Circadian rhythms and melatonin metabolism in patients with disorders of gut-brain interactions

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Circadian rhythms are cyclic patterns of physiological, behavioural and molecular events that occur over a 24-h period. They are controlled by the suprachiasmatic nucleus (SCN), the brain’s master pacemaker which governs peripheral clocks and melatonin release. While circadian systems are endogenous, there are external factors that synchronise the SCN to the ambient environment including light/dark cycles, fasting/fed state, temperature and physical activity. Circadian rhythms also provide internal temporal organisation which ensures that any internal changes that take place are centrally coordinated. Melatonin synchronises peripheral clocks to the external time and circadian rhythms are regulated by gene expression to control physiological function. Synchronisation of the circadian system with the external environment is vital for the health and survival of an organism and as circadian rhythms play a pivotal role in regulating GI physiology, disruption may lead to gastrointestinal (GI) dysfunction. Disorders of gut-brain interactions (DGBIs), also known as functional gastrointestinal disorders (FGIDs), are a group of diseases where patients experience reoccurring gastrointestinal symptoms which cannot be explained by obvious structural abnormalities and include functional dyspepsia (FD) and irritable bowel syndrome (IBS).

Food timing impacts on the production of melatonin and given the correlation between food intake and symptom onset reported by patients with DGBIs, chronodisruption may be a feature of these conditions. Recent advances in immunology implicate circadian rhythms in the regulation of immune responses, and DGBI patients report fatigue and disordered sleep, suggesting circadian disruption. Further, melatonin treatment has been demonstrated to improve symptom burden in IBS patients, however, the mechanisms underlying this efficacy are unclear. Given the influence of circadian rhythms on gastrointestinal physiology and the immune system, modulation of these rhythms may be a potential therapeutic option for reducing symptom burden in these patients.

Keywords: functional gastrointestinal disorder, functional dyspepsia, disorders of gut brain interaction, melatonin, circadian rhythm, irritable bowel syndrome
INTRODUCTION

Circadian rhythms are endogenously generated cycles of molecular, physiological and behavioural events that occur within an organism approximately every 24 h. These rhythms are created and maintained by independent transcriptional and translational feedback loops in peripheral tissues (known as peripheral clocks) which are controlled by the suprachiasmatic nucleus (SCN), the master pacemaker located in the hypothalamus (Plautz et al., 1997). The activity of these genes (including Circadian Locomotor Output Cycles Kaput, CLOCK; Brain and Muscle ARNT-Like 1, BMAL1; referred to as “clock genes”) drive circadian rhythms and can be synchronised to the ambient environment by external signals called zeitgebers (German for “time giver”) including light (Johnson et al., 1988), feeding times (Damiola, 2000), ambient temperature (Hastings and Sweeney, 1957), and physical activity (Edgar and Dement, 1991). Within the gastrointestinal tract (GIT), circadian cycles influence the immune system, microbiome and mucosal homeostasis (Rosselot et al., 2016).

Synchronisation of peripheral clocks is largely controlled by the hormone melatonin, the production of which is governed by the SCN and is entrained to the light/dark cycle. The melatonin cycle conveys information about daily light/dark cycles to synchronise peripheral clocks, therefore stabilising and coupling circadian rhythms (Redman et al., 1983). Dysregulation of these rhythms is associated with a number of metabolic and inflammatory diseases including obesity, metabolic dysfunction and disorders of gut-brain interactions (DGBIs) (Voigt et al., 2019).

Disorders of gut-brain interactions, including functional dyspepsia (FD) and irritable bowel syndrome (IBS), are a group of disorders with a strong association with sleep disturbances but with relatively little known about circadian involvement (Koh et al., 2014; Yamawaki et al., 2014). These patients experience reoccurring GI symptoms which cannot be explained by obvious structural abnormalities (Drossman, 1999). FD is a multifactorial DGBI primarily affecting the upper GIT and is defined as having one or more of the following symptoms: early satiety, postprandial fullness, or epigastric pain or burning, in the absence of structural disease (Futagami et al., 2018). These symptom profiles can be used to subtype patients into postprandial distress syndrome (PDS) which describes symptoms of postprandial fullness and early satiety, and epigastric pain syndrome (EPS) which incorporates epigastric pain and burning, however, there is significant overlap between these profiles (Stanghellini et al., 2016). IBS is characterised by abdominal pain associated with changes in stool consistency with no underlying evidence of organic disease and is subtyped based on stool consistency (Camilleri et al., 2012). Importantly, over 40% of the global population experience GI symptoms associated with these conditions (Sperber et al., 2021), highlighting the need to better understand the mechanisms underlying symptom onset and chronicity. Further, alterations in immune profiles, microbiota composition and physiology of the GIT are linked to DGBIs (Burns et al., 2021), all of which are associated with chronodisruption and as such, it is likely that altered circadian rhythms are involved in the pathophysiology of these conditions. This review aims to discuss the evidence for circadian abnormalities in DGBIs with a focus on FD and IBS.

