



INFLAMMATORY BOWEL DISEASE



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The Role of Sleep in Inflammatory Bowel Disease

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Abstract

Normal sleep plays a pivotal role in maintaining the homeostatic balance between energy metabolism and the innate immune function within the gastrointestinal (GI) tract. While sleep is primarily centrally regulated in the hypothalamus by light-dark cycles, the majority of peripheral tissue exhibits circadian automaticity in function. This peripheral circadian function is especially evident in the GI tract, particularly as it relates to digestion

Sleep dysfunction is reported in the majority of patients with inflammatory bowel disease (IBD). Patients with both active and inactive disease exhibit patterns of sleep dysfunction. Findings of sleep dysfunction also correlate with poor Quality Of Life (QOL) indices and exacerbation of GI symptoms.

The GI flora is affected by circadian function and itself undergoes circadian variation in composition. Disruptions to normal sleep, such as that seen with circadian dysrhythmia, can lead to dysbiosis and contribute to disease progression. Disorganized sleep causes a direct up-regulation of pro-inflammatory cytokines. Additionally, sleep disturbances promote intestinal dysbiosis, a known driver of the inflammatory cascade. Lastly, sleep dysfunction may also potentiate inflammatory effects through up-regulation of stress hormone expression (i.e. steroid hormones), namely ghrelin and leptin.

Several therapeutic options targeting restoration of normal sleep could potentially have a role in the management of IBD by offsetting the pro-inflammatory mediators that result from sleep dysfunction. Melatonin supplementation has an established role in the treatment of sleep dysfunction but it may also have added benefit through its independent anti-inflammatory properties. Tumor necrosis-alpha (TNF- α) inhibitors, frequently used for IBD treatment, may positively affect sleep function in these patients which directly in turn mediates inflammation.

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Introduction

Sleep plays a critical role in the metabolic function of the gastrointestinal (GI) tract. Diurnal variation in energy metabolism, gene transcription, and microbiome composition, all contribute to the maintenance of a healthy gut [1]. Circadian dysrhythmia and sleep dysfunction result in alterations of metabolic function which is thought to play a pivotal role in the pathogenesis

of various GI diseases including gastroesophageal reflux disease (GERD), non-alcoholic fatty liver disease (NAFLD), functional GI disorders (including reflux hypersensitivity, dyspepsia, and irritable bowel syndrome (IBS)), GI cancers (esophageal, pancreatic, and colorectal cancers), as well as inflammatory bowel disease (IBD) [2]. Additionally, GI disease (in particular those



characterized by inflammation) are independently thought to contribute to the development of sleep dysfunction thus illustrating the complex relationship between GI disease and sleep and the so-called 'vicious cycle' [3].

Although the phenotypic manifestations differ for IBD, both Crohn's Disease (CD) and Ulcerative Colitis (UC) are thought to originate, in part, from a disordered inflammatory response to intestinal dysbiosis. Emerging data suggests a close relationship between circadian disruption, sleep dysfunction, and intestinal dysbiosis, all of which are catalysts in the inflammatory cascade [4]. Here, we focus on the downstream effects of sleep dysfunction and circadian alteration on disease activity in IBD.

Normal circadian rhythm

The majority of cells exhibit circadian variation within some component of their metabolic activity [4]. Central regulation of sleep control occurs in the suprachiasmatic nucleus (SCN) of the hypothalamus, and is modulated by the daily light-dark cycle to control expression of circadian CLOCK genes [5]. The GI tract undergoes daily circadian variation in metabolic activity as well. Autonomous pacemaker cells drive circadian rhythmicity via gene expression, "CLOCK" genes [6]. This circadian rhythmicity is evident in its patterns of gastric acid secretion, enzyme production, colonic pressures, and colonic contractions, which ultimately contribute to the regulation of gut motility, nutrient absorption, and cell proliferation [1]. Circadian oscillation is independent from central control, and is primarily hepatic and intestinal driven and regulated by content, frequency, and timing of food intake. Additionally, the circadian cycle has several effects on energy metabolism. Peripheral circadian oscillation can affect intracellular respiration and metabolic activity within GI epithelial cells [7]. Circadian oscillation is also seen with hepatocytes and islet cells where activity can modify insulin secretion, bile acid production, and lipid metabolism [8-10]. This is evident in the linkage between circadian dysrhythmia and diseases of compromised hepatic function, such as alcohol-related fatty liver disease (ALF), non-alcohol related fatty liver disease (NAFLD), and the metabolic syndrome [10,11] Further, daily fluctuation in gene expression results in variation in GI epithelial barrier function, and can thus modify microbiome interactions and microbial energy consumption.

