times each day can all can disrupt central and/or peripheral circadian rhythms (Figure 3). In the United States of America and Europe, approximately 15–20% of the workers have non-standard work hours (e.g., permanent night shifts or rotating shifts) and most, if not all, of these workers suffer from circadian misalignment. In addition, it is estimated that anywhere from 30–80% of the population suffers from social jet lag [5,6].

Sleep is influenced by many factors but perhaps one of the most critical are circadian rhythms. The central circadian clock in the SCN regulates the production of melatonin from the pineal gland and this is one mechanism by which circadian rhythms influence sleep. Disruption of circadian rhythms suppresses melatonin production; therefore, sleep disturbances may be one manifestation of circadian rhythm disruption. Disruption of circadian rhythms and poor sleep quality can both impact gastrointestinal (GI) tract function and both are linked to GI symptoms and disease [7–11]. Moreover, there is ample evidence supporting an increased incidence of GI symptoms among shift workers which often suffer from circadian misalignment and disrupted sleep [12–15].

An individual’s preference in behavior including sleep is called a chronotype. Chronotype reflects a tendency toward morningness (i.e., early bird), eveningness (i.e., night owl), or an intermediate type that falls in the middle. Although evidence suggests that an evening chronotype is associated with a myriad of chronic illnesses, there has not been sufficient evidence to determine if chronotype contributes to functional GI illness in a meaningful way [16,17]. However, recent data demonstrates that inflammatory bowel disease (IBD) patients with an evening chronotype may have more aggressive disease course [18,19]. Therefore, there is an urgent need to better understand how circadian rhythm disruption impacts GI

health. In this review we will discuss how circadian rhythms influence the GI tract and how circadian rhythm disruption can negatively influence GI function and contribute to pathology.

(2.0) CIRCADIAN REGULATION OF THE GASTROINTESTINAL TRACT

The GI tract is essential for survival. Much of GI physiology has been observed to follow regular diurnal fluctuations (i.e., fluctuations that occur during each day) including cell proliferation, motility, hormone production, gastric acid production, nutrient absorption, intestinal permeability, the intestinal microbiome (structure and function), and mucosal immunology, just to name a few [20,21]. These fluctuations appear to be governed by a number of factors including: (1) endogenous circadian regulation (e.g., expression of transporters), (3) secondary biological consequences of circadian regulation such as hormone production and temperature fluctuations, (3) behavioral factors such as sleep/wake cycles and/or rest/activity cycles (may be dependent or independent of circadian regulation), or (4) a passive response to food intake and nutrient availability (Figure 2). Most likely a combination of these mechanisms contributes to diurnal variations in GI physiology; however, there is rhythmic expression of clock genes in the mouse colon and these rhythms persist under constant conditions such as fasting, demonstrating that rhythms are not strictly governed by food availability and that circadian rhythms play an important role in GI function [22].

Below is a brief summary of diurnal fluctuations in the GI tract. The list of circadian-regulated GI function found below is by no means exhaustive, but represents those functions that have been most comprehensively examined to date. For the sake of brevity, citations are limited to reviews when possible and the reader is encouraged to peruse these elegantly written summaries and the citations therein.

(2.1) Cell Proliferation.

The entire intestinal epithelium is replaced every 3–5 days by the activity of intestinal stem cells. There is ample evidence demonstrating that cell cycle regulation is governed by circadian rhythms. The normal circadian rhythms observed in wild type mice are disrupted by genetic manipulation of the circadian clock. For example, both *BMAL1* mutant mice and *Clock* mutant mice demonstrate disrupted rhythmic cellular proliferation in the GI tract [23,24]. The majority of human studies utilize cancer cell lines and these data recapitulate the findings in mice. Indeed, down-regulation of *Per2* in human oral squamous cell carcinoma promotes cellular proliferation as does overexpression of human *Clock* in a colorectal cancer (CRC) cell line [25,26]. Based on these data, it is plausible that circadian rhythm disruption influences GI disorders that are impacted by changes in cell proliferation such as inflammatory bowel disease (IBD), cancer, and intestinal repair following intestinal resection or surgical anastomosis.

(2.2) Motility.

Diurnal variations in GI motility have been observed throughout the entire GI tract in humans including in the stomach, small intestine, colon, and rectum [3]. The importance of the circadian clock in the regulation of GI motility has been demonstrated in mice. Wild type mice show rhythmic changes in stool output, intracolonic pressure, and colonic muscle contractility which are altered in mice with a mutation in the molecular circadian clock (i.e., *Per1/2* double knockout) [27,28]. Indeed, polymorphisms in components of the molecular circadian clock (i.e., *Clock* and *Per3)* are associated with poor gastric motility in humans [29]. Thus, it is likely that disruption of circadian rhythms negatively impacts GI motility and thereby intestinal disorders in which dysmobility is a feature such as irritable bowel syndrome (IBS), functional dyspepsia, gastroparesis, GI symptoms in diabetes, and Parkinson's disease, just to name a few.

(2.3) Protein Digestion and Absorption.

Proteins are hydrolyzed (i.e., digested) in the intestinal lumen to amino acids, dipeptides, and tripeptides by pancreatic enzymes and intestinal enzymes located at the brush border of intestinal epithelial cells. Amino acids are absorbed by several transporters while dipeptides and tripeptides are transported across the intestinal barrier via the high-capacity, low-affinity peptide transporter 1 (PEPT1). PEPT1 is a proton-dependent peptide co-transporter; therefore, peptide absorption is dependent on the establishment of a proton gradient by the sodium-proton exchanger (NHE3). Expression of *NHE3* is influenced by food availability but it also exhibits a circadian rhythm. *NHE3* contains a putative E-box within its promoter and is speculated to be a clock-controlled gene; therefore, circadian rhythms appear to be important in rhythmic expression of *NHE3* [30–34] (Figure 1). Studies of mice with a genetic modification that disrupts the molecular circadian clock have been useful in demonstrating that that the circadian clock plays a role in protein absorption. Specifically, mice that have both *Cry1* and *Cry2* (critical components of the molecular circadian clock) knocked out have blunted expression of NHE3 [35]. Therefore, protein consumption would be expected to be altered in subjects with circadian rhythm disruption.