REGULATION OF THE CENTRAL CIRCADIAN CLOCK

Light is the primary zeitgeber for the SCN and determines the phase of the circadian clock. The retina carries photic information via the retinohypothalamic tract to the SCN which will adjust the circadian phase (phase shift) based on the ambient light levels (Berson, 2002). Exposure to natural daylight at high intensities advances the circadian clock, affecting sleep duration, and improving sleep quality (Roenneberg et al., 2003; Boubekri et al., 2014). In contrast, light exposure at evening and nighttime will delay the clock, leading to later sleep cues (Wright et al., 2013; Wams et al., 2017). A well reported example of this is the use of smartphones before bedtime, this has been shown to lead to decreased sleep quality, longer sleep onset latency and delays in sleep which shortens sleep duration (Lemola et al., 2015; Christensen et al., 2016).

Feeding/fasting patterns also cause phase shifts within the circadian system, and this may be of importance in diseases of the GIT. Sustained patterns of feeding/fasting can synchronise peripheral clocks and erratic eating patterns can disrupt this coordination. This has been demonstrated in mice, whereby restricting access to food during the inactive phase caused a phase shift in peripheral clocks (Damiola, 2000), as indicated by increased PER2 and BMAL1 mRNA expression in the stomach (Laermans et al., 2014). Late meals result in delayed Period 2 (PER2) mRNA rhythms in adipose tissue (Wehrens et al., 2017), and reduced calorie intake can also initiate a phase shift in peripheral clocks (Luna-Moreno et al., 2009; Arellanes-Licea et al., 2014). The nuclear receptor subfamily, Reverse Strand of Gene Encoding Thyroid Hormone Receptor (REV-ERB), is involved in rhythm generation in the circadian system and acts to regulate clock outputs in metabolic pathways (Buge et al., 2012; Cho et al., 2012). This is seen in mice lacking REV-ERBα, who lose daily food intake rhythms, as well as in mice living in constant darkness (Sen et al., 2018), highlighting the impact of food intake in the regulation of circadian rhythms and demonstrates its importance in maintaining normal physiological functioning. This may to some extent explain why patients with FD report reduced symptom burden when altering their meal habits to include smaller portions and more regular feeding schedules (Duncanson et al., 2021). Importantly, modulation of feeding patterns may have utility as a clinical approach for re-synchronising circadian clocks.

Transcription and Translational Control of Circadian Rhythms

The negative limb of the feedback loop involves CLOCK and BMAL1 genes, which form heteromeric complexes during the day to activate the transcription of PER1, PER2, PER3, Cryptochrome 1 (CRY1), CRY2, REV-ERB and retinoid-related orphan nuclear receptor (ROR) genes (Figure 1). After sufficient protein levels
of nuclear PER and CRY are reached over the course of the day, CLOCK and BMAL1 gene expression is then repressed at night. As PER and CRY protein production begins to decline in the early morning, the cycle continues (Sharman, 2000; Mrosovsky et al., 2001). The positive limb of the feedback loop involves REV-ERB decreasing BMAL1 gene expression and ROR increasing BMAL1 gene expression (Bae et al., 1998, 2000; Preitner et al., 2002). These gene expression changes occur in multiple organ systems, including the GIT where circadian rhythms influence the physiology of digestion and motility. Consequently, alterations in physiological function, such as changes in permeability or transit times, may result in dysregulation of the circadian cycle.

