Biochimie 209 (2023) 20–36

Contents lists available at ScienceDirect

Biochimie

journal homepage: www.elsevier.com/locate/biochi

Melatonin and inflammatory bowel disease: From basic mechanisms to clinical application

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ARTICLE INFO

Article history:
Received 3 July 2022
Received in revised form
25 October 2022
Accepted 14 December 2022
Available online 17 December 2022

Keywords:
IBD
Melatonin
Sleep disturbances
Inflammation
Intestinal bacteria
IBD treatment

ABSTRACT

Inflammatory bowel disease is a chronic inflammatory disease and has periods of recurrence and remission. Improper immune responses to gut flora bacteria, along with genetic susceptibility, appear to be involved in causing this complex disease. It seems dysbiosis and oxidative stress may also be involved in IBD pathogenesis. A significant number of clinical studies have shown an interesting association between sleep disturbances and IBD. Studies in animal models have also shown that sleep deprivation has a significant effect on the pathogenesis of IBD and can aggravate inflammation. These interesting findings have drawn attention to melatonin, a sleep-related hormone. Melatonin is mainly produced by the pineal gland, but many tissues in the body, including the intestines, can produce it. Melatonin can have an interesting effect on the pathogenesis of IBD. Melatonin can enhance the intestinal mucosal barrier, alter the composition of intestinal bacteria in favor of bacteria with anti-inflammatory properties, regulate the immune response, alleviate inflammation and attenuate oxidative stress. It seems that, melatonin supplementation is effective in relieving inflammation and healing intestinal ulcers in IBD animal models. Some clinical studies have also shown that melatonin supplementation as an adjuvant therapy may be helpful in reducing disease activity in IBD patients. In this review article, in addition to reviewing the effects of sleep disturbances and melatonin on key mechanisms involved in the pathogenesis of IBD, we will review the findings of clinical studies regarding the effects of melatonin supplementation on IBD treatment.

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https://doi.org/10.1016/j.biochi.2022.12.007
0300-9084/

1. Introduction

Inflammatory bowel disease (IBD (is a long-standing inflammatory disease of the digestive tract. The peak of disease incidence is at a young age. IBD has periods of recurrence and relief, and is considered a long-life disease. Crohn's disease and ulcerative colitis are two major types of the disease that are very similar to each other [1,2]. A major theory about the cause of IBD suggests that IBD can be caused due to an improper immune response to gut microbes in genetically predisposed individuals [1]. Epidemiological studies indicate an increase in the prevalence of the disease in different communities. In particular, IBD seems to be highly prevalent in some European countries. Much of the research on IBD focuses on the diagnosis and treatment of this disease. Efforts to find non-invasive methods to reduce the rate of unnecessary colonoscopies continue in the field of diagnosis, and some laboratory markers such as fecal calprotectin have been promising in this regard [3]. In the field of treatment, efforts are still underway to find ways to increase the period of clinical remission. Current therapies focus on targeting the immune system and pro-inflammatory cytokines such as TNFα. Despite significant improvements, relapse can still occur in a relatively short period of time. In some cases, such as acute severe ulcerative colitis, surgery may be needed to treat the disease. In recent years, many studies have been conducted to better understand the pathogenesis and find ways to treat IBD more effectively. Clinical studies have reported an interesting association between some nutritional factors such as zinc, folate, and vitamin B12 and IBD [4–7]. Also, changes in levels of antioxidant enzymes and lipid peroxidation index (MDA) have been reported in patients with IBD [8–10], indicating oxidative stress in patients with IBD. Some studies have even suggested the use of antioxidants to treat IBD [11]. The anti-oxidant and anti-inflammatory properties of melatonin along with evidences regarding the relationship between sleep disturbances and IBD have led to much attention being paid to melatonin in recent years. Melatonin is a hormone that is mainly secreted by the pineal gland and plays a key role in regulating the circadian rhythm and sleep-wake cycle. However, this hormone appears to be secreted by many cells in the body and has several roles, including antioxidant, anti-inflammatory, and anti-tumor roles [12,13]. Melatonin appears to affect various aspects of the immune system that are important in IBD. Melatonin also has the ability to alter the composition of intestinal bacteria, which may be helpful in improving IBD. In this article, after a brief overview of the pathogenesis of IBD, we will discuss the relationship between melatonin and events involved in the pathogenesis of IBD. Finally, we will review the most interesting findings on the efficacy of melatonin in the treatment of IBD.

2. A brief overview on IBD pathogenesis

IBD is a complicated disease and various factors may contribute to the pathogenesis of this disease. A detailed review of the events contributing to IBD pathogenesis requires a separate article; however, this section attempts to provide a summary of the most important events. Briefly, the intestinal epithelium blocks the penetration of intestinal bacteria into the lamina propria, which locates beneath the intestinal epithelium. The intestinal epithelium, the surface of which is covered with a layer of mucus, is known as the intestinal mucosal barrier. A group of intestinal epithelial cells known as goblet cells are involved in mucus production and epithelial repair. Another group of intestinal epithelial cells called paneth cells are involved in the production of antimicrobial peptides, including defensin [14]. It seems that the number and secretory ability of goblet cells are significantly reduced in patients with active UC [15]. The efficiency and health of the intestinal mucosal barrier depend on the tight junction between adjacent epithelial cells. A number of proteins, including Zo-1, occludins, junctional adhesion molecules (JAM) cadherin E and claudins, play an important role in maintaining these tight junctions and mucosal barrier integrity [16]. One of the key events that occur in IBD is the disruption of these tight junctions and the weakening of the intestinal mucosal barrier, which leads to increased intestinal permeability and increased penetration of intestinal bacteria into the lamina propria (Fig. 1). Lamina propria contains a number of immune cells and there is a balance between immune tolerance and defense against pathogens and infiltrating intestinal bacteria. In inflammatory bowel disease, persistent and excessive infiltration of intestinal bacteria causes the enhanced recruitment of innate immune cells, including neutrophils, macrophages, NK cells, and dendritic cells, into the lamina propria (Fig. 1). These cells can detect bacterial patterns through receptors such as toll-like receptors (TLRs) and nucleotide oligomerization domain (NOD) [1,14,17]. Dendritic cells can migrate to Peyer's patches and mesenteric lymph nodes, where they initiate adaptive immune response by delivering antigens to naive T cells. Naive $CD4^+$ T cells differentiate into different subtypes of $CD4^+$T cells under the influence of different cytokines. $CD4^+$ T cells are very important in the pathogenesis of IBD (Fig. 1) [1,14,18,19]. These $CD4^+$ T cells migrate to the lamina propria. The secretion of pro-inflammatory cytokines, ROS and chemokines by innate immune cells enhances this migration. Tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL6), interleukin-12 (IL-12), interleukin-23 (IL-23) are among the most important pro-inflammatory cytokines produced by innate immune cells [1,14,20,21].