(2.4) Carbohydrate Digestion and Absorption.

Carbohydrates consist of monosaccharides (glucose, fructose, galactose), disaccharides (lactose, sucrose), and polysaccharides (starch, cellulose). There is ample evidence demonstrating circadian regulation of carbohydrate digestion and absorption. For example, the production of enzymes required for carbohydrate digestion (e.g., disaccharidases) demonstrates a circadian rhythm as do transporters required for carbohydrate absorption [36]. Enterocytes absorb monosaccharides from the intestinal lumen using transporters such as sodium-dependent glucose transporter (SGLT1/2), glucose transporter 5 (GLUT5), and GLUT3. The function of these transporters relies directly or indirectly on circadian rhythms. In fact, mice that have a mutation in the molecular circadian clock (i.e., specifically the *Clock* gene) do not show circadian fluctuations in *Sglt1*, *Glut2*, or *Glut5* [37]. Because of this, it is proposed that these transporters are controlled by the molecular circadian clock (Figure 1). It should be noted that subjects with disrupted circadian rhythms such as shift workers and those with social jet lag have increased risk of metabolic syndrome and

associated abnormal carbohydrate homeostasis as well as insulin resistance suggesting that carbohydrate digestion/absorption may be altered [38].

(2.5) Lipid Absorption.

Lipids are insoluble and must be emulsified with bile salts in the intestinal lumen in order to be absorbed. Hydrophobic lipids are partitioned into bile salt micelles and they are taken up into enterocytes using both diffusion and protein-mediated transporters. Uptake via diffusion occurs when fatty acid concentrations are high in the lumen but evidence shows that lipid absorption demonstrates a diurnal variation [39]. For example, absorption of triglycerides and cholesterol demonstrates a diurnal fluctuation that is associated with variation in the production of apolipoprotein B-lipoproteins (ApoB) and the intestinal microsomal triglyceride transfer protein (MTP) (Figure 1) [40]. These fluctuations are absent in mice that have a mutation in the molecular circadian clock (i.e., *Clock* mutant mice) demonstrating the importance of circadian rhythms in regulating normal variations observed in lipid absorption [37]. Indeed, shift workers with evidence of circadian rhythm disruption as well as individuals with social jet lag have increased risk of dyslipidemia [38].

(2.6) Electrolyte Absorption.

There is a substantial amount of evidence demonstrating that kidney-mediated electrolyte homeostasis is under circadian regulation; however, the colon also regulates electrolyte balance and appears to be under circadian regulation [36,41]. Absorption of Na^+ and Cl^- predominantly reflects the activity of two transporters, the Na^+/H^+ exchanger called NHE3 and the $Cl^-/HCO3^-$ exchanger. Aldosterone drives the changes in these receptors and aldosterone exhibits circadian fluctuations which may be what is driving changes in electrolyte absorption [42]. Alternatively, expression of these transporters may be directly controlled by the molecular circadian clock. For example, *NHE3* expression is regulated by the CLOCK/BMAL1 heterodimer via the E-box found within the *NHE3* promotor region [32,35]. Genetic manipulation of the molecular circadian clock in mice (i.e., *Cry1/Cry2* double knock out and *Clock* mutant mice) blunts the expression of the Na+/H+ exchanger *NHE3* mRNA [35,37]. Thus, chronobiology may be considered in the management of patients with GI disorders and electrolyte imbalance.

(2.7) Intestinal Barrier.

The GI tract is in continuous contact with dietary antigens and the microbiome and the intestinal barrier prevents these potentially pro-inflammatory contents from permeating the intestinal mucosa and eliciting inflammation. Accordingly, dysfunction of the intestinal barrier (i.e., gut leakiness) can promote or exacerbate inflammation-mediated diseases including those in the GI tract. Recent data demonstrates that there are diurnal fluctuations in intestinal barrier integrity [43,44]. Daily variations in barrier integrity may be due to direct effects of circadian regulation of tight junction protein expression or perhaps trafficking of tight junctions between the membrane and intracellular compartments [45]. It is not surprising then that, disruption of the host circadian rhythm can negatively impact the function of the intestinal barrier. In mice, disruption of rhythms (i.e., light:dark shifting or *Clock* gene mutation) impairs intestinal barrier integrity [45]. In addition, circadian rhythm disruption in the host makes the intestine barrier more susceptible to leakiness induced by a

secondary insult. Alcohol consumption promotes intestinal hyperpermeability in both humans and mice [45,46]. The importance of the molecular circadian clock in this phenomenon is highlighted in a study demonstrating that alcohol-induced barrier dysfunction are inhibited when *Per2* or *Clock* are knocked out in Caco-2 cells (immortalized intestinal epithelial cells that model the intestinal barrier) [47]. Moreover, the alcohol-induced effects on the intestinal barrier are exacerbated when combined with circadian rhythm disruption *in vivo*--an effect that is observed in both mice and humans. Alcohol-induced barrier dysfunction are exacerbated in mice with either environmental circadian disruption (i.e., chronic shifts in the light:dark cycle) or genetic circadian disruption (i.e., whole animal mutation of *Clock*) [45]. Similarly, circadian misalignment exacerbates alcohol-induced effects on the barrier in humans. Human night shift workers have an exacerbated response to alcohol compared to day shift workers without circadian rhythm disruption [46]. These observations may be the consequence of circadian-mediated effects on the intestine directly or they may be mediated through other mechanisms such as the intestinal microbiota [48–51].

(2.8) Intestinal Microbiota.