Peripheral Circadian Rhythms in the Gastrointestinal Tract

Circadian rhythms are a main regulator of digestion and absorption of nutrients, epithelial barrier function, motility and microbial activity. For example, saliva flow rate and secretory levels are diurnal (Dawes, 1972) salivary glands express clock genes (Zheng et al., 2012), suggesting regulation by circadian cycles. In the stomach, gastric acid secretion (Moore and Halberg, 1997), suggesting that melatonin plays a specific role in GI homeostasis. There is mounting evidence to suggest that many functions within the GIT are controlled by the circadian system, and therefore disruptions to this system may be involved in disease and loss of homeostasis. Restoration of rhythmicity may be an effective management approach for several GI conditions, including DGBIs. One major limitation of this area of research is that these gene expression feedback loops have not been extensively studied within the GIT of humans in health or disease. However, a significant body of work has focussed on melatonin as a surrogate indicator of circadian synchronicity, given its regulation of peripheral and circadian clocks.

MELATONIN

Given its importance in maintaining peripheral clocks, one potential avenue for restoring circadian rhythmicity may be supplementation with melatonin. In the GIT, melatonin is produced by enterochromaffin cells in the mucosa (Raikhlin and Kvetnoy, 1976) and aids in regulating both the immune system (Lardone et al., 2010) and intestinal motility (Figure 2; Harlow and Weekley, 1986; Storr et al., 2000). The concentration of melatonin in the GIT is suggested to be up to 400 times higher than in the pineal gland (Huether, 1994) and while pineal melatonin can enter the GIT through the circulatory system, GIT levels are independent of pineal levels (Bubenik and Brown, 1997), suggesting that melatonin plays a specific role in GI homeostasis.

There are two G-protein coupled melatonin membrane receptors, melatonin-1 receptor (MT1) and MT2. These receptors are found throughout the gut but are more localised to the large intestine and are involved in regulating motility, pain and signal transduction (Steblová et al., 2010; Söderquist et al., 2015). There have been suggestions of an MT3 receptor capable of binding melatonin, however, sequencing has reclassified this as the quinone reductase two enzyme (Nosjean et al., 2000). The function of this enzyme is not fully understood but is

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The role of melatonin in the intestinal immune system. Melatonin is produced from the pineal gland, and it influences circadian rhythms and immune function. It is also secreted in the gut from enterochromaffin and immune cells where it regulates GIT motility, immunity and the microbiota. Adapted from Ma et al. (2020) Medicinal Research Reviews. Image created using Biorender.com.

hypothesised to transform quinone substrates into highly reactive compounds that can cause cellular damage and increase levels of reactive oxygen species (Calamini et al., 2008). Functionally, melatonin is believed to inhibit this enzyme which would explain its antioxidant and anti-inflammatory effects (Sharma and Haldar, 2006; Túnez et al., 2007). Due to the location of melatonin receptors throughout the GIT and their involvement in signal transduction and oxidation, decreased melatonin levels may participate in inflammation and disease processes within the GIT.

**Melatonin and Gastrointestinal Motility**

Melatonin is involved in regulating GI motility through its dose-dependent excitatory and inhibitory effects on GI smooth muscle (Harlow and Weekley, 1986; Merle et al., 2000). Small doses of melatonin drive accelerated transit in the intestine and high doses reverse this effect, suggesting therapeutic capacity for melatonin in improving motor abnormalities frequently associated with DGBIs. Melatonin also decreases the force of spontaneous contractions in the ileum and colon, with one study demonstrating that melatonin can reduce the inhibitory non-adrenergic, non-cholinergic response in the GIT of rodents (Storr et al., 2002). This may be due to the reduced smooth-muscle inhibitory junction potential and inhibition of nitric oxide synthase activity at enteric synapses, suggesting that the site of melatonin action may potentially be neuronal rather than smooth muscle. This is an important consideration in the context of DGBIs, where proximity of nerve fibres to effector cells such as mast cells has been associated with abdominal pain (Barbara et al., 2004). These findings suggest that melatonin dosage affects GI motility and can impact on gastric emptying, however, the exact mechanism remains unclear and the therapeutic utility of specific melatonin dosages in improving motility abnormalities warrants further investigation.