$CD4^+$ T cells, in turn, produce significant amounts of cytokines and chemokines, leading to more recruitment of leukocytes in to lamina propria and enhancement of inflammation (Fig. 1). These successive cycles of inflammation continue due to the continuous infiltration of intestinal bacteria into the lamina propria, leading to chronic inflammation and IBD. In IBD, the population of regulatory T cells also appears to be declining and their function may be impaired [2,22]. These cells are involved in regulating of effector $CD4^+$T cells activity, maintaining immune tolerance, and

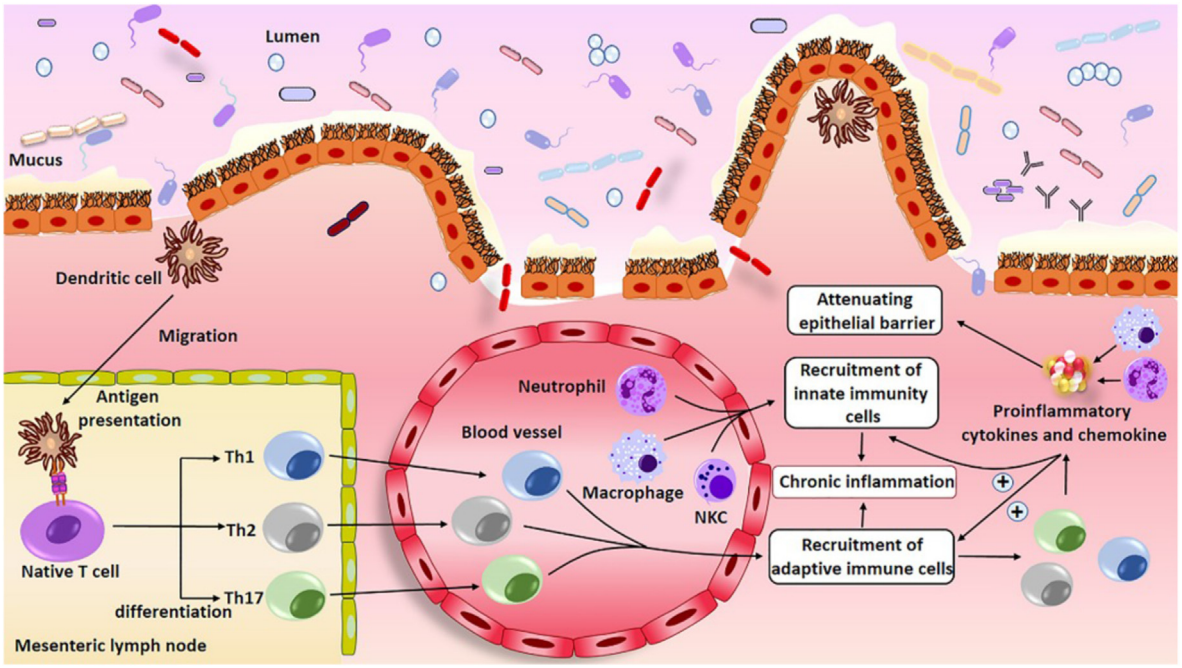

Fig. 1. Some important events of IBD pathogenesis. In IBD, disruption of the intestinal mucosal barrier leads to increased penetration of intestinal bacteria into the lamina propria. The innate immune response begins first, and innate immune cells such as neutrophils and macrophages are involved. After detecting bacterial antigens, dendritic cells can migrate to secondary intestinal lymph organs, such as the mesenteric lymph nodes, and initiate an adaptive immune response by presenting antigens to naive CD4 + T cells. These cells can differentiate into effector $CD4^+$ T cells such as Th1, Th2, and Th17. These effector cells enter the circulation and are then recruited to the lamina propria under the influence of pro-inflammatory cytokines and chemokines secreted by innate immune cells. Effector $CD4^+$ T cells, in turn, can secrete pro-inflammatory cytokines and chemokines that boost the recruitment of immune cells, leading to augmentation of inflammation.

attenuating inflammation [1,23]. Interestingly, inflammation can further disrupt the intestinal mucosal barrier and cytokines such as TNF-α, IFN-γ and IL-6 may play a key role in this regard [1,24,25]. IL-6 can also affect intestinal epithelial cells and enhance NF-κB production in these cells. NF-κB can enhance neutrophil recruitment by increasing intercellular adhesion molecule-1 (ICAM-1) [26], which may lead to enhancement of inflammation. The role of NF-κB in the pathogenesis of IBD is not limited to this and this transcription factor appear to play a key role in the production of pro-inflammatory cytokines such as IL-6 and TNF-α, IL-1β [27]. Patients with IBD appear to have high levels of NF-κB in intestinal tissue [28], indicating the importance of NF-κB in IBD pathogenesis. In overall, disruption of the intestinal mucosal barrier, increased penetration of intestinal bacteria into the lamina propria and impaired regulation of the immune response can be considered as the main events contributed in the pathogenesis of IBD.

3. Melatonin synthesis and functions in the gut

As mentioned in the introduction, melatonin is a hormone that is mainly secreted by the pineal gland. Melatonin is synthesized from tryptophan, a very important amino acid, following several enzymatic reactions (Fig. 2). First, tryptophan is converted to 5-hydroxytryptophan by tryptophan hydroxylase, then 5-hydroxytryptophan is converted to serotonin by aromatic amino acid decarboxylase. Serotonin can be acetylated by serotonin N-acetyltransferase to N - acetylserotonin, N - acetylserotonin is converted to melatonin by hydroxyindole-O-methyltransferase (HIOMT) [29].

Melatonin degradation can be enzymatic or non-enzymatic (Fig. 2). In one of the enzymatic pathways, melatonin is hydroxylated by cytochrome P450 monooxygenases (CYP1A2, CYP1A1 and, CYP1B1) to 6-hydroxymelatonin, which can be conjugated to sulfate or glucuronate.

In another enzymatic pathway melatonin is oxidized by myeloperoxidase (MPO) or indole amine-2,3-dioxygenase (IDO) and eventually converted to N1-acetyl-5-methoxykynuramine (AMK). N1-acetyl-N2-formyl-5-methoxycycinoramine (AFMK) is also produced as an unstable intermediary in this pathway. It seems that some inflammatory mediators such as interferon γ (IFN - γ) can enhance the expression of IDO in large intestine [30]. Non-enzymatic degradation of melatonin occurs through its interaction with oxidizing species, resulting in the production of a diverse range of melatonin metabolites [31,32].

Melatonin production is not limited to the pineal gland. Studies have shown that there is a significant amount of melatonin in the intestinal tissue so that the intestinal melatonin content appears to be 400 times higher than in pineal gland [33]. It seems that intestinal enterochromaffin cells (ECs) are able to produce melatonin and the expression of serotonin-N-acetyltransferase and hydroxyindole-O-methyltransferase has been reported in the gut. In addition, melatonin can enter the gut through diet. Some intestinal bacteria may also be able to synthesize melatonin. A part of the intestinal melatonin content also appears to come from the pineal gland [33,34]. However, some studies have shown that removal of the pineal gland has no significant effect on intestinal melatonin content [35].