Gene expression

The major genetic regulatory controllers of circadian oscillation in somatic metabolic function include the CLOCK and Bmal-1 transcription factors [12,13]. The protein products of these genes dimerize and bind to E-box, a transcription regulating site, that up-regulates expression of transcription regulators starting with period circadian protein homolog (PER-) 1 and PER-2 and Cryptochrome Circadian Regulator (CRY-) 1 and CRY-2 (which regulate circadian control of metabolic function such as lipid metabolism and gluconeogenesis) [3,14-16]. These downstream regulator proteins, PER and CRY, form a complex that feeds back to inhibit CLOCK: BMAL dimer activity, creating an oscillatory (circadian) pattern of expression [17]. In addition, CLOCK and Bmal-1 genes promote transcription of nuclear receptors that modulate catabolism of macromolecules, including fatty acids [18,19].

Epidemiology of sleep dysfunction in IBD

Nearly a third of adults in the United States (US) report that they do not get the 7 hours of sleep recommended for opti-

mal health and well-being [20]. This equates to over 70 million Americans suffering from a chronic sleep disorder [21]. Sleep dysfunction has been linked to GI symptoms (bloating, abdominal pain, diarrhea, and constipation) and GI disease, including gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), IBS, IBD, colorectal cancer, and liver disease [22]. Sleep is reportedly disrupted in 60% of IBD patients although it is important to note that it is difficult to ascertain the cause and effect relationship. It has been reported that IBD patients have poorer sleep quality, prolonged sleep latency, and increased use of sleeping pills when compared to controls [23,24]. The supporting body of evidence that has assessed sleep in IBD patients has commonly used both subjective and objective measures. In studies utilizing subjective assessments of sleep quality, the Pittsburgh Sleep Quality Index (PSQI) is typically utilized. It is a questionnaire that evaluates overall sleep health and is comprised of six domains: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping aids, and daytime dysfunction [25]. Objectively, nocturnal polysomnography (PSG) is the gold standard in assessing sleep, although wrist actigraphy is also used [26].

Prevalence of sleep disturbance has been demonstrated to be present both in those with active and inactive disease [27]. Even during periods of remission, patients with IBD have a higher prevalence of impaired sleep quality and impaired quality of life (QOL) when compared to healthy controls [28,29]. Disease specific QOL indices (the IBD Quality of Life Scale (IBDQ) Questionnaire) are inversely correlated with reported sleep quality [28,29]. When compared to inactive IBD, patients with active IBD had increased daytime sleepiness which strongly correlated with sleep quality and QOL [30]. These findings were corroborated in several other studies wherein patients with active disease had a higher incidence of sleep disturbances when compared to patients considered to be in remission (78% vs 35%) [31]. More recently, in a study of 37 active and 71 inactive CD patients and 61 controls, the Crohn's Disease Activity Index (CDAI) scores significantly correlated with poor PSQI scores ($p < 0.0001$) [32].

Conversely, it is important to note there have also been studies showing no correlation between disease activity and sleep quality. In a cross-sectional study of 166 patients with IBD, 67.5% of patients reported an abnormal PSQI. The poor sleep was associated with disability and poor quality of life as demonstrated in previous studies [33]. Interestingly, clinical measures of disease activity, type of disease (CD or UC), disease extent or phenotype was not shown to correlate with sleep quality [27,33]. However it is important to note that this is a cross-sectional study and that the lack of sleep is based on self-reported measures and lack of objective measurement of sleep. The self-reporting questionnaires and small sample sizes certainly can limit the interpretation and clinical applicability.

Overall, these studies suggest a relationship between disease activities and sleep disturbances. More importantly, it demonstrates that patients with IBD have poorer sleep quality when compared to controls. Additionally, these studies provide insight on possible subclinical disease activity in patients with inactive disease and poor sleep, although few studies have correlated subjective sleep scores with endoscopic pathology. One study did note a PSQI > 5 had a 83% positive predictive value of subclinical histological inflammation, independent of their clinical status [34]. These findings suggest in patients in remission, subclinical inflammation may be influencing their poor sleep.

There is limited research on objective measures of sleep disturbance in IBD patients. Assessment of sleep quality has been studied using wrist actigraphy and PSG. When comparing inactive IBD to IBS and controls, the study using PSG demonstrated the inactive IBD group had mean sleep efficiencies under 85% and almost twice the amount of stage 1 sleep and arousal indexes when compared to controls [28]. In a home PSG study, patients with inactive disease reported less REM sleep and longer periods of oxygen desaturation below 90% when compared to controls [35].