**Melatonin and Intestinal Microbial Metabolism**

Melatonin levels affect both the microbes and production of microbial metabolites including biotin, butyrate, proline and propionate (Liang and Fitzgerald, 2017) which are involved in GIT homeostasis and regulation of the immune system. In addition, the microbiota is also important in modulating tryptophan metabolism, an essential amino acid that contributes to normal growth and health. Tryptophan is the precursor to serotonin and melatonin and has immunomodulatory properties (Höglund et al., 2019) that affect gastric emptying (Geeraerts et al., 2011) and barrier function (Scott et al., 2020). Studies have shown that the microbiota can directly regulate peripheral tryptophan levels by stimulating serotonin production from enterochromaffin cells (Yano et al., 2015). However, over 90% of tryptophan is oxidised into kynurenine via the kynurenine pathway by the microbiota (Badawy, 2017), and this metabolite has been linked to inflammation (Nelp et al., 2019). Additionally,
increased kynurenine levels have been associated with depressive-like behaviours (O’Connor et al., 2009). In the large intestine, commensal microbes, including *C. sporogenes* and *R. gnavus*, also work to convert tryptophan into tryptamine (Williams et al., 2014), an indolamine metabolite. Tryptophan can also be metabolised into indole by *E. coli*, *Clostridium* and *Bacteroides* species (Lee and Lee, 2010), which leads to the production of nicotinamide adenine dinucleotide, a coenzyme that is integral for host metabolism (Kotake and Masayama, 1936). Indole has a protective capacity in the GIT by stimulating the production of glucagon-like peptide 1 (GLP-1) from enteroendocrine L cells (Natividad et al., 2018). Given the tryptophan-serotonin metabolic pathway is impaired in patients with DGBIs (Gao et al., 2020), modulation of this pathway may improve symptoms in these conditions.

**Melatonin and the Immune System**

Melatonin may also be required for immunomodulation, given the enzymes and receptors required for melatonin synthesis are widely found on immune cells. For example, both N-Acetyltransferase and Hydroxyindole-O-Methyltransferase are required for melatonin synthesis and are produced in T-cells (Carrillo-Vico et al., 2004). Subsequent melatonin synthesised from T-cells is believed to be involved in regulating IL-2/IL-2R expression (Lardone et al., 2010), a key player in regulating T-cell proliferation (Willerford et al., 1995). There is also suggestion that melatonin may regulate differentiation of T helper (Th) response pathways. Melatonin has been suggested to promote Th1 mediated responses by up-regulating IL-2 and IFN-γ production by CD4+ cells (Garcia-Mauriño et al., 1997) and it was shown that melatonin increased the production of IFN-γ by murine splenocytes (Colombo et al., 1992). In contrast, another study found that melatonin increased IL-4 secretion, in conjunction with downregulation of IL-2 and IFN-γ, suggesting a Th helper 2 response (Shaﬁ et al., 1998). In addition, the chronic administration of melatonin in mice increased the production of IL-10 and decreased TNF-α which further highlights a skew toward a Th helper 2 response (Raghavendra et al., 2001). While the literature implicates melatonin in enhancing the T cell response, these conflicting results may suggest melatonin is not associated with a speciﬁc T cell subset, but rather is involved in modulating the T cell response with the aim of restoring G1 homeostasis. Alternatively, there may be a dose dependent response to melatonin that skews toward a Th1 or Th2 response.

Melatonin also enhances antigen presentation through increasing MHC class II expression and the production of IL-1 and TNF-α (Pioli et al., 1993). These findings were supported by investigation of the proteome of shift workers with circadian misalignment, which showed that proteins in multiple pathways linked to antigen presentation and interferon signalling were abnormal (Depner et al., 2018), suggesting an altered adaptive immune responses in relation to daily activities. A further study evaluating circulating white blood cells and the association with sleep patterns (Hoopes et al., 2021) found that irregular sleep patterns are associated with an increased total white blood cell count and circulating neutrophils, lymphocytes and monocytes. This may be associated with the immunomodulatory capacity of melatonin to regulate natural killer cells (Lewiński et al., 1989), neutrophils (García-Mauriño et al., 1999; Peña et al., 2007) and macrophage (Barjavel et al., 1998) responses. Further, melatonin inhibits neutrophil accumulation during inflammation, preserving mucosal cell integrity through reduction of neutrophil-mediated damage (Ercan et al., 2004), suggesting alterations in melatonin release associated with irregular sleep patterns may contribute to inflammation. In animal models of dextran sodium sulphate-induced colitis, 7 weeks of daily intraperitoneal melatonin administration reduced the severity of intestinal inflammation (Pentney and Bubenik, 1995). However, while acute melatonin treatment limits acute inflammatory damage, treatment is deleterious to chronic models of colitis (Marquez et al., 2006). This may be because acute administration of melatonin reduced the activity of myeloperoxidase, an enzyme that increases reactive oxidant species (Pattison et al., 2012), while the harmful impact of chronic melatonin administration may be due to its immunostimulatory effects. As such, the dosage of melatonin likely determines the impact on the immune system, however, it is clear that melatonin plays an important role in regulating circadian rhythms, the immune system and gastrointestinal physiology. Therefore, dysregulation of this hormone may contribute to disease presentation.