Melatonin content of gut may change at different ages.For example, one study showed that older mice (22–24 mo) had higher ileal and colonic melatonin content than younger mice (2–5 mo) [36]. However, the results of electrochemical measurements of another study have shown that the colonic release of melatonin decreases with age [37]. Another study has also shown that the melatonin content of stool is reduced in aged mice compared to young mice. The results of this study also suggest that there is no significant difference in the expression of melatonin receptors and

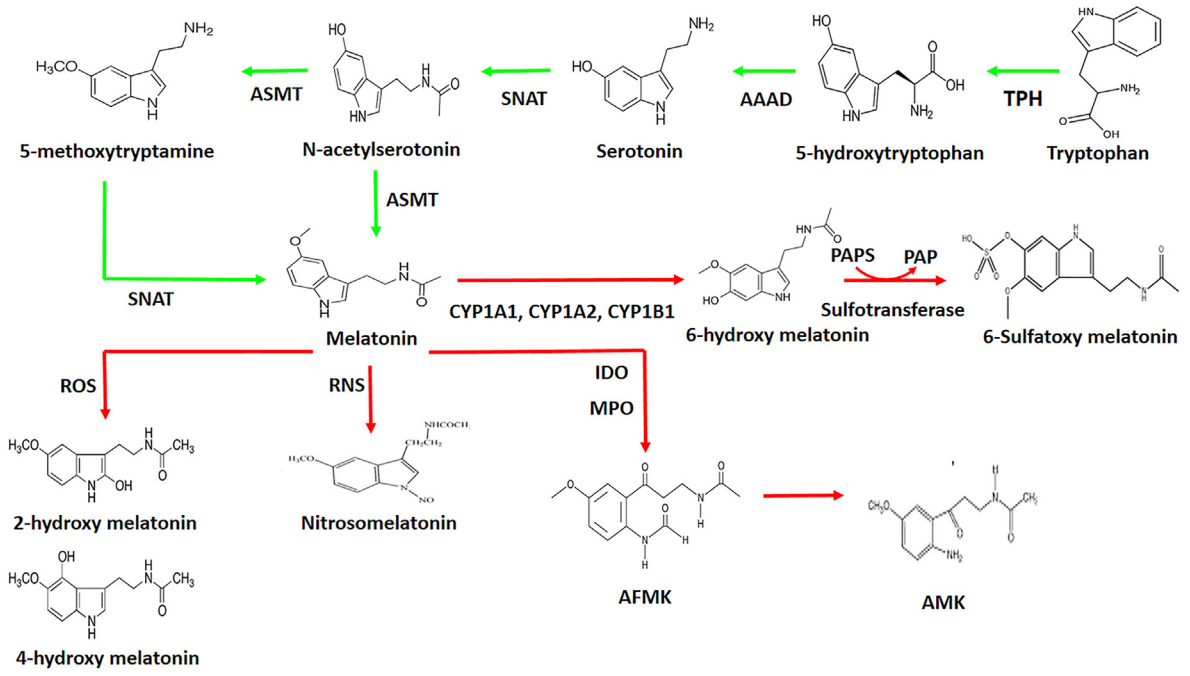

Fig. 2. Synthesis and degradation of melatonin.

acetylserotonin O-methyltransferase (also known as hydroxyindole-O-methyltransferase), which is involved in the synthesis of melatonin, in the colon tissue between young and old mice [38]. Therefore, it is necessary to conduct more studies, especially on human colon tissue samples, to clarify the effect of age on colonic melatonin content. Besides, considering that the onset of IBD is often at a young age, investigating the relationship between of this effect and the occurrence of IBD can be an interesting topic for future studies.

In addition to paracrine function, melatonin produced in the gut can be secreted into the portal vein as a hormone [31]. Melatonin exerts its effects through melatonin receptors; however, some melatonin functions are receptor independent. Melatonin-1 receptor (MT1) and MT2 are melatonin membrane receptors that belong to the GPCR family and have 55% overall homology with each other. MT3 is an enzyme known as quinone reductase 2 (QR2). This receptor is involved in detoxification and metabolism of xenobiotics. Melatonin appears to exert protective effects against oxidative stress through this receptor. All three receptors are present in the colon tissue. In addition, melatonin has nuclear receptors that belong to the retinoid Z receptor (RZR) or retinoid orphan receptor (ROR) subfamily. It should be noted that melatonin may also interact with other receptors, such as the serotonin receptor (5-HT) and the cholecystokinin B receptor (CCK2) [39].

It seems that melatonin can increase the secretion of cholecystokinin and slow down peristalsis movement through the MT-2 receptor, which results in increased digestion and absorption of food. Besides, melatonin may reduce intestinal motility in high doses, but in low doses it has the opposite effect and increases intestinal motility [40]. Moreover, melatonin may relax the gut by weakening the contractile effects of serotonin [41].

Melatonin may reduce the absorption of cholesterol in the gut. However, it seems that melatonin can increase the absorption of amino acids by enhancing the expression and function of amino acids transporter [42,43]. Melatonin also appears to be involved in the secretion of chloride by colon cells [44]. In addition to these, melatonin also has significant effects on intestinal bacteria, oxidative stress and immune regulation, which will be discussed in detail in the following sections.

4. Melatonin and IBD: smart molecule with key roles?

The high content of melatonin in the gastrointestinal tract and some observations about the association of sleep disorders with IBD led to hypotheses about the possible association between melatonin and IBD. The previous section summarizes the most important events involved in the pathogenesis of IBD. In this section, we will review the most interesting findings about the effect of melatonin on above mentioned events.

4.1. Sleep disturbance and IBD: is there a relationship?

Sleep is considered one of the biological activities of the body that affects many physiological functions of the body, including the immune response, which is a crucial player in IBD pathogenesis [45]. Sleep is regulated by two processes: sleep/wake homeostasis and circadian rhythm. Sleep/wake homeostasis refers to the internal neurophysiological tendency of the body to sleep or wake. For example, after being awake for a long time, the neurophysiological drive to sleep is strengthened.

Circadian rhythms can be defined as 24-h patterns that coordinate biological functions with environmental patterns and are very important in body health [46,47]. In fact, the circadian clock, settled in the suprachiasmatic nucleus (SCN) of the hypothalamus, directs the daily regulation of a significant number of physiological functions such as sleep [48].

Receiving the light signal from the retina by the hypothalamus can lead to the entrainment of the expression of clock genes in the SCN. The increase in SCN activity in the light phase inhibits the activity of paraventricular nucleus neurons (PVN), eventually leading to reduction of melatonin secretion from pineal gland. Noteworthy, PVN are involved in stimulating the secretion of melatonin from the pineal gland [49]. Therefore, it is obvious that the secretion of melatonin increases in the dark phase, so that its

peak concentration is in the hours after midnight (between 2 and 4) [50]. Melatonin, in turn, acts on the SCN and is involved in the phase-shifting of the circadian clock through MT2 receptors.

Melatonin plays a central role in sleep regulation. The effects of melatonin on the SCN through MT1 receptors are involved in sleep induction. In addition, peripheral vasodilatory effects of melatonin can reduce the body's core temperature and thereby stimulate sleep [49]. Accordingly, the results of a meta-analyses on clinical studies have clearly shown that melatonin can reduce sleep-onset latency [51]. Another meta-analysis on 19 clinical studies with a total of 1683 subjects showed that melatonin, in addition to reducing sleep onset latency, can elevate total sleep time and enhance overall sleep quality [52]. The results of a study on 105 children with attention-deficit/hyperactivity disorder (ADHD) and sleep onset insomnia showed that melatonin can have beneficial effects in improving sleep onset and increasing total sleep time [53]. These results suggest that melatonin may be useful in improving pre-sleep disturbance and enhancing sleep quality.

Interestingly, it seems that the circadian rhythm in the secretion of melatonin may be abnormal in IBD patients [54]. Besides, findings from a clinical study showed that plasma melatonin levels in the early morning samples significantly decreased in UC patients compared to healthy individuals [55]. A study in mice also found that decreased melatonin levels may be associated with impairment of gut barrier [56]. In addition, as mentioned in the previous section, it is possible that IFN-γ, which is produced in significant amounts during IBD, could induce the expression of IDO, an enzyme involved in the degradation of melatonin in the large intestine of mice [30], indicating the possibility of increased melatonin degradation following inflammation. Although the relationship between the aforementioned changes in the secretion and metabolism of melatonin with sleep disorders in IBD is not yet clearly known, several clinical studies indicate the high rate of sleep disorders in patients with IBD.