The intestinal microbiome is the collection of organisms that reside in the GI tract including bacteria, fungi, and viruses. The intestinal microbiota exhibits daily variations in both the abundance of certain bacteria as well as bacterial function (e.g., energy harvest, DNA repair); however, emerging data suggests that these fluctuations may not be self-sustained and instead require an intact circadian rhythm in the host. For example, the intestinal microbiota from mice with genetic circadian disruption (e.g., knockout of *Per1* and *Per2*) do not exhibit an intrinsic oscillation [50]. In addition, studies have demonstrated that circadian disruption in the host (i.e., light:dark shifting, *Clock* gene mutation) result in dysbiosis which is an abnormal intestinal microbiota community structure [52,53]. The communities of bacteria from circadian disrupted mice are characterized by an increase in the relative abundance of putative pro-inflammatory bacteria and a decrease in bacteria that are suggested to have beneficial effects on the host [52,53]. The interaction between the intestinal microbiota and the intestinal barrier is not well understood, but may include a combination of factors such as the production of microbiota-derived metabolites (e.g., short chain fatty acids) and microbiota-mediated effects on the immune system and the production of factors such as mucins and anti-microbial peptides by the intestinal epithelium [54,55]. Additional research is necessary to better understand the crosstalk between the intestinal epithelial cells and the microbiota. However, it is clear that disruption of the host circadian rhythm can markedly impact the intestinal microbiota which may make the host more susceptible to pro-inflammatory diseases.

(2.9) Immunity.

Circadian rhythms regulate much of innate and adaptive immunity including the development of specific immune cell lineages, the number of circulating immune cells, trafficking of immune cells, expression of pattern recognition receptors, secretion of complement factors, phagocytic activity, production of cytokines, and the production of other immune mediators such as histamine [56–58]. These observations have important functional consequences. For example, the ability to respond to an acute inflammatory insult

such as lipopolysaccharide (LPS, found in the outer membrane of gram negative bacteria) differs greatly depending on the time of day, with animals being most sensitive at the beginning of the active phase [59]. Similar observations have been noted for other infectious agents such as L. Monocytogenes [60–63]. These time of day-dependent observations appear to correspond to a time when there are more leukocytes found in the tissue (increased migration due to increased adhesion molecule expression and chemokine production) and enhanced sensitivity to the pathogens due to increased expression of components of the innate immune system (pattern recognition receptors such as toll like receptors (TLR)) [64–66]. Symptoms associated with certain chronic inflammatory conditions also exhibit a circadian rhythmicity including arthritis, asthma, and allergy which peak at particular times of the day [57]. It is not surprising then that disruption of circadian rhythms can lead to immune dysfunction which can manifest as increased susceptibility to infection and cancer and/or unchecked tissue and systemic inflammation. For example, mice that undergo a chronic jet lag model (i.e., mimics one transatlantic flight per week for four weeks) have increased IL-6 production upon administration of LPS compared to non-circadian disrupted mice [67]. Similar effects are observed in humans whereby circadian or sleep disruption modifies immune function resulting in inflammation [68]. This immune dysregulation is significant because it can cause collateral damage to tissues if immune activation is sustained. In addition, inflammation can disrupt the circadian clock by altering core components in the molecular circadian clock which conceivably initiates a feed forward cycle contributing to additional immune dysregulation [69]. There is much left to be understand about the nuances of how circadian rhythms govern and interact with the immune system.

(2.10) Conclusion.

Taken together, it is clear that circadian rhythms govern much of GI physiology. It is understandable then how abnormalities in circadian function may (at best) disrupt GI function with the potential to alter host metabolism and (at worst) initiate events that promote pathology and disease. The mechanisms that underlie this circadian regulation likely involve diurnal fluctuations in gene transcription--be it the production of proteins that are critical for cell cycle progression, hormones that control GI motility, digestive enzymes or transporters that control digestion and absorption, or the expression of tight junctions that are critical for intestinal barrier integrity (Figure 3). Much of the literature demonstrating these effects use global disruption of circadian rhythms (e.g., light:dark cycle shifting, whole animal genetic mutations) and because these manipulations influence circadian rhythms in systems outside of the GI tract (e.g., endocrine mediators, immune system) it is challenging to determine if the effects of circadian manipulation are directly through effects on the GI tract itself or involve a mechanism that originates outside of the GI. Future studies utilizing GI tract-specific manipulations of circadian gene expression will be helpful in determining the relative contribution of the GI tract itself on these functions. However, directly or indirectly, circadian rhythms influence much of GI physiology and disrupting these rhythms alters normal GI function and can cause disease.

(3.0) CIRCADIAN RHYTHMS, SLEEP, AND GASTROINTESTINAL DISEASE

Individuals with GI disease often complain of poor sleep quality. Sleep is one consequence of circadian rhythms therefore it is possible that poor sleep may reflect circadian rhythm disruption. Alternatively, sleep disturbance might result in circadian rhythm disruption which may promote disease pathogenesis. Given the intertwined relationship between sleep and circadian rhythms is it often difficult to parse out the relative contribution of these two processes in disease pathogenesis. For example, shift workers often have circadian misalignment as well as disrupted sleep (e.g., short sleep). Therefore, additional in-depth studies will be necessary to fully characterize the relative contribution of circadian rhythms and sleep in subject populations. Below is a summary of some GI disorders and diseases for which there are data demonstrating that circadian rhythms (and/or sleep) are important. This list is far from exhaustive and only represents those disorders and diseases that have been most comprehensively examined to date. For the sake of brevity, citations are limited to reviews when possible and the reader is encouraged to peruse these elegantly written summaries and the citations therein.

(3.1) Metabolic Syndrome.

Metabolic syndrome is a collection of metabolic abnormalities including obesity, dyslipidemia, insulin resistance, and hyperglycemia. Factors such as inactivity and consumption of an excess of calories primarily drive the development of metabolic syndrome but, the potential contribution of circadian disruption and sleep deprivation are increasingly being recognized [70–73]. Circadian rhythms and sleep regulate a wide range of normal metabolic functions including patterns of energy expenditure, hormone production, and energy metabolism [74–78]. It is not surprising then that shift work (often associated with circadian misalignment and sleep disturbances) is associated with a high incidence of metabolic disease [78–81]. There are a variety of potential mechanisms by which disrupted circadian rhythmicity or sleep can influence metabolism. For example, circadian rhythm disruption and sleep deprivation are associated with increased hunger and reduced hormonal signals associated with satiety (e.g., leptin) which may contribute to over-eating [78,82,83]. In addition, circadian rhythm disruption is associated with a reduction in melatonin production and interestingly, melatonin may be important in the regulation of glucose levels (by way of effects on β-cells in the pancreas) which is another possible mechanism by which circadian disruption can promote metabolic syndrome [84–86]. Finally, consumption of food at an inappropriate time (i.e., during the resting phase) may by itself be sufficient to induce adverse metabolic consequences. For example, eating a high fat diet during the rest phase results in greater weight gain than if the same number of calories were consumed during the active phase [87]. It is often difficult to differentiate between the effects of circadian misalignment and sleep deprivation and these studies are no exception; however, there is sufficient evidence that the effects of circadian misalignment cannot be fully explained by effects on sleep suggesting that, at least in part, disruption of normal circadian rhythms can promote metabolic syndrome [78,83,88].