**Melatonin and Sex Steroid Hormones**

While there is no consensus regarding the specific differences and mechanisms at play, it is clear that sex differences exist in circadian rhythms and melatonin metabolism (Cipolla-Neto et al., 2021) which may in part explain the higher prevalence of DGBIs in women (Burns et al., 2021). In healthy women, the intrinsic circadian period of melatonin and body temperature are shorter (Duffy et al., 2011) and females also tend to wake up earlier, with morning chronotypes (Adan and Natale, 2002; Cain et al., 2010). The circadian patterns of glucocorticoid hormone secretion and clock gene expression also display sex differences, with testosterone suggested to modulate rhythmicity in the adrenal glands of mice (Kloehn et al., 2016) and the secretion of glucocorticoid hormone conveys key timing information to both the central and peripheral circadian system (Balsalobre et al., 2000; Lamia et al., 2011). As such, the effects of sex hormones on adrenal gland rhythmicity may link to the dysregulation of stress hormones, such as corticotropic releasing hormone in DGBIs (Tanaka et al., 2016; Kano et al., 2017) but this relationship remains largely unexplored.

Melatonin plays an important role in regulating sex steroid hormones and influences the synthesis and release of gonadotropin releasing hormone (Bittman et al., 1985). For example, a study in males with gonadotropin releasing hormone deficiencies demonstrate that treatment with testosterone decreased melatonin levels back to within normal ranges (Luboshitzky et al., 1996). While the influence of melatonin on male sex steroid hormones is not fully understood, it helps regulate testosterone secretion and influences the growth, proliferation and secretory activity of testicular cells (Frunieri et al., 2017). Melatonin is also involved in multiple pathways for regulating the physiology of Sertoli cells (Yang et al., 2014)
and influencing spermatogenesis (Espino et al., 2011; Moayeri et al., 2018). In terms of female reproductive hormones, there is evidence that the oral contraceptive pill increases melatonin levels (Boivin et al., 2016). Melatonin synthesis occurs in the ovary (Itoh et al., 1997), oocytes (Sakuguchi et al., 2013) and placenta (Iwasaki et al., 2005); and the ovaries have been shown to express the MT1 and MT2 receptors (Niles et al., 1999; Woo et al., 2001), however, the specific implications of melatonin production and metabolism in the female reproductive tract are not fully understood. While there are a number of sex differences with regard to circadian cycles and melatonin levels, there are considerable inconsistencies reported between studies (Gipolla-Neto et al., 2021), likely due to confounding factors such as the contraceptive pill (Kostoglou-Athanassiou et al., 1998) and age (Fernandez et al., 1990), making it hard to draw firm conclusions about the biological consequences of such differences. However, it appears the contribution of sex to circadian rhythmicity may link to the sex differences reported in DGBI prevalence and physiology.