For example, A study of 110 patients with IBD and 66 healthy individuals showed that sleep quality impairment was significantly higher in patients with IBD than in healthy individuals [57]. Another study reported a variety of disorders such as sleep latency, sleep fragmentation, and increased rate of sleeping pill use among IBD patients. The study also reported that there was a significant correlation between sleep quality and disease severity in patients with IBD [58].

The results of a meta-analysis have also shown that sleep quality in IBD patients is poorer than healthy people, and this poor quality is more explicit in patients with active IBD [45]. In fact, active disease can also be a secondary cause of sleep disturbance in IBD patients because complications such as diarrhea and abdominal pain can affect the quality of sleep [59]. Several studies have reported this issue. For example, a study of 318 patients with IBD reported that 77% of patients with active disease and 49% of patients with inactive disease had poor sleep quality [60]. In another study of 65 patients with IBD, sleep disturbances were reported in 78% of clinically active IBD patients and 35% of patients in the remission phase, indicating a link between sleep disturbances and disease activity [61]. An interesting cross-sectional study showed that the clinical symptoms of IBD, including diarrhea, bloating, and abdominal pain, were positively correlated with sleep disturbances in IBD patients who were in clinical and endoscopic remission [62]. In another study using the Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality, it was reported that there was a significant association between poor sleep quality and clinically active IBD, and that abnormal PSQI had a remarkable positive predictive value (83%) in prediction of histologic inflammation in patients with IBD [63].

In addition to these, the results of a study on patients with ulcerative colitis showed that early morning plasma levels of melatonin are lower in patients with active disease than in patients in the remission phase. However, this difference was not statistically significant (78.30 ± 45.72 pg/ml vs 46.51 ± 28.76 $p = 0.138$) [55]. These results suggest that active IBD may have a greater effect on melatonin secretion and metabolism, and further strengthens the hypothesis of the relationship between sleep disorders in IBD and changes in melatonin secretion and metabolism. Undoubtedly, conducting more studies in this field will clarify more aspects of this issue.

Some studies have also shown that there is a relationship between sleep disorders and disease recurrence in IBD patients. For example, one study in a large population showed that the risk of active disease increased 2-fold in patients with Crohn's disease who were in remission and suffering from sleep disorders [64]. Poor sleep quality in IBD patients appears to be associated with worse prognosis at 6 months [65]. A study of 136 Japanese IBD patients reported that 44% of these patients had sleep disorders. This study also showed that sleep disturbances are a risk factor for disease flare in one year (OR 3.09, 95% CI 1.47–6.43) [66]. These clinical findings are very interesting and important because these findings create the hypothesis that it may be possible to prolong the remission period by treating sleep disorders.

However, a recent study showed that sleep efficiency was not significantly associated with disease activity in IBD patients [67]. In another new study that used PSQI to assess sleep quality in IBD patients, it was reported that sleep disturbances in these patients were not directly related to disease activity but were associated with patients' moods such as depression [68]. In a study of 61 patients with Crohn's disease and 60 healthy controls, sleep quality was assessed objectively using actigraphy and measurement of melatonin metabolites in urine. The results of this study showed that although according to PSQI, sleep disorders are more common in patients with Crohn's disease, objective measures do not show a significant difference in sleep parameters between the patient and control groups [69]. Therefore, more studies are needed, especially on the large population of IBD patients (both CD and UC).

In addition to these, it seems that some other circadian rhythm disorders maybe associated with IBD. For example, a clinical study conducted on 115 IBD patients showed that social jet lag (>2 h) exists in 40% of patients with Crohn's disease whose have severe/complicated disease. The results of this study also showed that there is a significant relationship between later chronotype and worse SIBDQ [70]. Besides, the results of a study on mice also suggest that shifting of the light-dark cycle can be related to increasing the progress of colitis and intensifying inflammation [71].However, the relationship between these observations and melatonin levels in IBD patients is still unclear.

In general, considering the role of melatonin in regulating the circadian rhythm and sleep, the aforementioned findings may be attributed to melatonin levels and justifies the need to focus on the importance of melatonin in IBD. In the following sections, we will discuss the effects of melatonin on the important events involved in IBD pathogenesis.

4.2. Melatonin, intestinal barrier and IBD

As noted above, the destruction of the mucosal barrier of intestine leading to increased intestinal permeability is one of the key events in IBD pathogenesis. Various studies have shown that the mucosal layer in active IBD is thinner and more discontinuous, the number of goblet cells is reduced, and the expression of some proteins which are involved in maintaining tight joints, including claudins 5 and 8, Junctional adhesion molecule-A (JAM-A) and ZO-1 are attenuated [15,72–75].

There appears to be a very interesting association between melatonin, intestinal mucosal barrier, and intestinal permeability. Sleep deprivation appears to reduce melatonin levels, which may lead to decreased goblet cell number, increased pro-inflammatory cytokines, decreased anti-inflammatory cytokines, weakened antioxidant defenses, enhanced NF-κB pathway activation, and colonic mucosal injury [56]. A study in mice with DSS-induced colitis showed that deprivation of sleep for three days could increase the number of infiltrating cells and exacerbate colon mucosal damage, while, treatment with melatonin at a dose of 10 mg/kg intraperitoneally for 3 days before the induction of colitis significantly weakens these effects and reduces inflammation in the colon tissue [76].

Studies have shown that melatonin could attenuate the effect of ethanol on increasing intestinal permeability in rats [77,78], suggesting a role for melatonin in preventing increased intestinal permeability. It seems that, melatonin may protect intestinal mucus under psychological stress in mice and has positive effects on increasing goblet cell number and enhancing ZO-1 expression [79].

One study found that sleep deprivation reduced the expression of key proteins of tight junctions including Claudin-1, Occludin and ZO-1 in mice intestinal tissue, but, melatonin can increase levels of these proteins significantly (Fig. 3) [80]. In addition, sleep deprivation appears to reduce adiponectin expression in colitis mice model colon tissue, while melatonin can increase adiponectin expression [81,82]. Adiponectin can significantly increase the expression of ZO-1 and occludin and enhance intestinal barrier integrity in mouse models of colitis [83].

Some studies on mice have shown that sleep deprivation may increase IL-1β and TNF-α levels and decrease IL-10 levels [56,80]. As noted in the previous section, TNF-α plays an important role in weakening the intestinal mucosal barrier. A study in rat models of colitis showed that melatonin reduced serum TNF-α level. This study also showed that colonic injury was significantly reduced in melatonin-treated rat models of colitis [84]. The results of a study on Caco-2 cells have suggested that melatonin can protect the integrity of intestinal epithelial cells and attenuate the effect of IL-1β on increasing para-cellular permeability [85]. On the other hand, it seems that melatonin can increase IL-10 levels in the intestinal tissue of mice [80]. The results of a study on Caco-2 monolayers showed that IL-10 can have an anti-inflammatory role and strengthen the intestinal epithelial barrier [86].

All these findings suggest that melatonin through various mechanisms including enhancing the expression of key proteins of tight junctions such as ZO-1, increasing the number of goblet cells, reducing the levels of pro-inflammatory cytokines such as TNF-α, increasing the levels of cytokines with anti-inflammatory properties including IL-10 and enhancing adiponectin expression can strengthen the intestinal mucosal barrier. These very interesting findings may justify the clinical observations mentioned in the previous section about the association between sleep disturbances, disease activity, and disease flare in patients with IBD. Since disruption of the intestinal mucosal barrier is one of the earliest and most important events involved in the pathogenesis of IBD [15], further studies on the effect of melatonin on the intestinal mucosal barrier are necessary.