Using wrist actigraphy, in a cross-sectional study of 37 adults with IBD, poor sleep quality did correlate with GI symptoms [36]. The study found inter-daily stability of the rest-activity rhythms (RAR) to be associated with GI symptoms in those with IBD, such as heartburn/reflux and gas/bloating, whereas intra-daily variability of the RAR was associated with heartburn/reflux solely [36]. The authors concluded poor sleep did not correlate with disease severity with no statistically significant difference between those with and without active disease. Further, there were no statistically significant differences between GI symptoms in those with and without disease, suggesting these patients may have comorbid IBS. Further studies examining these associations are necessary given the limitations of a cross-sectional study. Contrary to these findings, a recent study of a mixed cohort of 72 patients (28 subjects in remission, 22 subjects with mild disease activity, and 22 subjects with moderate to severe disease activity) reported disease severity to be a significant factor that leads to sleep dysfunction in CD.²⁴ Compared to subjects in remission or in those with mild disease, those with moderate to severe CD spent a significantly longer time awake after falling asleep (44.3 minutes versus 49.1 minutes versus 65.8 minutes, respectively; $P < 0.05$). Further, those with moderate to severe CD had significantly lower sleep efficiency compared with those with remissive CD (86.6% vs. 89.9%). The study concluded moderate to severe CD disease activity was significantly associated with an increased amount of fragmented sleep.

Overall, both active and inactive IBD patients have poorer sleep parameters as assessed through objective and subjective measures. The findings illustrate that the correlations between subjective and objective measures of sleep vary between studies. In fact, in a study of 121 subjects, subjective measures of poor sleep in CD patients did not correlate with objective measures of sleep quality [37]. This indicates additional factors that may be influencing subjective sleep measures that are not captured with objective criteria. Further, subjective and objective assessments ascertain different domains of sleep that are not mutually exclusive [24].

Microbiome variation in normal and dysfunctional sleep

The composition of commensal gut flora undergoes daily variation [38]. Changes in feeding pattern and gut circadian function can alter the timing of this daily variation, and it is believed that this daily oscillation contributes to changes in effectiveness of macronutrient metabolism [39]. Circadian dysrhythmia may lead to loss of this daily variation and lead to abnormal energy harvest and metabolism [40,41]. Acute sleep dysfunction such as jet-lag, or change in wake or bedtime, has been demonstrated to contribute to compositional alterations in the colonic microbiome [42]. The microbiome changes seen in chronic sleep dysfunction, however, may have some persistence despite therapeutic improvement in sleep parameters [43].

Sleep dysfunction contributes to decreases in bacterial diversity, epithelial barrier function, microbial mucosal adherence, and an increase in inflammatory changes affecting the GI epithelium [44]. This has been demonstrated in murine models, where disruption of the circadian rhythm led to the loss of epithelial barrier integrity [45]. In mice fed with high-fat, high-sugar diets, 12-hour light:dark (LD) phase shifts altered the commensal microbiome as seen by a decrease in *Bacteroidetes* spp and an increase in *Firmicutes* spp (a pro-inflammatory driver) [46]. Local dysbiosis is thought to result in a localized inflammatory response [47]. This commensal dysbiosis impacts the microbe-epithelial interactions and ultimately affects epithelial cells and its role in maintaining barrier function [47].

Sleep dysfunction and inflammation

Sleep dysfunction and circadian dysrhythmia alter innate immunity and trigger the inflammatory cascade, adding to the chronic inflammatory state of IBD [48]. The relationship between circadian dysrhythmia and IBD is demonstrated by the dysregulation of the immune system leading to an abnormal production of pro-inflammatory biomarkers and alterations in gut-brain axis through neurohormonal changes [48,49]. The altered immune and neurohormonal systems are directed by cytokines such as tumor-necrosis-factor-alpha TNF- α , IL (interleukin-) -6, -12 and neurohormones including cortisol, estrogen, catecholamines, γ -amino-butyric acid (GABA), ghrelin, and leptin. Together, they play a key role in sleep dysfunction and IBD.

Cytokines and pro-inflammatory biomarkers

An increase in pro-inflammatory biomarkers has been seen in partial sleep deprivation, continuous sleep deprivation, sleep restriction, and sleep fragmentation, although levels vary with sleep deprivation durations [48,50,51]. In IBD murine models, circadian rhythm disruption promoted intestinal inflammation, worsened disease severity, propagated inflammatory cytokines, and had an overall increased mortality rate compared to IBD controls [52,53]. In dextran sodium sulfate (DSS) challenged mice, with drug-induced colitis, LD phase shift or disruption of the circadian rhythm increased weight loss, myeloperoxidase (MPO) levels, histopathologic confirmed tissue injury, and mortality [52,53]. Similar models looking at the level of inflammatory cytokines confirmed elevated IL-1 β , IL-18, IL-6, TNF- α , IFN- γ , CCL-2, CCR-2, and iNOS mRNAs in the LD phase shift group [54,55]. Light and dark cycle also regulated TNF bursts that involved bone marrow hematopoietic stem and progenitor cells, providing replenishment of cells not only for blood cell production but also for host immunity [56]. Conversely, TNF may play a role in feedback regulation of CLOCK gene expression [57]. The induced TNF- α in sleep dysfunction suppressed expression of PER-1, -2, and -3 genes and interfered with normal circadian rhythm [58].