(3.2) Traveler's Diarrhea.

Traveler's diarrhea is a GI disorder that results in loose stools and abdominal cramps after the acquisition of pathogens. Typically, this occurs when individuals from developed nations (e.g., North America, Europe) travel to developing nations (e.g., Central America, Africa, the Indian subcontinent, south-east Asia) [89]. Exposure to pathogens is the critical feature associated with traveler's diarrhea; however, it is important to consider the important role of the host immune response in the susceptibility to the development of traveler's diarrhea. The immune system is regulated by circadian rhythms [58,60,90–92]. Accordingly, anti-bacterial response differs throughout the day with susceptibility to bacterial infection higher at certain times of the day [93,94]. As might be expected, circadian rhythm disruption alters mucosal and systemic immunity including the ability of the immune cells to produce cytokines and other functions necessary for defense against pathogens [65,95–97]. Therefore, circadian disruption due to travel (i.e., jet lag) may impair the ability of the immune system to mount an appropriate immune response. Circadian rhythm disruption induced by genetically manipulating the molecular clock results in drastic differences in immune function compared to wild type mice. For example, *Clock* knockout mice produce fewer pro-inflammatory cytokines than wild type mice whereas Cry knockout mice produce more cytokines [92,94]. *Bmal1* knockout mice and *Per2* knockout mice have increased mortality following exposure to *E. Coli*-derived lipopolysaccharide (LPS) compared to wild type mice with similar results obtained for *L. monocytogenes* infection [60–63]. Clearly, an intact circadian clock is important in the fight against bacterial invasion. Finally, circadian rhythm disruption by itself can cause intestinal microbiota dysbiosis including an increase in pro-inflammatory bacteria as well as a loss of beneficial commensal bacteria [52,53]. The intestinal microbiota dysbiosis resulting from circadian rhythm disruption and a loss of commensals could be an opportunity for pathogenic bacteria to cause traveler's diarrhea.

(3.3) Peptic Ulcer.

An ulcer is a sore that develops on the lining of the esophagus, stomach, or duodenum. Several reports suggest that there is an association between shift work, sleep disorders, and peptic ulcer disease [98–100]. The development of gastroduodenal ulcers is multi-factorial (e.g., male sex, smoking, stress, H. Pylori) and there are several mechanisms by which circadian rhythm disruption may promote the development of ulcers [101,102]. For example, circadian rhythm disruption could result in an imbalance between protective and harmful mediators such as trefoil factor (TFF2) and gastrin [103–105]. Alternatively, it is suggested that shift work may enhance the ulcerogenic potential of the *H. Pylori* infection [106,107]. While shift work does not universally result in peptic ulcers, but, there is sufficient evidence where perhaps screening for *H. Pylori* infection in shift workers is warranted. Finally, stress has been identified as a well-established risk factor for the development of peptic ulcer. It may be that shift work and the resulting circadian rhythm disruption is a biological stressor that increases gastric acid secretion and reduces mucosal defense [108,109].

(3.4) Gastroesophageal Reflux Disease.

Gastroesophageal reflux disease (GERD) is characterized by heartburn, acid regurgitation, and/or esophageal mucosal damage. One of the main complaints of individuals with GERD

is symptoms at night, which is attributed to nocturnal reflux [110]. Indeed, there are diurnal fluctuations in gastric acid production resulting in gastric pH being the lowest during late evening/early morning [111]. Recently, studies demonstrate that night shift work is associated with an increased risk of developing GERD and/or erosive esophagitis (a complication of GERD) compared to day shift workers [112,113]. This could occur via a couple different mechanisms. The expression of circadian clock genes (or clock controlled genes) is altered in esophagus tissue of GERD patients and these changes are significantly correlated with GERD severity [114]. In addition, there may be an important mechanistic role for melatonin which increases esophageal sphincter pressure, increases anti-inflammatory molecules in the esophageal mucus, and decreases gastric acid production, these observations are interesting and future studies are necessary to better understand the mechanisms that are involved [115]. Subjects with circadian rhythm disruption have reduced production of melatonin and this could contribute to esophageal sphincter dysfunction and greater amounts of gastric acid production. In addition, it could be that circadian rhythm disruption mechanistically promotes esophageal damage by impairing cell proliferation or cell repair. While there is not an overwhelming body of literature showing that night shift work is associated with GERD, there is enough evidence to suggest that avoidance of night shift work should be considered for severe or proton pump inhibitor-refractory GERD.

(3.5) Inflammatory Bowel Disease.

Inflammatory bowel disease (IBD), including both Crohn's disease (CD) and ulcerative colitis (UC), is characterized as a relapsing and remitting disease and has no cure. Sleep is one manifestation of circadian rhythms and it is possible that disruptions in sleep may indicate underlying circadian rhythm disruption. There have been a number of studies looking at sleep in IBD subjects. Studies reveal that subjects with IBD have poor sleep quality and quantity that correlates with a worse IBD-specific quality of life scores and disease activity and is associated with increased risk of flare in CD [116–119]. In addition, histologic inflammation in IBD patients is associated with sleep disturbance [120]. Disruption of circadian rhythms causes intestinal barrier dysfunction, intestinal microbiota dysbiosis, and intestinal inflammation, all of which are factors that promote IBD pathogenesis [46,52,53]. Studies in animals support the premise that it is circadian rhythm disruption that worsens IBD. Circadian disruption promotes IBD-like intestinal pathology in an animal model of IBD (i.e., dextran sodium sulfate, DSS) [121]. Unfortunately, there is a dearth of literature regarding circadian assessments in subjects with IBD. One epidemiologic study reports no association between shift work and hospitalization of patients with IBD [122]. However, a polymorphism in the molecular circadian clock gene *Per3* is associated with increased use of immunosuppressive drugs and stricturing/fistulizing phenotype in CD [123]. In addition, some IBD patients, especially those with CD, have evidence of circadian disruption and social jet lag that is associated with a more aggressive CD phenotype (fistulizing/stricturing) [124,125]. While there are data to support that IBD patients have circadian rhythm disruption, additional studies are needed. Chronotype may be an overlooked factor contributing to IBD, specifically that an evening chronotype may be associated with poorer outcomes and more aggressive disease course [18,19,126]. However, it is important to note that the relative contribution of chronotype compared to the involvement of other factors such as circadian rhythms, sleep duration or other sleep factors

have not been well examined. We speculate that the effects of circadian rhythm disruption on IBD may be the result of impaired ability of intestinal cells to regenerate (i.e., cell proliferation) following inflammation-mediated damage and/or mucosal immune dysregulation [23].