4.3. Melatonin, intestinal microbiota, dysbiosis and IBD

Dysbiosis (unfavorable alteration in microbial composition) is an important event in the pathogenesis of IBD. There are probably more than 1000 species of bacteria in the gastrointestinal tract. These bacteria, which are considered as gut normal flora, can be beneficial for the host. One of the most important beneficial effects of gut bacterial flora is the development of the intestinal immune

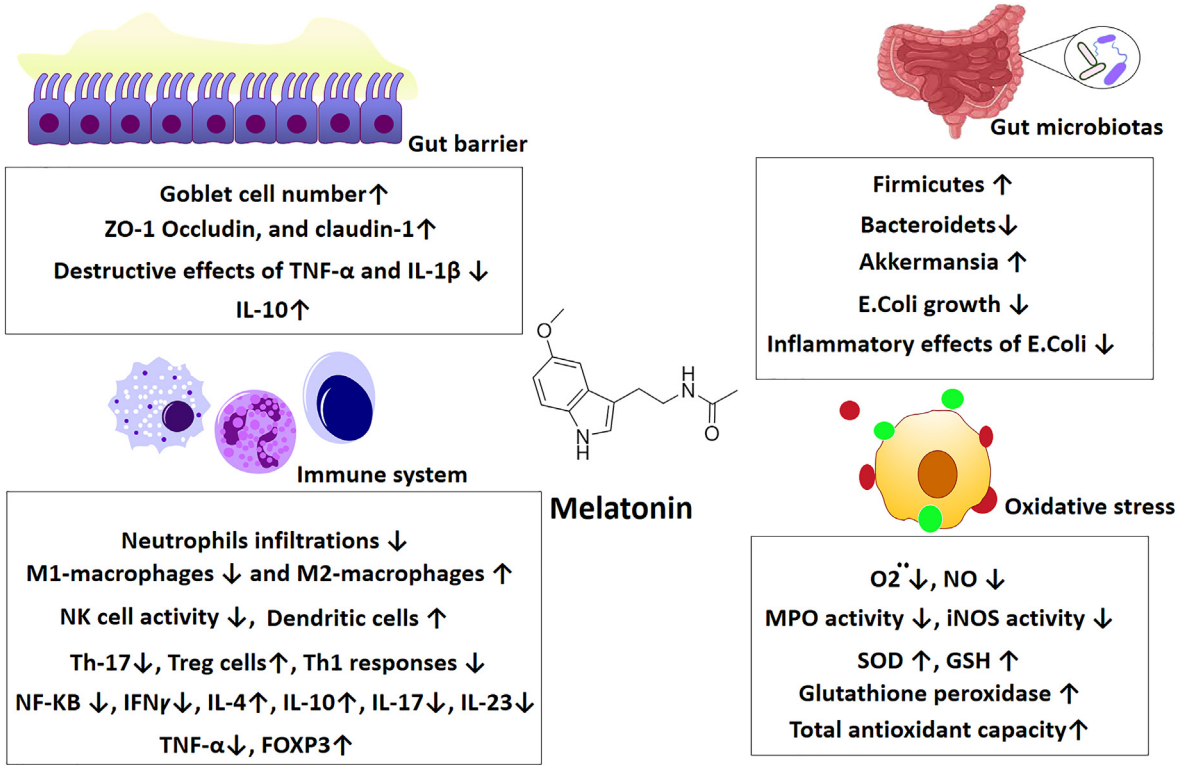

Fig. 3. Possible effects of melatonin on important factors involved in the pathogenesis of IBD.

system and defense against pathogens [87]. As the results of studies on germ-free mice have shown, the lack of intestinal microbial flora impairs the immune response [88]. The presence of intestinal bacterial flora may also be essential for the health and proper functioning of the intestinal barrier. [87,89]. On the other hand, the presence of intestinal bacteria may be necessary to induce colitis in mice [89].

Regarding the composition of intestinal bacterial flora it should be noted that, although bacterial diversity in the gut is significant, firmicutes, bacteroidetes, proteobacteria and actinobacteria constitute about 99% of intestinal bacteria in healthy individuals [87]. Some intestinal bacteria appear to have anti-inflammatory properties while others appear to have inflammatory capacity. It seems that, the composition of intestinal flora bacteria in IBD patients undergoes changes. In IBD, the balance between these two groups of bacteria appears to shift toward bacteria with inflammatory capacity [87].

Various studies have shown that beneficial bacteria decrease in IBD patients but an increase in the number of bacteria such as Escherichia coli) E. coli (was reported. One study showed that the proportions of bacteroides spp increased in the intestinal tissue of patients with IBD, while the proportions of faecalibacterium prausnitzi decreased. In addition, the findings of this study showed that total bacterial DNA concentration in blood and intestinal tissue samples of IBD patients is higher than healthy individuals [90]. Another study showed that the Firmicutes/Bacteroidetes ratio and the count of Faecalibacterium prausnitzii species decreased in patients with active IBD [91].

Faecalibacterium prausnitzi appears to have anti-inflammatory properties and can enhance IL-10 production. Decreased populations of this bacterium may be associated with recurrence of Crohn's disease after surgery [92]. Studies on mice models of IBD have indicated that Lactobacillus acidophilus can also attenuate the production of pro-inflammatory cytokines produced by Th17 cells, including TNF-α, IL-6, IL1-β and IL-17, while it can induce Treg cells and IL-10 production [93,94].Besides, it seems that, treatment with this bacterium can be helpful in the improvement of colitis in IBD mouse models [94,95].

Besides, Akkermansia muciniphila can improve colitis in IBD mouse models and reduce the levels of pro-inflammatory cytokines including TNF-α and IL-6 [96]. Interestingly, this bacterium is also reduced in IBD patients [97].

E. coli, especially adherent-invasive E coli (AIEC), play an important role in the pathogenesis of IBD and appear to increase in the intestinal tissue of IBD patients [98,99]. E. coli appears to be associated with increased expression of pro-inflammatory cytokines including TNF-α and IL-17 in IBD patients [100].The results of a study on epithelial cell monolayers have suggested that AIEC can impair the integrity of the intestinal epithelial barrier, which is one of the major events involved in IBD pathogenesis [101]. Some studies indicated that the expression of CEACAM6, a surface adhesion molecule, is increased in the intestinal epithelium of IBD patients and this molecule may act as a receptor for adherent E. coli [102–105]. The results of in-vitro investigation on Caco-2 cells have suggested that TNF-α and IFN-γ may enhance CECAM6 expression in intestinal epithelial cell [102].

There is probably an interesting link between sleep disturbances, melatonin, and the composition of intestinal bacteria, which may be important in the pathogenesis of IBD. Chronic sleep fragmentation appears to alter the composition of mice intestinal bacteria, including a decrease in the proportion of lactobacillaceae families [106]. As mentioned above, the proportion of these bacteria in the intestinal tissue of patients with IBD is reduced.

