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Chairman of Chinese Digestive Psychosomatic Union
Chief of Chinese Association of Psychosomatic Digestive Diseases
Professor of Department of Gastroenterology

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The role of circadian rhythms in digestive psychosomatic disorders

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Abstract: Digestive psychosomatic disorders (DPSD) are prevalent in the clinics of physical and mental diseases. Their diagnosis and treatment are facing enormous challenges. The pathophysiological mechanisms underlying various symptoms of DPSD are still not fully identified. Circadian clocks are present in most organisms and mediate the interplay between the environment and physiological processes. The central circadian pacemaker is in the suprachiasmatic nucleus in the hypothalamus and is responsible for biological rhythms regulated by the light/dark cycle. Peripheral tissues show circadian oscillations that are coordinated by the central pacemaker. Circadian rhythms regulate a variety of gastrointestinal processes (including cell proliferation, immune homeostasis, gastrointestinal motility, gastric acid secretion, gut permeability and microbial balance and metabolism) through modulation of organ specific clock-controlled genes. Gastrointestinal symptoms are prevalent among shift workers and time-zone travelers, both of which are under conditions associated with disruption of biological rhythms. Disruption of circadian rhythmicity may lead to aggravation of DPSD. The purpose of this review is to discuss the potential role of biological rhythms in gastrointestinal diseases including gastroesophageal reflux disease, functional dyspepsia, irritable bowel syndrome, and inflammatory bowel disease. It also discuss the potential influence of biological rhythm disruption on brain–gut axis and intestinal microbiota. Finally, it discusses the remaining questions and challenges in this novel area of research.

Key words: circadian rhythms;digestive psychosomatic diseases; gastrointestinal motility;brain–gut axis;functional dyspepsia;irritable bowel syndrome;inflammatory bowel disease

Abbreviations: CD:Crohn's disease; DPSD:digestive psychosomatic diseases; FD:functional dyspepsia; GERD:gastroesophageal reflux disease; IBS: irritable bowel syndrome; IBD:inflammatory bowel disease; SCN:suprachiasmatic nucleus; UC: ulcerative colitis

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Introduction

Circadian rhythm is an internal biological clock, which enables to sustain an approximately 24-hour rhythm in the absence of environmental cues [1]. The circadian rhythm plays a crucial role in people's life. It can be affected by cosmic events related to the universe and earth, environmental factors (light, night and day duration, seasons), and life styles [2]. Normally, clocks adjust physiological responses to anticipated stimuli times. Disruption of circadian clocks/rhythms exacerbates several chronic diseases[3]. In mammals, the circadian clock mechanism consists of cell-autonomous transcription-translation feedback loops that drive rhythmic, 24-hour expression patterns of core clock components [4,5]. The mammalian suprachiasmatic nucleus (SCN) is considered to be a major component of the biological clock implicated in the temporal organization of a variety of physiological, endocrine, and behavioural processes [6]. A growing body of evidence indicates that many of these rhythms are progressively disturbed during senescence [7]. The molecular basis for biological rhythms is so-called "clock genes". The first negative feedback loop is a rhythmic transcription of period genes (PER1, PER2, and PER3) and cryptochrome genes (CRY1 and CRY2) [8]. PER and CRY proteins form a heterodimer, which acts on the CLOCK/BMAL1 heterodimer to repress its own transcription [9]. PER and CRY proteins are phosphorylated by casein kinase 1 delta, which determines the cycle length and speed of the circadian clock [10,11]. The second loop is a positive feedback loop driven by the CLOCK/BMAL1 heterodimer, which initiates transcription of target genes including E-box cis-regulatory enhancer sequences [12]. Disturbance of circadian rhythms may be associated with the occurrence of mental diseases such as depression and other diseases such as gastrointestinal (GI) diseases, cardiovascular disease and diabetes [13-15].

The 2017 Nobel Prize in Physiology or Medicine has been awarded to Jeffrey C. Hall, Michael Rosbash, and Michael W. Young for their pioneering efforts to elucidate the molecular mechanisms that drive organisms' inner biological clocks. Scientists are now looking to improve treatment of various diseases by coordinating delivery of drugs with a patient's clock [16]. The GI tract is subject to many circadian rhythms. Alterations in circadian physiology have been suggested to be associated with a variety of GI disorders including gastroesophageal reflux disease (GERD), functional dyspepsia (FD), irritable bowel syndrome (IBS), constipation, inflammatory bowel disease (IBD), and GI dysmotility [17-21]. The identification of the molecular mechanisms driving circadian rhythms now allows researchers to approach GI disorders from a chronobiological perspective [22]. The fundamental discoveries of how the circadian clock regulates the daily cycles of human physiology have important implications for pharmaceutical drug development.