(3.6) Colorectal cancer.

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the most prevalent cancer in the digestive system. Cancer cells rely on disrupted cellular control of proliferation, differentiation, DNA damage repair, and apoptosis, all of these processes are tightly regulated by the circadian clock [127,128]. For example, *Bmal1* plays a key role in the regulation of cancer cell-cycle progression and DNA damage response [129]. In contrast, mice with an abnormal molecular circadian clock (i.e., *Per2* knockout mice) have an increase in hyperplasia and neoplasia in response to radiation as well as increased polyp formation in mice that are genetically susceptible to developing polyps (i.e., $APC^{min/+mice}$) [130,131]. In addition, environmental disruption of circadian rhythms achieved by repeatedly altering the light:dark cycle worsens intestinal inflammation and the development of polyps in mice predisposed to do so (i.e., APC^{lox468} mice) [48]. Studies in humans are equally as compelling. Overexpression of the circadian gene *Per1* in human cancer cells lines reduces colony formation and alters the expression of cancer-relevant genes such as *c-MYC* and *p21*. Indeed, alterations in circadian clock genes and proteins including *Clock*, *Bmal1*, and *Per* are observed in cancerous tissue in the colon [132–136]. For example, *Clock* mutations are frequently observed in CRC and *Per3* is often down-regulated CRC tissue [134,136]. Several studies demonstrate that shift work increases the risk of developing CRC but this effect is not universally observed [137,138]. Mechanistically, circadian disruption may promote CRC by influencing a wide variety of cancer-related phenomena including dysregulated cell proliferation and immune dysfunction. Thus, avoidance of circadian disruption (e.g., shift work) or chronotherapy (e.g., light therapy, discussed below) to correct circadian misalignment may be considered in the management of patients with CRC and also may be a prevention strategy for those at high risk of developing CRC. High-quality clinical trials in chronobiology are critically needed to respond to this unmet need.

(3.7) Others.

There is a litany of other GI disorders and diseases that are suggested to be impacted by circadian rhythms and/or sleep including IBS, visceral pain, acute appendicitis, cholecystitis, pancreatitis, and pancreatic cancer [139–141]. Interestingly, length of hospital stay for uncomplicated (non-perforated) appendicitis is also influenced by circadian rhythms with surgeries performed later in the day resulting in hospital stays that are 60% longer than surgeries performed in the early hours of the day [141]. This may have to do with circadian variations in cell proliferation and/or immune function.

(3.8) Conclusion.

On the whole, there is evidence to suggest that circadian rhythm disruption promotes GI disease (Figure 3). The underlying theme for many of these diseases is inflammation. There are many different mechanisms by which circadian rhythms can influence inflammation. Two obvious ones are intestinal barrier dysfunction and intestinal microbiota dysbiosis;

however, there are also potential mechanisms that originate outside of the GI tract such as effects on the immune system. Future studies will be necessary to better understand the mechanisms by which how circadian disruption promotes or exacerbates GI disease. This understanding will allow for the development of effective circadian-directed treatments.

(4.0) CHRONONUTRIOTION & CHRONOTHERAPEUTICS

(4.1) Chrono-Nutrition.

The time of food consumption can impact a wide variety of physiological processes (sleep/wake cycle, body temperature) and has a dramatic effect on health with important implications for obesity and metabolic syndrome. Chrono-nutrition refers to consumption of food in coordination with the daily rhythm of the body, specifically taking into account the time of food consumption in addition to the usual considerations of amount and nutritional content of food. For example, individuals with a later chronotype tend to have a higher body mass index (BMI) compared to those with an earlier chronotype which likely stems from the fact that those individuals with a later chronotype tend to eat more calories later in the day [142,143], highlighting the importance of time of food consumption. Chrono-nutrition may be especially important when considering metabolic syndrome and metabolic pathologies such as obesity and diabetes [144,145]. Two recent studies demonstrate that consumption of the majority of calories early in the day improves metabolic markers and results in greater weight loss compared to subjects who ate the majority of their calories later in the day [146,147]. Indeed, bariatric surgery to correct obesity is less successful in individuals who tend to consume calories late in the day compared to early eaters [148]. Although circadian disruption is associated with metabolic syndrome, it may be possible to mitigate some of the adverse metabolic consequences by limiting caloric consumption. For example, rats undergoing shifts in the light:dark cycle to mimic shift work gain weight at a faster rate than their non-disrupted counterparts; however, this observation can be mitigated when food availability is limited to the active phase [149]. In conclusion, eating strategies that are mindful of the time of food consumption (e.g., large breakfast and small dinner) or restricting food to day light hours (e.g., restricted feeding) may be beneficial to mitigate some of the adverse effects of circadian misalignment on metabolism. Time of food intake robustly regulates circadian rhythms in the intestine; therefore, a circadian-friendly eating strategy may help realign peripheral rhythms in the intestine with the central circadian rhythm and this may help mitigate the development or progression of GI disease.

(4.2) Chrono-Pharmacology.