It appears that melatonin can increase Firmicutes/Bacteroidetes ratio and attenuate dysbiosis in the intestinal tissue of sleep-deprived mice [107]. A study of mouse models of colitis showed that in these mice Bacteroidetes were the most abundant phylum and Firmicutes were significantly less, while treatment with melatonin could reverse this pattern by increasing Firmicutes and decreasing Bacteroidetes [108]. However, another study has shown that sleep deprivation reduces the frequency of Bacteroidetes and increases Firmicutes in the gut of mice, while melatonin supplementation can reverse this pattern by increasing Bacteroidetes and decreasing Firmicutes [56]. Therefore, more studies are needed in this regard.

In addition to these, it seems that melatonin can increase the proportion of Lactobacillus in the mice intestinal tissue [109,110]. Sleep deprivation appears to reduce Faecalibacterium in the gut of mice, while melatonin can significantly increase the population of these bacteria [56]. Melatonin may also increase the population of akkermansia in the mice intestinal tissue (Fig. 3) [56,110,111]. Sleep deprivation also appears to reduce these bacteria [56]. All of these findings support the hypothesis of a link between sleep disorders and IBD.

In addition, a recent study showed that treatment of intestinal epithelial cells with melatonin could inhibit the growth of E. coli (Fig. 3) [112]. Melatonin may also attenuate the inflammatory effects of this bacterium. One study on rats showed that E. coli-induced pyelonephritis could increase serum TNFα levels, while melatonin treatment could reduce this cytokine levels [113].

According to all of above-mentioned results, melatonin may be effective in treating IBD by increasing the population of bacteria that decrease in IBD, such as Lactobacillus, Faecalibacterium, and akkermansia, as well as inhibiting the growth of bacteria such as E. coli, which play a destructive role in IBD pathogenesis. This hypothesis needs to be seriously considered in future studies.

4.4. Melatonin, immune system and IBD: a smart regulator?

As discussed in the previous sections, the immune system plays a key role in the pathogenesis of IBD. The disruption of the intestinal mucosal barrier and the change in the composition of the intestinal bacteria discussed above are among the important causes of inappropriate and dysregulated immune response in IBD.

So far, the role of immune cells including neutrophils, macrophages, dendritic cells, $CD4^+$effector T cells and regulatory T cells in the pathogenesis of IBD has been extensively studied. The cytokines secreted by these cells play a very important role in the pathogenesis of IBD. Consecutive cycles of inflammation and the continuous production of large amounts of pro-inflammatory cytokines, including TNF-α, may further weaken the intestinal mucosal barrier. The NF-κB signaling pathway mediates the production of these pro-inflammatory cytokines and is one of the key signaling pathways involved in inflammation and IBD pathogenesis.

Interestingly, receptors and enzymes that synthesize melatonin are present in immune cells, which may indicate the role of melatonin in regulating the function of immune cells. Melatonin can also affect the NF-κB signaling pathway and affect the production of cytokines. In this section, all of these will be discussed in detail. Fig. 3 also summarizes the most important findings reviewed in this section.

4.4.1. Melatonin and innate immune cells

Innate immune cells, including neutrophils and macrophages, are important in the pathogenesis of IBD. Neutrophils, also known as PMNs, can play an active role in the immune system through phagocytosis and the secretion of antimicrobial compounds. Chemotaxis and the migration of these cells from the bloodstream to the site of injury, infection, or inflammation is one of the key

events of the innate immune response.

Regarding the role of neutrophils in the pathogenesis of IBD, relatively contradictory results have been reported from animal models. Some studies have shown that targeting neutrophils with anti-neutrophil antibodies can attenuate colitis, while others have shown that neutrophil depletion using antiserum or blocking the adhesion of these cells with Using Anti-L-selectin mAb can aggravate colitis [114,115]. However, in human studies, increased neutrophil infiltration is considered as one of the parameters of IBD histological activity and in IBD histological activity scoring systems is one of the important variables [116,117].

Sleep restriction appears to increase the number of neutrophils [118].However, one study showed that sleep deprivation could impair neutrophil phagocytic ability and impair NADPH oxidase activity in these cells [119]. Melatonin appears to affect various aspects of neutrophil function. It seems that melatonin can attenuate neutrophil infiltration to the intestine in rats [120]. Melatonin may inhibit L-selectin shedding in human neutrophils, as demonstrated by an in-vitro study [121], thereby affecting the adhesion of these cells. The results of a study on isolated human neutrophils have shown that melatonin and AFMK may attenuate the ability of neutrophils to produce pro-inflammatory cytokines, including TNF-α and IL-8 following LPS, a bacterial component, stimulation [122]. Some studies have also shown that melatonin may attenuate apoptosis in human neutrophils [123]. A study of zebrafish showed that melatonin in low doses could enhance the recruitment of neutrophils to the site of injury [124]. All of the above findings may indicate a precise regulatory mechanism that melatonin exerts on neutrophils and may be important in the pathogenesis of IBD.

Due to the relationship between the increase in neutrophil infiltration and the histological activity of IBD, which was mentioned above, melatonin's regulatory effects on neutrophils may play an important role in reducing the disease activity. Interestingly, there are limited evidences to suggest that melatonin production in the colon tissue may increase during the active phase of IBD. For example, the results of a study on patients with ulcerative colitis in the acute and active phase of the disease, showed that the expression of HIOMT and the number of enterochromaffin cells in the colon tissue, and the urinary secretion of 6-sulfatoxymelatonin are increased [125], which indicates an increase in the production of melatonin in the colon tissue in the active phase of IBD. This increase may represent a melatonin dependent compensatory mechanism to attenuate inflammation in active phase of IBD. Besides, one study on rat models of IBD, showed that melatonin treatment (intra-rectally at a dose of 10 mg/kg once daily) significantly improved Nancy scores, an established scoring system for assessing the histological activity of colitis. This improvement is especially evident in the samples obtained from the ascending colon, so that grade 0 was reported in 11 samples out of a total of 12 samples [126]. These results may also suggest the role of colonic melatonin in reducing disease activity in active IBD. However, there is not much information regarding the role of melatonin in different phases of IBD and it is necessary to conduct more studies on this interesting topic in the future.

In addition to neutrophils, it seems that melatonin also affects macrophages. The role of macrophages in the pathogenesis of IBD is also very important. These cells originate from monocytes in body tissues. In short, macrophages are activated through classical and alternative pathways. Classic pathway-activated macrophages named M1 macrophages and have pro-inflammatory properties, while alternative-pathway-activated macrophages named M2 macrophages can have anti-inflammatory properties [1]. It seems that IFN-γ and LPS can induce the classical pathway while cytokines such as IL-4 and IL-13 are involved in the activation of macrophages through the alternative pathway [127,128].

M1 macrophages can secrete significant amounts of pro-inflammatory cytokines, including IL-1β, IL-23, IL-6 and TNF-α, while M2 macrophages can secrete cytokines with anti-inflammatory properties, including IL-10 and TGF-β [129]. M1 macrophages have a high ability to present antigen and phagocytosis, are involved in inducing the Th1 and Th17 response and are associated with tissue damage, while M2 macrophages are mainly involved in regulating immunity and tissue repair and can induce the Th2 response [130].

The polarization of macrophages and the balance between M1 and M2 macrophages are important in the pathogenesis of various diseases including IBD. In experimental colitis, M2 macrophages and IL-10 appear to decrease, while M1 macrophages, IL-23, and TNF-α may be increased [131]. Inhibition of M2 macrophage polarization may exacerbate colitis and shifting the polarity of macrophages from M1 to M2 has been proposed as a therapeutic approach for the treatment of IBD [131–133].