The up-regulated cytokine response seen in animal studies are also evident. The loss of sleep up-regulates the inflammatory cascade which results in elevated TNF- α and IL-6 cytokines [59]. These elevated cytokines are associated with IBD activity [48]. Inhibitors of these cytokines have been a target for directed therapeutic agents [60,61]. Anti-TNF- α agents such as infliximab, adalimumab, golimumab, and certolizumab pegol are currently used for induction and maintenance of UC and CD, and anti-IL-6 antibodies such as tocilizumab and PF-04236921 show promising remission rates in active crohn's disease [62-64]. These agents with known efficacy in IBD propose an interesting question of its effect in sleep as TNF- α and IL-6 are dys-

regulated in circadian dysrhythmia. In patients with treatment resistant major depression, infliximab significantly decreased the spontaneous arousal index and sleep period time, suggesting an improvement of sleep alteration [65]. In patients with rheumatoid arthritis under anti-TNF- α treatment, a significant improvement of sleep quality or PSQI were reported [66]. Similar results were shown in patients with ankylosing spondylitis and psoriatic arthritis who received anti-TNF- α therapies and in patients with rheumatoid arthritis treated with tocilizumab [67-70].

The production of IL-12 follows a circadian rhythm which has a nocturnal peak although nocturnal wakefulness disrupts normal production [71]. In murine models, mice with psoriasis that were subjected to sleep deprivation showed an increased level of IL-12 [72]. The IL-12 also serves as a key component in the inflammatory cascade involved in IBD [73]. IL-12 induces IFN- γ and Th-1, which in turn modulates T cells and NK cells, ultimately leading to intestinal inflammation [74]. The given pathophysiology of IL-12 led to the development of IL-12 inhibitor, ustekinumab as a therapeutic option. Ustekinumab is an anti-IL-12/23 antibody that is currently used for induction and maintenance phase of moderate to severe UC and CD [75,76]. The effect of ustekinumab on patients with sleep impairment and moderate to severe CD has been investigated [77]. The study demonstrated that there was a significant improvement in sleep quality evidenced by a decrease in total Jenkins Sleep Evaluation & Questionnaire (JSEQ) scores in patients treated with ustekinumab at week 6 [77].

C-Reactive Protein (CRP) is an acute phase reactant that is formed in response to inflammatory stimuli [78]. This is synthesized in the liver through via IL-1, IL-6, and TNF [79]. The association of CRP with sleep has been linked whereby increased levels were associated with total and partial sleep deprivation [80]. In IBD patients, CRP can serve as a predictor of sleep impairment [81]. The IBD patients with a higher level of CRP (defined as level greater than 8 mg/dL) were more likely to have poor sleep when compared to the patients with normal CRP levels [81]. The association of CRP and sleep impairment is likely bidirectional whereby sleep dysfunction and active IBD perpetuates a sustaining cycle.

Neurohormonal changes

The bi-directionality of the gut-brain axis involving neuronal, hormonal, metabolic, immunologic, and microbial signals allows the brain to monitor physiologic and inflammatory changes of the gut [49]. The disruption of the gut-brain axis resulting from chronic inflammation mainly involves the hypothalamic-pituitary-adrenal (HPA) axis, sympathetic-parasympathetic system, autonomic nervous system, and the limbic system [49]. Neurohormonal changes from HPA axis have been shown to modulate the sleep-wake cycle [82]. Sleep dysfunction commonly results in hyperactivation of this axis [82]. Cortisol, a product of HPA axis, is closely associated with the sleep-wake cycle and physiologic homeostasis. It shows a reciprocal relationship between HPA and sleep regulation [82]. Cortisol level rises during early sleep and peaks at early morning before declining gradually throughout the day. The hyperactivation of HPA axis with sleep dysfunction produces a higher level of cortisol, induces sleep fragmentation and, in turn, worsening the perpetual loop of HPA axis and sleep dysfunction [82]. The elevated cortisol level as a result of sleep dysfunction directly affects the gastroenteric

system with increased gut permeability [83-85]. This result of increased gut permeability is also seen in models with psychosocial stressor that induces increased level of cortisol [84]. A proposed mechanism of increased intestinal permeability is mediated by the degranulation of mast cells [84]. The proposed thesis underlying chronic inflammation and increased permeability is demonstrated in which translocation of bacteria through the intestinal barrier incites an inflammatory reaction [84,86]. The rise of cortisol in sleep dysfunction parallels the physiologic stress induced intestinal permeability.