There are circadian variations in pharmacokinetics, pharmacodynamics, and drug metabolism. However, attention is now being given to selecting the appropriate time of day to administer a drug that takes into account circadian variations in gene expression and cellular processes. It is proposed that more than 80% of FDA-approved drugs target cellular processes that demonstrate a circadian rhythm; therefore, administering drugs at the time of day that best aligns with these endogenous rhythms may increase therapeutic efficacy [6]. For example, a clinical trial demonstrated that administration of a drug to control blood

sugar was more effective when administered at night compared to the day [150]. A recent paper has shed light on a potential mechanism for this time of day effect which shows that the glucose transporter *SGLT2* exhibits diurnal fluctuations in gene expression with expression being higher at night [151]. Similar time of day effects have been observed with chemotherapeutic agents administered for CRC and it is possible that this may have to do with circadian fluctuation of cell proliferation or immune function [152]. Therefore, effective pharmacological interventions may not only require administration of the right drug but also may be dependent on administering the right drug at the right time [153].

(4.3) Chrono-Therapeutics.

Circadian rhythm disruption and poor sleep are often associated with a decrease in melatonin production (or loss of the appropriate rhythmic production of melatonin). Melatonin supplementation has been suggested as a therapy for GI disease. Melatonin is an anti-oxidant that may be beneficial to blunt inflammatory processes associated with GI disease and in addition has important regulatory functions in the regulation of esophageal sphincter function and gastric acid production [115,154]. Exposure to light robustly entrains central circadian rhythms and light therapy is a well-established method to correct circadian misalignment. Indeed, light therapy has been useful for the treatment of metabolic disorders, pain management and depressive disorders, all of which are conditions that are associated with circadian rhythm disruption [155]. Although it is plausible that light therapy could also be useful for the treatment of GI disorders, further high-quality clinical trials are required before recommending it in clinical practice. As already mentioned above, the time of food consumption can be used to entrain peripheral clocks in the GI tract and may be a viable approach to selectively target rhythms in the GI tract.

(4.4) Conclusion.

There are several opportunities for circadian-directed interventions ranging from the simple to the more complex. Approaches that are easily to implement include circadian hygiene which entails maintaining consistent patterns in sleep:wake cycles and eating times as well as eating primarily during daylight hours. Other approaches are more challenging but are still viable such as exposure to bright light in the morning while others will require more research to be implemented clinically such as time of drug administration. Certainly, the coming years will shed light on the utility of these circadian-directed approaches to prevent and mitigate GI disease.

(5.0) EXPERT OPINION

More than three decades have passed since the identification of circadian rhythms in the GI tract. This topic has garnered increased attention in recent years because of the prevalence of circadian disruption in our 24/7 society including travel across multiple time zones, shift work, the use of light emitting devises at night, light pollution, societal demands resulting in social jet lag, eating at irregular times, and late-night eating. It is important to note that circadian rhythm disruption by itself may not be inherently pathogenic, as disruption by itself is often not sufficient to induce disease. For example, not all shift workers develop

disease. We believe that disruption of circadian rhythms decreases resiliency of the host resulting in increased susceptibility to developing diseases. In essence circadian rhythm disruption may be able to convert a genetic or lifestyle susceptibility into a disease phenotype. For example, alcohol-induced intestinal barrier dysfunction combined with circadian rhythm disruption exacerbates the development of steatohepatitis [45]. Studying the molecular mechanisms by which circadian disruption promotes disease could identify critical signaling pathways and novel therapeutic target to prevent disease in genetically susceptible and high-risk subjects.

One such at risk population that could benefit from this approach are African Americans. African Americans have poor outcomes for several GI diseases as well as other inflammation-mediated diseases compared to other racial groups even when socioeconomic factors are considered [156,157]. Several studies demonstrate that African Americans have alterations in their circadian rhythms (i.e., a longer tau) which makes them more susceptible to being circadian disrupted [158–160]. This observation may account for poor GI and other disease outcomes in African Americans. Studies to determine if circadian-directed interventions and/or circadian hygiene modify the incidence and/or disease course in the African American population could answer this important question. If circadian rhythm disruption is indeed a risk factor for the development and progression of GI disease in at-risk populations (e.g., shift workers), then studies are necessary to fully determine the utility of circadian-directed interventions or circadian hygiene to prevent or modify disease course. Such treatments may include light therapy, melatonin administration, regulated sleep/wake and eating time. Another opportunity to incorporate circadian-minded approach is consideration of the time that a therapeutic agent is administered. This thoughtful chrono-therapy approach has an opportunity to increase therapeutic effectiveness of the drug like chemotherapy and decrease toxicity.

There are multiple challenges and obstacles for circadian biology to become part of mainstream health care. First, the majority of data supporting the biological importance of circadian system have been obtained from *in vitro* or *in vivo* animal studies; thus, more human studies are required to establish the translational value of these data. Unfortunately, studying circadian rhythms in humans is cumbersome, expensive, and sometimes impractical. Comprehensively evaluating circadian rhythms requires collection of multiple samples over the course of 24–48 hours (typically a minimum of six) and while this is possible (albeit burdensome) for the collection of saliva and blood this is not feasible for the collection of GI samples (e.g., collection of tissues via biopsy). The other factor making rigorous, in-depth circadian studies challenging is that studies have to be conducted in the laboratory in order to control for the numerous variables that can impact circadian rhythms such as sleep, light exposure, time of eating, and temperature. There is an unmet need to discover novel methods to assess circadian rhythms accurately and practically. Recent technical advances include wearable devices like acto-watch, *in silico* computational modeling, as well as human-derived enteroids/colonoids that can monitor circadian rhythms/genes over several days from intestinal samples taken at only a single time. In the future, these approaches may prove useful to study aspects of can provide an opportunity to study circadian system and also assess the impact of intervention on circadian rhythms in humans.

Another challenge is to determine if the deleterious biological effects of disrupted circadian rhythms is due to influencing sleep. This could impact how we design interventions targeting either circadian rhythms or sleep. In addition, based on studies conducted to date it is not clear if circadian disruption promotes disease or circadian disruption is a consequence of the disease. Although these are very real challenges that experimentalists face and must solve through careful longitudinal and interventional studies, it has limited practical impact. Circadian rhythm disruption and sleep disruption typically happen together and interventions such as circadian and sleep hygiene can be implemented together (and chrono-therapy has great promise to improve sleep). Furthermore, even if circadian rhythm disruption is a consequence of disease, correcting circadian rhythm could (and should) improve disease course since circadian disruption promotes inflammation.