**Mechanisms of Chronodisruption**

Studies highlight a relationship between sleep disturbances, mental health and GI dysmotility (Nojkov et al., 2016; Kim et al., 2013; Saeed and Galal, 2017), linking chronodisruption to altered GI function. This is further supported by the observation that those with chronic insomnia have a higher prevalence of GI problems (Taylor et al., 2007; Bhaskar et al., 2016; Hyun et al., 2019). While the mechanisms underpinning these observations are not fully understood, polymorphisms in PER3 are associated with increased susceptibility to Crohn’s disease (CD) and a more severe symptom profile (Mazzoccoli et al., 2012). In inflammatory diseases, including CD, disrupted circadian rhythms can both provoke and worsen the inflammation (Preuss et al., 2008; Tang et al., 2009). Further, polymorphisms in CLOCK and PER genes are associated with decreased gastric motility in the morning (Yamaguchi et al., 2015) and animal studies have demonstrated that PER1/2 knockout mice have decreased colonic motility (Hoogerwerf et al., 2010), suggesting that dysregulation of circadian rhythm drives GI symptoms. In addition, mice with deficient PER1/2 genes had decreased GI barrier integrity due to impaired cell division (Pagel et al., 2017). Importantly, under inflammatory conditions, there was a loss of Paneth and goblet cells and a decrease in transcription of barrier protective genes, indicating reduced barrier protection in Per1/2 mice (Pagel et al., 2017), highlighting that regulated circadian rhythms are essential for mucosal barrier integrity. In addition, feeding rhythms were disrupted in CLOCK mutant mice and restricted feeding recovered the appropriate rhythm (Yoshida et al., 2015), highlighting the importance of food intake when considering disruption to the circadian system. These studies suggest that alterations to circadian rhythms have a major impact on GI physiology and inflammatory pathways and may cause decreased barrier integrity. Further, these studies highlight the potential for restoring circadian rhythms in reducing disease flares and burden of GI disease on patients. One approach for restoring normal rhythm appears to be through control of feeding times. Normally, ghrelin secretion increases before a meal and declines postprandially (Cummings et al., 2001). However, this suppression of postprandial ghrelin is blunted in night workers (Schiavo-Cardozo et al., 2013), where feeding patterns are altered, highlighting circadian systems regulate hormone secretion. Night shift participants also had greater body fat mass percentage, lower insulin sensitivity and higher triglyceride levels compared to dayworkers (Schiavo-Cardozo et al., 2013), indicating increased adiposity and metabolic alterations. There is also evidence that chronodisruption influences GIT inflammation. Following an intermittent fasting schedule where participants fasted for 14–15 h each day for 25–30 days, resulted in decreased pro-inflammatory cytokines (Faris et al., 2012). Further, short-term fasting reduced circulating monocytes and markers of inflammation (Jordan et al., 2019), highlighting the importance of food intake timing in the regulation of GIT hormone secretion and immune function. These studies provide evidence that restricted feeding may realign the circadian system and help with symptom management, although this has not yet been extensively explored in GI disease cohorts.

Chronodisruption from altered light-dark cycles also leads to increased intestinal permeability (Summa et al., 2013) and alterations in the GIT microbiome (Wei et al., 1975; Kim et al., 2019). Shifts in the light/dark cycle causing chronic circadian misalignment resulted in a loss of colonic barrier function in mice (Tran et al., 2021). Sleep deprived mice have lower melatonin concentrations in colonic tissue in addition to increased colonic abundance in Erysipelotrichales and Enterobacteriales, which may induce inflammation, and decreased Lactobacillales, which is a beneficial bacterium in the GIT (Park et al., 2020). A further study (Deaver et al., 2018) found mice previously exposed to abnormal light-dark cycles demonstrated an altered GIT microbiota with increased abundance of Ruminococcus torques, associated with decreased intestinal barrier integrity, and subsequent loss of Lactobacillus johnsonii, a bacterial species which helps maintain the GIT epithelial cell layer. The increase in Ruminococcaceae spp. and decrease in Lactobacillaceae spp. is a common microbial profile seen in DGBI patients (Kassinen et al., 2007; Lyra et al., 2009; Rajilæ-Stojanovë et al., 2011; Saulnier et al., 2011; Wang et al., 2013), suggesting these species may be associated with decreased integrity of the mucosal barrier. Further, there was a down regulation of genes involved in regulating important metabolic processes including 3-hydroxybutaryl-CoA dehydrogenase, acetaldehyde dehydrogenase, LPS export system permease protein and 3-deoxy-manno-octulosonate cytidyltransferase (Deaver et al., 2018). These four genes are linked to tryptophan metabolism (Edenberg, 2007; O’Connor et al., 2009; Trefely et al., 2020) and downregulation of gene expression would therefore affect tryptophan metabolism, likely impacting on the availability of downstream products including serotonin and melatonin. These findings demonstrate that a loss of microbial richness may be involved in decreased GIT barrier integrity, mucous degradation (Hoskins et al., 1985), and immunomodulation (Pridmore et al., 2004). Moreover, decreased plasma melatonin levels and altered cytokine secretion has been demonstrated to cause mucosal injury in sleep deprived mice (Gao et al., 2019). There was an increase in catalase, superoxide dismutase and glutathione...
peroxidases which are antioxidant enzymes, associated with having decreased activity in IBS patients (Gurel, 2013). There was also upregulation of the proinflammatory cytokines IL-1, IL-6 and TNF-α, and the autophagic proteins, ATG5 and Beclin1. A concurrent downregulation of PCNA indicated increased cell autophagy and decreased cell proliferation (Gurel, 2013). Collectively, the immune profiles and the loss of microbial richness implicate chronodisruption with decreased enterocyte renewal and tight junctional protein levels and decreased integrity of the mucous layer. These studies highlight sleep deprivation can promote intestinal dysbiosis and aggravate GI disease and subsequently, improved sleep quality may help with symptom management. Further, given that supplementation with melatonin improved mucosal integrity in animal models of sleep deprivation (Gao et al., 2019, 2021), the therapeutic benefit of melatonin may be linked to strengthening of the intestinal barrier to reduce contact of luminal antigens with the mucosa.