The impact of exogenous corticosteroids as a treatment for inflammatory diseases is well established, and the effect of systemic steroids on sleep is also well described in inflammatory conditions such as rheumatoid arthritis. Systemic steroids in active rheumatoid arthritis patients resulted in poor sleep quality and shorter duration of sleep [87]. In patients with IBD, fatigue, which is directly associated with sleep quality, was shown to be increased in those who received systemic steroids [88].

Estrogen dysregulation in sleep dysfunction is evident in post-menopausal women [89,90]. The loss of ovarian production of estradiol commonly affects the normal circadian rhythm [91]. This associated sleep disruption is mitigated with estrogen replacement therapy [90]. Estrogen influences the gastroenteric system through widely present estrogen receptors (ER) α and β in colonic epithelial cells [92]. The ER- α receptors has a role of colonic homeostasis by maintaining gut barrier integrity. In estrogen negative mice and IBD patients, estrogen receptor- α expression is significantly reduced in the colonic mucosa of active IBD [92,93]. This deficiency is inversely correlated to the level of IL-6 [93]. The deficiency of the ER- β receptors allows increased gut permeability, which results in further inflammation [92,93].

γ -Amino-Butyric Acid (GABA) is a neuropeptide that is widely expressed in the SCN. Although the exact mechanism of action of GABA in the SCN is still much debated, the role of GABA in circadian rhythm is shown in a model with Vesicular GABA Transporter (VGAT) deficient mice [94]. The VGAT deficient group showed an increase in burst firing of SCN indicating coordinated GABA secretion is needed to maintain and stabilize normal circadian rhythm [94]. The neuropeptide in the enteric system has recently revealed its role in DSS-induced mouse model. The murine model demonstrated that GABAergic signals are up-regulated in colorectal mucosa epithelium. Additionally, the GABA treated DSS group were more likely to have intestinal damage, which suggests that GABA inhibits intestinal barrier integrity and allows bacterial translocation. Interestingly, GABA has shown to suppress inflammatory cytokines such as TNF- α , IFN- γ , and IL-12 within the colonic tissues [95]. We speculate that GABA's role in decreasing intestinal barrier integrity and promoting cytokine release contribute to chronic inflammation in IBD.

Catecholamines

Catecholamines are monoamines produced in different organs as a response to homeostatic changes. Epinephrine (E) and norepinephrine (NE) are mainly produced in postganglionic sympathetic nerve fibers and adrenal medulla, and dopamine (DA) is produced in the brain or substantia nigra [96]. Catecholamines are produced in synchrony both with circadian rhythm and in response to stress [97-99]. Circadian disruption, however, creates alteration in catecholamine dynamics. In murine models, rats that underwent 1 month of circadian desynchrony or in constant light showed at least a 2-fold decrease in

E, NE, and DA [100].

Catecholamines regulate blood flow, innate immune system, nutrient absorption, and motility within the GI system [96]. The neuropeptide links the CNS and immune or lymphoid organs, such as the enteric system, through sympathetic, peptidergic, and sensory nerve fibers [101]. The sympathetic nervous system serves both pro-inflammatory and anti-inflammatory roles in the enteric system [102]. The difference in its role relies on the specific receptors. β 2-adrenergic receptors are thought to be anti-inflammatory through suppression of pro-inflammatory cytokine release [103,104]. The anti-inflammatory role is evident in the DSS-colitis murine model in which sympathetic denervation led to worse outcomes of colitis [105]. In patients with IBD, β -blocker usage showed an increase in disease relapse [106]. As opposed to β 2-adrenergic receptors, α -adrenergic receptors show pro-inflammatory response [107]. In addition, α 2-adrenoceptor antagonists in DSS-induced murine colitis down regulate pro-inflammatory cytokines TNF- α and IL-1 β and ameliorated colitis [108]. Although there is limited data on the α 2-adrenoceptor antagonists in IBD patients, this proposes a direction for future therapeutic implications. Overall, given the complicated effects of catecholamine and its receptor response, the exact mechanism of catecholamine in sleep dysfunction and IBD is largely to be determined.

Ghrelin

Ghrelin is a gastric pro-kinetic, orexigenic, and adipogenic peptide that is secreted mainly from the stomach [109]. Ghrelin secretion is oscillatory, following the circadian rhythm and peaking in the biological evening [110,111]. Changes however are also based on the sleep-wake pattern. Postprandial ghrelin levels were increased in the sleep misalignment group compared to that of sleep aligned [110,112]. The altered ghrelin level with sleep disturbance is also observed in liver cirrhosis patients, and interestingly a treatment with ghrelin restored circadian disruption in murine models with steatohepatitis [113]. In murine models, intestinal inflammation is associated with an elevated level of ghrelin level [114]. However, exogenous ghrelin imposed anti-inflammatory responses on colitis-induced rats in conjunction with restoring colitis induced blood flow and decreasing mucosal DNA synthesis [114-116]. In human subjects, ghrelin level was increased in the colonic mucosa of UC patients with active disease [117]. The elevated ghrelin level in sleep disruption and IBD may be a response to physiologic stress, and thereby may be an additional therapeutic target for IBD treatment.