Another challenge is how to provide circadian-directed interventions cost effectively. This challenge can only be overcome by engaging engineering research laboratories, lighting and device industries, and public health officials. Indeed, engineering laboratories have begun to study the impact of different lights sources on circadian rhythms in order to identify “non-disrupting” evening lights without compromising visual impact and it is reasonable to believe that this goal will be achieved in a rather short period of time. Then, one needs to engage lighting and device industries to adopt these new technologies. Focusing the attention of the general public on the detrimental effects of circadian and sleep disruption will allow these industries to see commercial benefit and adopt these new approaches and implement them in their products. Lastly, public health officials and policy makers should get on board to create circadian friendly environments at home, work, and even the street using high intensity light during the day and “non-disrupting” light in the evening. This policy could be encouraged through tax incentive and rebate programs. The cost saving benefits achieved by preventing of disease would be expected to more than offset the costs.

More work needs to be done to identify optimal, personalized circadian approaches to prevent and treat GI disorders and diseases. The ultimate goal is a personalized medicine approach where the circadian phenotype for each patient is obtained and that evaluation is used as the basis for recommendations for optimal times for eating, sleep, and taking medication. In the meantime, some common sense circadian-directed approaches can easily be implemented in the clinic to improve GI function and alleviate symptoms associated with GI disease. Examples, include directing patients to primarily consume food during daylight hours when possible and maintaining regular sleep wake cycles. We have found that these recommendations are acceptable to many GI patients who are seen in our GI clinics.

Work on circadian-directed interventions has just began. Our challenge is to continue high-quality research (especially in human subjects) and advocate for increased funding for human and translational research by the National Institutes of Health and foundations. It is encouraging that one of the provocative questions posed by the National Cancer Institute is to determine the role of circadian on development and disease course of cancers. As our knowledge of circadian biology increases, it may be possible to incorporate strategies that take advantage of circadian rhythms and chrono-therapy to (1) better understand the molecular mechanism of GI disorders and identify novel therapeutic targets, (2) identify subjects at risk of GI diseases, (3) identify potential modifiable lifestyle factors that play key

roles in disparity of incidence and disease course of GI diseases like colon cancer in minorities like African Americans and (4) develop circadian-directed intervention to prevent and/or treat these diseases.

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* of interest

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Article Highlights

- Circadian rhythms are 24-hour fluctuations in biology and behavior that are driven by a molecular circadian clock that is present in nearly every cell in the mammalian body including in the intestine
- Circadian rhythms govern much of gastrointestinal physiology including cell proliferation, motility, secretion, electrolyte balance, and the digestion and absorption of proteins, carbohydrates, and lipids
- Disruption of circadian rhythms may be a risk factor that promotes a wide variety of gastrointestinal conditions and diseases including traveler's diarrhea, peptic ulcer, gastroesophageal reflux disease, inflammatory bowel disease, and colorectal cancer
- Circadian-directed approaches may improve gastrointestinal symptoms and treatment (e.g., chrono-nutrition, chrono-pharmacology, chrono-therapeutics).
- Increased awareness of the important role of circadian rhythms in gastrointestinal health and disease may lead to innovative approaches to manage gastrointestinal health and mitigate disease

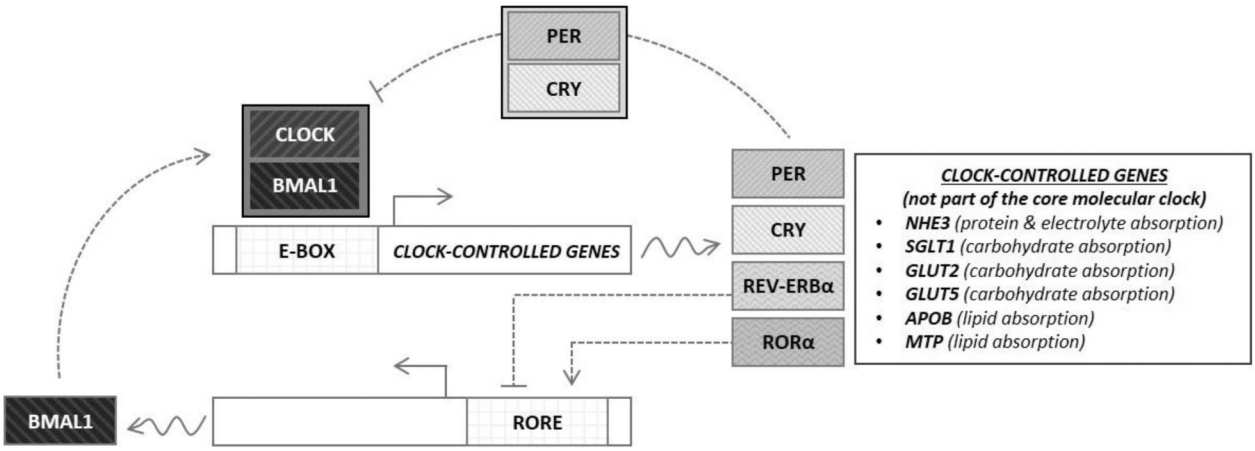

Fig 1.

The molecular circadian clock. CLOCK and BMAL are transcription factors that dimerize and initiate transcription of genes containing an E-Box in the promoter, these genes are called 'clock-controlled genes.' There are a large number of clock-controlled genes, but depicted are those that are critical for the molecular circadian clock. Following transcription and translation, PER and CRY dimerize and are translocated into the nucleus where they repress CLOCK-BMAL-mediated transcription, essentially repressing their own transcription. A secondary loop consists of transcription and translation of REVERBα and RORα the respectively inhibit and promote transcription of BMAL. CLOCK = circadian locomotor output cycles kaput, BMAL = aryl-hydrocarbon receptor nuclear translocatorlike 1 (ARNT1, also called BMAL1/2), PER = Period (Per1, Per2, Per3), CRY = Cryptochrome (Cry1, Cry2), RORα = retinoic acid-related orphan receptor, REV-ERBα = reverse transcript of erythroblastosis gene.