Functional correlation between daily rhythms and GI physiology coordinate the timing of our internal bodily functions. Healthy individuals have bowel movements during the day, but seldom at night. Colonic motility follows a rhythm as well: most people will have a bowel movement in the morning and rarely during the night [23]. Furthermore, it is well recognized that disruption of daily rhythms can lead to GI symptoms including bloating, abdominal pain, diarrhea, and constipation. Recent work indicated that the mouse colon possesses a functional circadian clock as well as a subset of rhythmically expressed genes that may directly impact on colonic motility [24]. In addition, indexes of colonic motility such as the colonic tissue contractile response to acetylcholine, stool output, and intracolonic pressure changes vary as a function of the time of day, but these variations are attenuated in mice with disrupted clock function [25]. These laboratory findings are supported by clinical observations. GI symptoms such as diarrhea and constipation are prevalent among shift workers and time-zone travelers, both of which are conditions associated with disruptions in biological rhythms [26]. These findings imply new insights into the role of clock genes in colonic motility and their potential clinical relevance [25]. The purpose of this review is to discuss the potential role of biological rhythms in GI disorders including GERD, FD, IBS, and IBD. It also discussed the potential influence of biological rhythm disruption on brain–gut axis and intestinal microbiota. Finally, we discussed the remaining questions and challenges in this novel area of research.

Circadian rhythm disruption in GERD

GERD is a common GI disorder caused by the abnormal reflux of the gastric contents, which leads to acid damage and inflammation of the esophagus. The typical reflux symptoms is heartburn [27,28]. Clinical data shows that GERD is closely associated with sleep disturbance and that circadian rhythms are correlated with symptom severity [29,30].

Studies have shown that diurnal rhythms of circadian-clock genes such as PER1, PER2, and CRY2 are present in normal esophagus, while these rhythms are disrupted in inflamed esophagus and correlate with GERD severity. Therefore, the circadian rhythm in the esophagus might be important for the response to erosive damage in GERD patients [31]. An animal study shows that circadian variability of clock genes, except CRY1, was present in the normal esophagus and was completely disrupted in rats with reflux esophagitis during the acute phase. The circadian variability of PER2, PER3, and Arntl returned to normal, while disruption of PER1, CRY2, and CLOCK was present in the chronic phase [22]. Therefore, changes in clock gene expression might play a role in the pathogenesis of GERD.

Disorder of circadian rhythm in FD

FD is characterized by a series of abdominal symptoms with no evidence of organic diseases that could explain the symptoms. Abdominal pain, bloating and early satiety are common symptoms of patients with FD[32]. FD is one of the most prevalent functional GI disorders, but its pathophysiological mechanisms are still unknown, although they are partially associated with gastric acid secretion, gastric motility, visceral hypersensitivity, impaired gastric accommodation and personal psychological factors[33]. The role of circadian rhythm disruption in the pathogenesis of FD are still unknown. A previous study shows that the prevalence of FD in rotating shift workers is similar to that in day workers [34].

H. pylori infection is suggested to be involved in the pathogenesis of FD [35]. It has been reported that H. pylori induces BMAL1 expression at the transcriptional level, leading to disruption of the circadian rhythm [36]. Evidence shows that BMAL1, a central role in the regulation of circadian rhythm genes, could transcriptionally regulate TNF-α expression [37]. Therefore, there may be a cascade amplification of rhythm gene-mediated inflammatory response upon H. pylori infection.

The circadian rhythm disturbance in the pathogenesis of IBS

The Rome criteria for IBS have been revised and are expected to apply only to the subset of Rome III IBS subjects with abdominal pain as a predominant symptom, occurring at least once a week. The Rome IV IBS population likely reflects a subgroup of Rome III IBS patients with more severe GI symptomatology, psychological comorbidities, and lower quality of life. Some studies have reported a higher prevalence of GI symptoms such as diarrhoea, bloating, and visceral pain among the rotating shift workers compared to daytime worker [19,34]. Rotating shift workers suffer more from disruption of circadian rhythms. In a previous study [34], 207 subjects were included with 147 rotating shift workers (71.0%), and 60 (29.0%) day workers. The prevalence of IBS in rotating shift workers was higher than that in day workers (32.7% vs 16.7%, $P < 0.05$). The multivariate analysis revealed that the risk factors for IBS were rotating shift work (OR, 2.36; 95% CI, 1.01-5.47) and poor sleep quality (OR, 4.13; 95% CI, 1.82-9.40). A higher prevalence of IBS among rotating shift workers could be directly associated with the circadian rhythm disturbance. The participation in rotating shift work and poor sleep quality were significantly associated with IBS, and rotating shift work itself was related with IBS, independent with poor sleep quality[19]. Therefore, disruption of circadian rhythms may have an important role in the pathogenesis of IBS.