Leptin

Leptin is an adipocyte-derived hormone that regulates food intake and metabolism [118]. Leptin levels follow a diurnal pattern, and the secretion of leptin is highest during the night and lowest during midday [119]. In murine models, LD cycle disrupted mice resulted in imbalance of energy homeostasis with reversal of diurnal pattern of leptin secretion [118,120,121]. Leptin shows pro-inflammatory activity in response to inflammatory stimuli including IL-1, IL-6, or LPS [122-124]. Leptin deficient mice showed a significant inflammatory response in DSS induced colitis [125]. The data on the expression of leptin in IBD patients, however, are rather conflicting. Some studies found that leptin levels positively correlate with IBD severity, while others have found reduced levels of leptin in IBD patients [126-129]. These studies, however, are partially limited by sample size. Further research is needed to conclude the exact role of leptin in IBD patients.

Therapeutic options for IBD and sleep dysfunction

Melatonin

Melatonin (N-acetyl-5-methoxy-tryptamine) is a pineal neurohormone responsible for regulating sleep-wake cycles. Melatonin is also produced by enterochromaffin cells in the GI tract [130]. In fact, the concentration of melatonin in the GI tract is 400-fold greater than that in the pineal gland [131]. Certain GI bacteria act as important regulators in melatonin synthesis by regulating the availability of tryptophan (Trp) to the host [132]. The metabolism of Trp is important in regulating sleep patterns as its direct metabolic product is melatonin [133]. In addition to its regulatory function when metabolized to melatonin, Trp plays an important role as an immunomodulator at the microbiome-host interface and insufficiency of this metabolite may alter the microbiome and impair intestinal immunity in IBD patients [134,135]. In fact, Trp deficiency has been implicated in patients with IBD [136]. It is unclear, however, if Trp deficiency precedes IBD or is a consequence of; suggesting the need for future studies regarding whether modification at this point in the Trp-melatonin pathway affects IBD [133,136].

Melatonin may be secreted into the lumen of the GI tract as a signaling link between host-commensal communication with the gut [137]. An indication of this signal has been observed with circadian swarming activity induced in *Enterobacter aerogenes* with melatonin, indicating a synchronization of multiple circadian pacemakers [38]. Melatonin is a key signaling molecule in the gut-brain axis and between the nervous, endocrine, and immune systems [138]. Both *in vivo* and *in vitro* studies have illustrated melatonin as a key neuro-immunomodulating chemical with both anti-inflammatory and pro-inflammatory effects [139-142]. Melatonin and melatonergic agonists can modulate immune function by potentiating signal cascades resulting in anti-oxidant and anti-inflammatory outcomes [143,144].

Melatonin potentiates anti-oxidant effects through free radical scavenging activity of the metabolites N(1)-acetyl-N(2)-formyl-5-methoxykynuramine (AFMK) and N(1)-acetyl-5-methoxykynuramine (AMK) [145,146]. Moreover, melatonin's role is to protect against oxidative stress [146]. The protective effects of melatonin were demonstrated to protect against ischemia/reperfusion-induced damage and oxidative damage-related disorders affecting the brain [147]. The anti-oxidant effects of melatonin as a therapeutic intervention have been studied in several other inflammatory diseases [148-150].

In addition to the circadian and anti-oxidant roles of melatonin, it can act as a direct immune-modulator [151]. The modulatory effect of melatonin on the innate and adaptive immune system is evidenced by the synthesis and storage of melatonin by immunocompetent cells and the presence of melatonin receptors in immunocompetent cells [152-154]. In reference to its direct immunomodulatory effects on cytokine production, melatonin has been implicated as both a pro- and anti-inflammatory regulator depending on the context. For instance, melatonin has been reported to stimulate the production of pro-inflammatory cytokines, such as IL-1 β , IL-2, IL-6, IL-12, TNF- α , and IFN- γ [155-157]. The ability of melatonin to enhance inflammatory cytokine production *in vitro* may be understood to reflect a pro-inflammatory state. *In vivo*, however, the relevance is far from certain, especially considering the anti-oxidative processes, anti-inflammatory, and decreasing free radical formation discussed herein. Further, the majority of the *in vivo* effects obtained are associated with shifts in size of leukocyte subpopu-

lations and clonal or sub-population expansion [158-160]. Melatonin's anti-inflammatory properties are demonstrated by a reduction in the pro-inflammatory cytokines: TNF- α , IL-1 β , IL-6, and IL-8, and an elevation in the level of anti-inflammatory cytokine IL-10 [158,161].