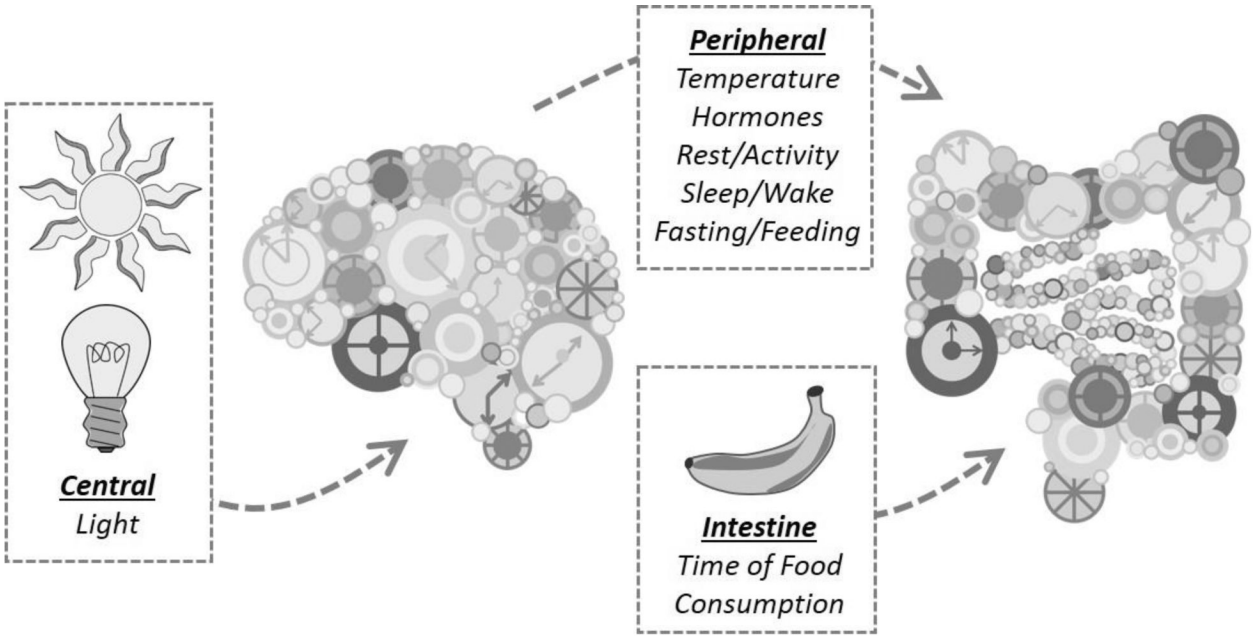

Fig 2.

Entrainment of central and peripheral circadian clocks. Light entering the eye is a primary factor entraining central circadian rhythms in the suprachiasmatic nucleus in the brain (known as the master pacemaker). The central circadian clock sets rhythms in peripheral tissues using a variety of methods including fluctuations in temperature, hormone production, and behaviorally via activities such as rest/activity, sleep/wake, and fasting/feeding. Circadian rhythms in the intestine can also be influenced by time of eating independent of input from the central circadian clock.

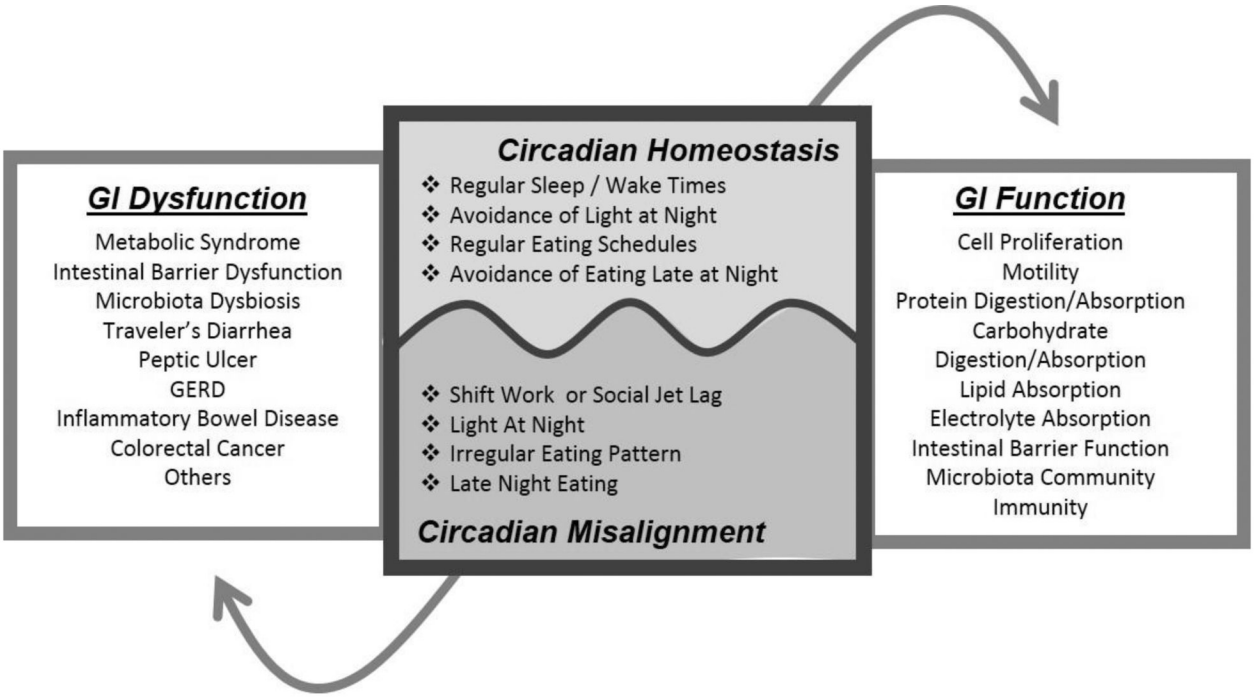

Fig 3.

Circadian regulation of gastrointestinal function and dysfunction. Circadian homeostasis is the consequence of consistent patterns of sleep/wake and eating and avoidance of eating late. Circadian homeostasis permits optimal gastrointestinal function. Conversely circadian misalignment including irregular schedules and late night eating promote disease and dysfunction in the gastrointestinal tract.