Although the association between sleep disorders and macrophage polarization in IBD and intestinal tissue has not yet been studied, fragmented sleep may be associated with enhanced M1 macrophage polarization [134].

It seems that melatonin can reduce M1 macrophages and shift the polarization of macrophages from M1 phenotype to M2 by enhancing STAT3 signaling in mice macrophages [135]. In addition, melatonin appears to attenuate the secretion of TNF-α and IL-1 by macrophages in rats with TNBS-induced colitis [136], indicating the role of melatonin in regulation of macrophages activity in colitis. The results of a study on THP-1 cell line suggested that, melatonin may also be able to increase the expression of IL-10 and TGFβ, which need to be carefully studied in IBD [137,138]. All of these findings suggest a possible role for melatonin in enhancing the polarization of macrophages toward the anti-inflammatory phenotype.

NK cells are another group of immune cells that can play a role in the innate immune response and appear to be involved in the pathogenesis of IBD. NK cells can both play a role in boosting inflammation and play a regulatory role. In fact, these cells can play a dual role [139,140]. The exact role of these cells in the pathogenesis of IBD is unclear and a small number of studies were done in this regard. One study showed that the frequency of CD16 (+) NK cells in the lamina propria of patients with IBD increased compared with healthy individuals. The findings also show that treatment with Azathioprine, a common drug in the treatment of IBD, can decrease the number of NK cells, attenuate the cytotoxicity of these cells, and reduce the ability of NK cells to produce IFN-γ [141]. Another study showed that treatment of Crohn's disease patients by 6-mercaptopurine, a common drug for Crohn's disease treatment, reduced the number of NK cells in the intestinal tissue, suggesting that NK cells may be targeted by 6-mercaptopurine [142].

However, a study of IBD mouse models showed that NK cells may play a protective role against colitis by attenuating the pro-inflammatory activity of neutrophils [143]. In addition, the results of a meta-analysis on studies conducted on IBD patients have shown that polymorphisms in killer immunoglobulin-like receptor (KIR) genes, which are surface receptors on NK cells, may be associated with IBD development susceptibility [144].

The association of melatonin with NK cells is also unclear. Sleep deprivation appears to increase NK cells activity [145]. The presence of MT-1 receptor, melatonin nuclear receptors and HIOMT has been reported in NK cells [146], indicating the possible effects of melatonin on NK cells. One in-vitro study found that melatonin may suppress NK cell activity [147], while, another study showed that melatonin could boost NK cell activity in aged mice [148]. Another study on mice showed that melatonin administration

could increase the number of NK cells in the spleen and bone marrow [149]. However, one study showed that melatonin administration had no effect on NK cell number in older mice [150]. Therefore, the relationship between melatonin and NK cells and the pathogenesis of IBD needs to be further studied, because according to the above findings, there is a possibility of smart regulation of proliferation and activity of NK cells by melatonin.

The association of melatonin with dendritic cells is also very interesting. These cells are one of the most important antigen-presenting cells that play a key role in synchronizing innate immunity with adaptive immunity. These cells initiate an adaptive immune response by migrating to Peyer's patches and mesenteric lymph nodes and presenting bacterial antigens to naive $CD4^{+}$T cells, which are important in the pathogenesis of IBD. In addition to inducing an adaptive immune response, dendritic cells are also involved in immune tolerance and are able to induce regulatory T cells (Treg). In fact, in the steady-state, the dendritic cells residing in the intestinal lamina propria are tolerogenic, while inflammation can induce the pro-inflammatory phenotype [151].

The expression of TLR2 and TLR4 appears to increase in the dendritic cells of patients with IBD, which may indicate an increase in the ability of these cells to detect bacterial antigens. On the other hand, IL-6 and IL-12 producing colonic dendritic cells appear to increase in Crohn's disease, while the number of IL-10 producing dendritic cells is similar to that of healthy controls [152]. TLR4 expression and IL-6 production in dendritic cells appear to be associated with disease severity in Crohn's disease. In addition, there appears to be an inverse relationship between TLR4 levels in dendritic cells and Faecalibacterium prausnitzii concentrations [153].

It has been demonstrated that myeloid dendritic cells secreted higher levels of IL-23 and lower levels of IL-10 in Crohn's disease. IL-23 is important in inducing the Th17 immune response [154]. The ability of dendritic cells to induce Treg cells in ulcerative colitis appears to be impaired, while these dendritic cells may have an enhanced ability to express IL-6 and TNF-α, and induce of IL-17, IL-13 and IFN-γ -producing $CD4^{+}$ T cells [155]. On the other hand, it seems that transferring dendritic cells and increasing the number of these cells in intestinal tissue in mice increases the severity of DSS-induced colitis, while ablation of dendritic cells can weaken colitis, which may indicate the importance of these cells in developing IBD [156].

The circadian clock seems to play an important role in the function of dendritic cells in inducing the Th1 response [157]. However, the effect of melatonin on dendritic cell function is still unknown. One study has shown that sleep increases the number of circulating IL-12 producing dendritic cells [158]. It has also recently been shown that melatonin has a stimulatory effect on Soay ram seminal gland dendritic cells and can increase the number and size of compartment of endosome [159]. On the other hand, murine intestinal CD103 (+) dendritic cells probably express Indoleamine 2,3-dioxygenase 1, and inhibition of this enzyme attenuates Treg induction and enhances Th1 and Th17 differentiation [160]. According to the results mentioned above, there is a possibility of a relationship between melatonin and dendritic cells, which requires further studies to provide clear results in this regard.

4.4.2. Melatonin and T cells

T cells are classified into CD4 + T cells and CD8 + T cells based on their surface markers. It seems that TCD4 + cells are very important in IBD and have been studied more, so in this section we will focus on these cells. CD4 + T cells are divided into two groups of effector and regulatory cells. Th1 and Th2 are among the most important effector T cells that are very important in the pathogenesis of IBD. All of these cells are derived from naive CD4 + T cells under the influence of various cytokines. IL-12 and STAT4 signaling play a key role in differentiating Th1 cells from naive CD4 + T cells. Th1 cells are involved in defense against intracellular pathogens, and secrete IFN-γ as a major cytokine. These cells can also secrete cytokines such as IL-2 and TNFα, which are important in the pathogenesis of IBD. IL-4 and STAT6 and GATA3 signaling play a key role in differentiating Th2 cells from naive CD4 + cells. Th2 cells secrete significant amounts of IL-4 and are often involved in enhancing humoral immunity and defense against extracellular pathogens [1,161].

It seems that, Th1 cells are associated with Crohn's disease and Th2 cells are associated with ulcerative colitis. Studies have shown that levels of IFN-γ, the major cytokine of Th1 cells, increase in the lamina propria of patients with Crohn's disease, while levels of major cytokines of Th2 cells, including IL-4 and IL-5, decrease. On the other hand, it seems that in the intestines of patients with ulcerative colitis, the levels of major cytokines of Th2 cells, including IL-4 and IL-5, increase, while IFN-γ may be normal or reduced [162,163]. One study in murine models of colitis showed that inhibition of IL-4 by antibody administration could ameliorate the disease [164].

Th17 cells are another group of T cells. Some of these cells have pro-inflammatory properties and can secrete cytokines such as IL-17 and TNF-α, which can be considered effector cells. Another group of these cells secrete IL-10, have anti-inflammatory and regulatory properties, and are named rTh17. TGF-β1, IL-6, IL-21, IL-1β, IL-23, orphan nuclear receptor RORγt and STAT3 signaling play a key role in developing Th17 cells [165,166]. STAT4 signaling in Th17 cells is also important for the production of IL-17 by these cells following IL-23 stimulation [166]. Th17 cells induced by IL-6 and IL23 may have inflammatory properties and are involved in autoimmunity, while Th17 induced by TGF-β and IL-6 may be regulatory (rTh17) [167].