With respect to phagocytes and lymphocytes, melatonin treatment enhances proliferation of NK cells, T and B lymphocytes, granulocytes, and monocytes [162]. In addition to enhancing proliferation and differentiation, melatonin can increase the number of Th (CD4+) lymphocytes, and augment their activity via antibody responses *in vivo* [163-165]. This has been demonstrated in pinealectomy murine models wherein the density of lymphocytes decreased significantly and was reversed by melatonin supplementation [166]. The expression of Th1-, Th2- and Th17-related cytokines in the serum of pineal exfoliated mice was found to be lower than that of normal mice however, as demonstrated in previous studies, these cytokine levels were restored with melatonin supplementation. Melatonin supplementation was also demonstrated to affect differentiation of Th17 cells. Additionally the B cell activation pathway was significantly inhibited after pineal exfoliation, compared with the normal group. Activation of B cells was also demonstrated in the group after four weeks of supplementation and returned to levels similar to that of normal group. These effects have implications in inflammatory conditions as a potential for immune-enhancement.

The anti-inflammatory actions of melatonin are multifactorial. Melatonin suppresses activation of the inflammasome NOD-like receptor 3 (NLRP3) [167]. NLRP3 is a key mediator of the innate host inflammatory response, an important effector of gut permeability, and known to interact with the microbiome [168]. It is activated by molecular signals such as bacterial by-products and microbial proteins, which then activates inflammatory cascades via chemokines. It has been proposed that the inflammasome is a precipitation of the dysbiosis that contributes to immune dysregulation such as those with IBD [169,170]. Concerning signaling, the well known inhibition of NF- κ B activation by melatonin has also been implicated in the suppression of NLRP3 [168,171]. Another key process in suppressing inflammation concerns melatonin's ability to inhibit TLR4 (toll-like receptor 4) activation via TLR4/NF- κ B signaling, which subsequently decreases expression of downstream pro-inflammatory cytokines [172].

Melatonin supplementation may offer new opportunities for a multimodal management of IBD. Although there is a substantial amount of evidence purporting the anti-inflammatory and immunomodulation effects of melatonin, the physiological role of melatonin in the intestinal tract is poorly characterized. However, *in vitro* models have demonstrated melatonin to act via local signaling pathways to modulate inflammatory processes at the intestinal level [173]. In an *in vitro* model of inflamed intestinal epithelium, melatonin was shown to attenuate an inflammatory response via a decrease in inflammatory mediators [173].

In murine models, melatonin has been shown to improve disease severity in trinitrobenzene sulfonic acid (TNBS)-induced colitis. This has been attributed to blocking transcription factors such as NF- κ B and reducing free radical formation [174]. The result is consistent with a previous study in a TNBS rat model wherein melatonin injection at 10 mg/kg/day for 15 days significantly decreased indicators of oxidative damage and increased the colonic level of glutathione [175]. The results of this study

imply a reduction in mucosal damage due to the anti-oxidant and anti-inflammatory effects of melatonin, which may be beneficial for IBD patients.

The effect of melatonin administration has also been tested DSS-induced colitis rat models. Melatonin improved DSS-colitis and reverted microbial dysbiosis in wild-type mice via TLR-4 signaling [176]. The study demonstrated that melatonin significantly increased goblet cells, antimicrobial peptides, and the ratio of *Firmicutes* to *Bacteroidetes* [176]. These findings were corroborated in another study that showed melatonin minimized weight loss and improved clinical disease indices in DSS colitis models [177].

The role of melatonin has been investigated in sleep-disruption colitis models as well. Supplementation with high dose melatonin (20 and 40 mg/kg) reversed sleep deprivation-induced mucosal and microbiome changes and improved the mucosal injury and dysbiosis of the microbiota in the colon of DSS murine models [45]. More recently, a study explored the underlying mechanism examining these changes wherein melatonin (10 mg/kg for 4 days intraperitoneally) alleviated circadian disruption-induced worsening of colitis in DSS-colitis mice [178]. The high mobility group box 1 protein (HMGB1) can act as a crucial link in the circadian rhythm-inflammation pathway [179]. HMGB1 is a member of the damage-associated molecular pattern (DAMP) family, that can be secreted as an inflammatory mediator by binding to TLR-4 and inducing a cytokine cascade [180]. Circadian disruption suppress melatonin levels and worsens colitis, which is associated with an increase in the levels of HMGB1, TLR4, NF- κ B, and inflammatory cytokines [178]. Together, the evidence supports that melatonin may decrease the progression of IBD by reducing stimulus for inflammation, oxidative stress, and the levels of pro-inflammatory cytokines [181].