DISORDERS OF GUT-BRAIN INTERACTIONS

Despite not being associated with mortality, DBGIs represent the most common diagnosis in gastroenterology, with over one-third of new patient consultations in secondary care gastroenterology clinics resulting in diagnosis of an DGBI (Shivaji and Ford, 2014). These patients are likely to account for more absenteeism from work, as well as reporting reduced productivity (Ballou et al., 2019), largely due to a lack of effective treatments for the conditions. Melatonin has been proposed as a potential therapy for IBS (Lu et al., 2005), however, specific mechanisms by which supplementation may improve the symptoms of DBGIs remain largely unknown. There is a strong correlation between DBGIs and sleep disturbances (Yamawaki et al., 2014; Yang et al., 2020; Koloski et al., 2021), indirectly indicating that circadian systems may be involved in their pathogenesis. Further, lifestyle factors including shift work have been associated with DGBI diagnosis (Knutsson and Bøggild, 2010; Nojkov et al., 2010; Kim et al., 2013), further supporting the hypothesis that dysregulated circadian cycles contribute to symptom chronicity in these patients. In addition, IBS patients reporting sleep disturbances were more likely to have higher symptom severity scores (Tu et al., 2017), linking circadian disruption to symptom manifestation. Rotating shift work is associated with increased psychological stress, poor quality sleep and greater experience of fatigue (Kim et al., 2013) which are all thought to contribute to a greater risk of chronic disease including cardiovascular disease and metabolic syndromes (Wang et al., 2011), demonstrating that an interruption to biological rhythmicity has significant impact on physiological function. This is also true in the GIT, where individuals performing rotating shift work and recovering from jet lag report increased incidences of GI symptoms including abdominal pain, constipation and diarrhoea (Caruso et al., 2004; Knutsson and Bøggild, 2010).

Acute tryptophan depletion is a method that reduces the availability of tryptophan in the brain and plasma, resulting in decreased serotonin and melatonin (Moja et al., 1988, 1989). As the microbiota metabolises dietary tryptophan the same decrease in serotonin and melatonin is likely reflected in the GIT. A study using this method on IBS patients (Kilkens, 2004) reported increased pain and urge scores as well as a lower perceptual threshold for first perception compared to placebo groups. As tryptophan is a precursor to melatonin, this suggests that melatonin may also be involved in visceral hypersensitivity and perception of pain. Additionally, tryptophan metabolite levels were significantly different between IBS and controls (Burr et al., 2019), demonstrated by a decrease in ten tryptophan metabolites (including indole-3-lactic acid and kynurenine) which were associated with sleep timing, hypothalamic-pituitary-axis hormones and (Burr et al., 2019), consistent with GIT melatonin influencing sleep and GI functioning that is altered in IBS.

With regards to FD, sleep disturbance is also more commonly reported in these patients compared to controls (Park et al., 2021). Further, symptom onset for a majority of patients is linked to eating and consequently some patients respond well to smaller, more regular meals (Duncanson et al., 2021). Interestingly, GI melatonin production is seemingly regulated by eating and food composition (Bubenik et al., 1996) rather than light/dark signals, suggesting abnormal melatonin production may be linked to FD symptom manifestation. In addition, serum and urinary melatonin concentrations are higher in patients with PDS compared to those with EPS and controls and there was a relationship between more severe symptoms and higher melatonin concentration (Chojnacki, 2011), suggesting chronodisruption in FD may result from abnormal melatonin