Clock disruption in IBD

IBD comprises a group of chronic, immune system-mediated inflammatory diseases that primarily affects the GI tract. The main subtypes of IBD are Crohn's disease (CD), ulcerative colitis (UC), and IBD-unclassified. A growing body of evidence has demonstrated a link between environmental factors that may affect circadian rhythms and intestinal health [38]. The persistent inflammation in GI tract in IBD may be due to host genetics, gut microbiome dysbiosis

and environmental factors, all of which may cause an altered mucosal barrier and decreased immune system function [39]. Circadian rhythm can affect key components of IBD disease, such as intestinal permeability [40], translocation of bacterial endotoxins and products [3], induction of intestinal dysbiosis [41] and production of pro-inflammatory cytokines [42]. All in all, among the environmental factors that may contribute to IBD pathogenesis, chrono-disruption of circadian rhythm has aroused widespread interest [43].

Deregulated immune function is closely related to aberrant intestinal inflammation in patients with IBD. Multiple aspects of immune func¬tion are under circadian control, such as host¬ pa¬thogen interactions, trafficking of leukocytes, and the activation of innate and adaptive immunity [42]. Thus disruption of circadian rhythm can lead to decreased immunity, contributing to the pathogenesis of IBD [44]. Another study suggested that alterations in expression of clock genes might be an early event in IBD pathogenesis. Young, untreated patients with IBD show reduced expression of clock genes in inflamed and non-inflamed intestinal mucosal samples [45]. Besides, higher sensitivity to inflammatory damage and deterioration of colitis were observed in mice subjected to a disruption of light-dark cycle [46].

Circadian dysrhythmia in brain–gut axis

The brain–gut axis is a bidirectional communication system between the central nervous system and the GI tract. Evidence suggests a bidirectional neurohumoral communication between the gut and brain. The timed feeding increases numbers and strengths of synapses, enhancing brain function. Intermittent fasting activates brain-derived neurotrophic factors, which are involved in mitochondrial biogenesis, DNA repair, and removal of oxidative stress products and organelles, hence increasing neuronal activation. Animal-based studies also indicate the neuroprotective and neurorestorative effects of intermittent fasting in chronic neurodegenerative disorders and acute brain injury. This protection occurs via enhanced antioxidant defenses and decreased inflammation [47]. Evidence suggests a role for the gut–brain axis and microbiota in mediating circadian effects on neurologic disorders [48]. Thus, circadian desynchronization is a potential enhancer of neurologic disorders.

Daily rhythmicity in intestinal microbiota

Intestinal microbiota, as a symbiotic biome, plays an important role in intestinal function. The intestinal microbiota undergoes diurnal compositional and functional oscillations that affect metabolic homeostasis, eliminates normal chromatin and transcriptional oscillations, but also causes genome-wide changes in both intestine and liver, thereby affecting the circadian rhythm of physiological progresses and increasing the susceptibility to diseases [49]. It is of great significance to study the circadian rhythms of intestinal microbiota and their interactions with host biological rhythms, furthermore, microbial metabolites directly affect circadian gene expression in the host [50]. A current study demonstrates that circadian disorganization can impact the intestinal microbiota [51]. The disrupted host circadian organization alters the circadian clock of the microbiota leading to a change in the intestinal microbiota community. The future studies evaluating microbial community function will be informative in determining the effects of circadian rhythm-induced changes on microbiome function including stress, inflammation, GI motility and the gut-brain axis.

Summary

In this review we discussed a variety of GI functions regulated by circadian rhythms and how dysregulation of these functions may contribute to the digestive psychosomatic diseases. Circadian rhythms regulate a variety of GI pathophysiological process including GI motility, microbiota, and inflammation. Disruption of circadian rhythms may lead to the promotion and/or exacerbation of a variety of GI disorders. In light of the growing understanding of circadian regulation in GI health and disease, preventive and therapeutic strategies from a chronobiological perspective are anticipated. Improved understanding of the mechanisms by which circadian rhythm disruption accelerates pathologies allows for discovery of diagnostic biomarkers and future targets for drug development. In the era of personalized medicine, the dimension of time needs to be brought into the equation within translational research and clinical medicine. 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 the digestive psychosomatic diseases. It is crucial to develop multicenter, multidiscipline collaborations between basic and translational scientists in the fields of circadian biology and GI motility and psychosomatic diseases.

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