The application of melatonin in clinical studies has been investigated in a limited capacity. In 2011, adjuvant treatment with melatonin in patients with UC was explored [182]. The 12-month study involved 60 patients with UC determined to be in clinical remission. The patients were randomized into two groups (placebo group: Mesalamine daily 2 x 1 gram daily versus interventional group: Melatonin 5 mg daily at bedtime in addition to mesalamine daily 2 x 1 gram daily). The placebo group reported significantly higher Mayo Clinic disease activity indices when compared to the melatonin group at 6 months, 9 months, and 12 months. Additionally, the melatonin group demonstrated lower CRP concentration levels when compared to the placebo group. These results indicate that adjuvant melatonin therapy may be a therapeutic option in sustaining remission in ulcerative colitis patients.

Most of data on ameliorative effect of melatonin on colitis come from animal studies. Further, the high doses used in the experimental animal models generate concern in the application of these doses in clinical trials. However, the safety profile of melatonin has been demonstrated to be tolerable in higher doses. For instance, a study evaluating 60 milligrams of intravenous melatonin during surgery demonstrated an excellent safety profile without complications [183]. Although there is a lack of data in the literature from clinical randomized studies on the therapeutic effectiveness of melatonin, the anti-oxidant and anti-inflammatory effects of melatonin have been extensively demonstrated in experimental animal models. Melatonin's effectiveness as a therapeutic modality in clinical trials should be investigated further to determine the effects for disrupted sleep

on the course of IBD.

TNF- α inhibitors

TNF- α inhibitors (infliximab, adalimumab, certolizumab-pegol, and golimumab) are used to treat various immune-mediated diseases, including IBD [184-186]. TNF- α inhibitors have demonstrated significant efficacy in achieving remission in IBD [187,188]. These agents block both metabolites of TNF, sTNF and tm TNF, which both play an active role in genesis of the inflammatory cascade [189]. Literature has demonstrated some benefit on sleep dysfunction with use of these agents in rheumatoid arthritis, ankylosing spondylitis, as well as in IBD patients [190-192]. Although the benefits may be secondary to decreased symptoms preceding the sleep disturbances [48]. Nonetheless, anti-TNF medications are widely used in the management of IBD. Improvements in sleep quality may be due to a systemic effect on the central nervous system or may be secondary to improvements in disease activity and decreased inflammation [193]. Vedolizumab, an $\alpha 4\beta 7$ anti-integrin, has been shown to be as effective as systemic anti-TNF- α inhibitors in improving sleep and mood quality in patients with moderate to severe IBD, suggesting the improvement is secondary to improved disease activity and decreased systemic inflammation [191]. The improvements were observed at 6 weeks and persisted up to 1 year. Since sleep disturbances are present in those with subclinical disease burden, further study of anti-inflammatory medications in those with inactive disease and sleep disturbances may shed light on the mechanisms that drive poor sleep.

Conclusions

Sleep disruption and IBD are closely linked. Patients with IBD are at high risk for sleep dysfunction. Circadian dysrhythmia can directly contribute to IBD pathogenesis through the activation of inflammatory and neurohormonal pathways or can indirectly promote pathogenesis through gut dysbiosis and subsequent cytokine response. TNF- α inhibitors are frequently used to treat IBD, but may also reduce sleep dysfunction in these patients. Melatonin use has demonstrated efficacy in sleep disorders, but its active role in modulating immune function suggests that it may be a promising option for both IBD symptoms as well as IBD-related sleep dysfunction.

Chapter highlights

Normal circadian rhythm

- Central circadian regulation occurs in the hypothalamus in response to the light:dark cycle.
- Peripheral circadian automaticity is present in GI tissues, and regulate metabolic activity in response to feeding time.
- CLOCK and Bmal1 gene expression and subsequent PER and CRY expression lead to these metabolic effects. Negative feedback is responsible for the oscillatory mechanism.

Microbiome variation in normal and dysfunctional sleep

- GI flora undergoes daily oscillatory variation in response to feeding patterns, and sleep dysfunction can lead to loss of this variation.
- Dysbiosis associated with sleep dysfunction can contribute to IBD pathogenesis.

Sleep dysfunction and inflammation

- Sleep dysfunction can lead to expression of pro-inflammatory cytokines that are associated with IBD pathogenesis.
- The inflammatory effects seen in IBD are potentiated by circadian dysrhythmia that manifests through changes in neurohormonal expression of cortisol, estrogen, GABA, and catecholamines, as well as through protein hormones including ghrelin and leptin.

Therapeutic options for IBD and sleep dysfunction

- Melatonin is synthesized in the GI tract and affects immune cell proliferation, microbiome-gut communication, and inflamma some activation.
- Melatonin supplementation may have therapeutic use in IBD as well as IBD with associated sleep dysfunction due to its many anti-inflammatory and circadian effects.
- TNF- α inhibitors are frequently used in IBD treatment and may improve IBD-related sleep dysfunction, though some of the benefit may be from direct disease-mitigating effect.

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