### TABLE 1 | Randomised clinical trials looking at efficacy of melatonin in patients with IBS.

| References          | Subjects                                                                 | Treatment                                                                                           | Outcome                                                                                                                                                                                                                                                                                                                                 |
|---------------------|--------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Lu et al., 2005     | (Originally 24 in total) 17 females (10 in Group A and 7 in Group B), diagnosis based on Rome II | 3 mg of melatonin or placebo every night for 8-weeks, 4-week washout period and then placebo or melatonin reversed | Improved bowel symptoms in IBS patients.                                                                                                                                                                                                                                                                                               |
| Saha et al., 2007   | 18 participants, 6 females (9 melatonin, 9 placebo), diagnosis based on Rome II | 3 mg of melatonin or placebo at bedtime for 8 weeks.                                                | Improved IBS and quality of life score, lower extracolonic IBS score.                                                                                                                                                                                                       |
| Song, 2005          | 40 participants, 24 females (20 melatonin, 20 placebo), IBS diagnosis based on Rome II criteria, global Pittsburgh sleep quality index score of greater than 5 | 3 mg of melatonin or placebo for 2 weeks                                                            | Improved abdominal pain scores.                                                                                                                                                                                                                                                                                                          |
| Chojnacki et al., 2013 | 80 postmenopausal females, IBS diagnosis based on Rome III, subtype into IBS-C and IBS-D | 3 mg of melatonin fasting and 5 mg at bedtime or placebo for 6 months                              | Decreased visceral pain, abdominal bloating and constipation.                                                                                                                                                                                                                                                                         |
production which inhibits regulation of the peripheral rhythms. This hypothesis can also be linked to the reported alterations in the FD microbiota, as small intestine biopsies from patients show a correlation between bacterial density in the mucosa of the small intestine and intensity of symptoms seen with food intake (Zhong et al., 2017). The low-grade mucosal inflammation, characterised by increased duodenal eosinophilia and mast cells in FD (Vanheel et al., 2014), and increased colonic mast cells in IBS (Walker et al., 2009) may also be the result of circadian disruption, however, this is largely unexplored so far.

**Therapeutic Evidence for Melatonin in Disorders of Gut-Brain Interactions**

Melatonin has been investigated as a therapeutic agent for FD and IBS, however, the efficacy remains unclear. A study on paediatric FD found that melatonin had no significant effect (Zybach, 2016), however, another study found that FD participants showed significant improvement in sleep quality and abdominal pain (Klupinska et al., 2007). Similarly, disturbances in melatonin metabolism and secretion have been suggested to play a role in the pathophysiology of IBS (Radwan et al., 2009). A number of studies have examined the therapeutic effects of melatonin on patients with IBS in multiple clinical trials (Table 1) and the results show improved symptoms, sleep and mental health scores with reduced abdominal pain compared to placebo groups (Lu et al., 2005; Song, 2005; Saha et al., 2007; Chojnacki et al., 2013), however, no clear mechanism for these improvements has been identified. One hypothesis for this is that IBS patients have increased enterochromaffin cells (Lee et al., 2008), suggesting melatonin production may be altered and therefore supplementation mitigates this to reduce symptom burden. Further, increased melatonin and aralkylamine N-acetyltransferase (an enzyme involved in the production of melatonin) concentrations were seen in the colonic mucosa of patients with IBS-diarrhoea (Lee et al., 2008; Chojnacki, 2013). Melatonin can also be metabolised to 6-hydroxymelatonin sulphate which is excreted in the urine and one study reported patients with IBS having increased levels of this metabolite (Wisniewska-Jarosinska et al., 2010). As melatonin inhibits the activation and proliferation of mast cells (Izzo, 2004; Maldonado et al., 2016), it suggests that increasing melatonin availability may suppress the inflammatory profiles seen in IBS, however, there is little work on the specific mechanisms by which this may occur.

**CONCLUSION**

Disorders of gut-brain interactions affect a significant proportion of the global population and a lack of effective therapeutics for these conditions highlight the need for further research in the mechanisms of these conditions. Melatonin is involved in the regulation of GIT motility and sensation and evidence suggests an increased enterochromaffin cell number in patients with DGBIs. Furthermore, melatonin receptors, MT1 and MT2, are associated with the circadian regulation of immune cells and enhanced immune responses in the GIT, however, these mechanisms are not well explored in DGBIs.

Sleep disturbances, shift work and irregular eating patterns have all been linked to increased incidence of DGBIs implicating involvement of the circadian system in the pathophysiology. GIT barrier function, motility and immunity are heavily influenced by the circadian system and are important for gut-brain signalling. Given that circadian patterns regulate physiology, the immune system and the microbiota in the GIT, the therapeutic targeting of circadian patterns may reduce immune activation in DGBI patients.

**AUTHOR CONTRIBUTIONS**

SF performed the literature review and wrote the original draft of the manuscript. EH, NT, SK, and GB reviewed and edited the manuscript. All authors approved the final version of the manuscript submitted for publication.

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