The IL-23/Th17 axis plays a very important role in the pathogenesis of IBD and targeting IL23 has been suggested as a therapeutic approach for the treatment of IBD [168]. Th17 cells in the non-inflamed intestine appear to be regulatory and secrete IL-17A along with IL-10, while in IBD the population of pathogenic Th17 cells secreting both IFNγ and IL-17A may be increased [169,170]. Some studies have reported an elevation in umber of Th17 cell and Th17 related cytokines in intestinal tissue samples of patients with IBD and this elevation is correlated with disease severity [171] It seems that more studies are needed to better identify the role of Th17 cells in the pathogenesis of IBD, and many dimensions are still unclear.

Regulatory T cells are another class of CD4 + T cells. These cells are involved in regulating the activity of effector T cells and immune tolerance. A group of these cells named nTreg originates from the thymus. Another group named iTreg differentiates from naive CD4 + cells in peripheral tissues. IL-2 and TGF-β play a key role in differentiating iTreg cells from naive CD4 + cells. ITreg cells are important in IBD pathogenesis and have been extensively studied. These cells are divided into two subgroups, TrL cells and Th3 cells. TrL cells appear to lack the forkhead box P3 (FOXP3) and secrete significant amounts of IL-10, while Th3 cells express FOXP3 and secrete large amounts of TGF-β [1].

FOXP3 is a transcriptional regulatory factor and is very important in regulatory T cell function. There may also be a group of Th17 cells in the gut of Crohn disease patients that are able to express FOXP3 [172]. It seems that the expression of FOXP3 requires the presence of IL-2, IL-15, and IL-7 and attenuation of the PI3K/AKT/mTORC signaling pathway [173].

In active IBD, apoptosis of CD4 (+) Foxp3 (+) Treg cells appears to increase in intestinal tissue and peripheral blood, whereas treatment with anti-TNF-α can attenuate apoptosis and increase

the number of these cells in the peripheral blood [174]. Based on the results of a study on animal models, it seems that the function of Treg cells may also be impaired in IBD [175]. However, some studies have reported an increase in Treg cells in the intestinal tissue and peripheral blood of patients with IBD [176]. Therefore, further studies in this regard are necessary. In addition, it seems that loss-of-function mutations in IL-10 and polymorphisms in the IL-10 receptor gene are associated with the development of early and severe IBD [177], indicating the importance of the anti-inflammatory function of this cytokine.

The effect of sleep disturbances on T cells is not yet clear. A clinical trial has shown that sleep restriction significantly reduces IL-2 levels, decreases the IL-2/IL-4 ratio, and increases TNF-α level. The results of this study suggest that sleep restriction may shift the balance between Th1/Th2 to Th2 [178]. A study of mouse models of IBD showed that sleep deprivation decreased IFN-γ and IL-10 levels, while IL-6 and TNF-α levels increased [80]. Another study on humans showed that early nocturnal sleep shifted the Th1/Th2 balance toward Th1 as indicated with increased blood IFN-γ/IL-4 ratio, while during late sleep it shifted toward Th2 and IFN-γ/IL-4 ratio is decreased [179]. The results of a study on mice suggested that sleep deprivation may increase the levels of IL-17A, the major cytokine of Th17 cells [180]. Sleep deprivation also appears to impair the proliferation and suppressive function of Treg cells in humans [181]. All these results may indicate the relationship between sleep and adaptive immunity and justify the results of some clinical studies about the relationship between sleep disorders and disease activity in IBD.

It seems that melatonin can also affect adaptive immune response. CD4 + T cells appear to express melatonin receptors, including MT1 and RZRα, and enzymes involved in melatonin synthesis, including HIOMT, indicating the effect of melatonin on these cells [146]. The results of some studies on rats and chickens suggested that melatonin can enhance T cell proliferation and inhibition of MT-1 receptor may attenuate T cells proliferation [182,183].

A study on Jurkat T cells have shown that inhibition of HIOMT can lead to decreased melatonin content and may also be associated with decreased IL-2 production [184]. Melatonin may be able to attenuate Th1 response, reduce the production of IFN -γ and the number of TNF-α secreting CD4 + T cells, and enhance the production of IL-4 and IL-10, as indicated in a study on patients with myasthenia gravis. Therefore, melatonin is likely to shift the Th1/Th2 balance to Th2. However, the results of a study have shown that melatonin is able to enhance IFN- γ production and activate human Th1 cells, but has little effect on IL-4 production [185–189]. Melatonin also appears to have the ability to reduce IL-4 levels in some situations [190]. These findings suggest that melatonin can regulate the Th1/Th2 ratio dependent on condition.

In addition, melatonin appears to inhibit the differentiation of Th17 cells and enhance protective Treg which can lead to amelioration of necrotizing enterocolitis in mice [191]. In addition, it appears that melatonin can reduce IL-17 and IL-23 in IBD mouse models, however, it has been reported that reduction in IL-23 is not statistically significant [192]. Melatonin appears to be able to increase IL-10-producing $CD4^+$ T cells in mice [193]. Besides, it has recently been shown that melatonin has the ability to enhance FoxP3 expression in human CD4 + T cells and augment Treg cells suppressive effects, as well [185]. In addition, some studies have also shown that melatonin can significantly increase IL-10 levels in IBD mouse models [192]. However, in some conditions, such as cholangiocarcinoma, melatonin may attenuate Foxp3 expression and increase TNFα production [194].

All of the above findings suggest that melatonin, as a smart regulator of the immune system and inflammation exerts different effects on the expression of different cytokines and different T cells depending on the condition. This immune regulation may be very important for improving inflammation in IBD, which suggests the therapeutic effects of melatonin in the treatment of IBD. Effects such as lowering TNF-α, regulating Th1/Th2 ratio, inhibiting Th17 cell differentiation, decreasing IL-17, stimulating the differentiation and enhancing suppressive function of Treg cells, and increasing IL-10 levels, indicate that melatonin should be further studied as a therapeutic agent for the treatment of IBD.

4.5. Melatonin, oxidative stress and IBD

Oxidizing agents are produced by cells under physiological and pathological conditions. Mitochondrial respiratory chains and NADPH oxidases are considered to be the main sources of these compounds. In the gastrointestinal tract, xanthine oxidase can be the main source of superoxide anion production, which is an important oxidant. In addition to beneficial roles such as defense against infectious agents and involvement in mitogenic response, oxidizing agents can also have destructive properties. Oxidizing agents can damage DNA, cause changes in the inflammatory response, and cause lipid peroxidation, all of which can be considered as destructive properties of these compounds. Therefore, cells are equipped with an antioxidant system that neutralizes excessive amounts of oxidizing agents and prevents their destructive effects. Oxidative stress occurs when the number of produced oxidants exceeds the ability of the antioxidant system to neutralize [195–197]. Hydroxyl and superoxide radicals, H2O2, as well as, nitric oxide are among the most important oxidizing agents. Catalase, glutathione peroxidase, superoxide dismutase, glutathione and vitamin E are among the important antioxidants.

Immune cells, including neutrophils and macrophages, can produce significant amounts of oxidizing agents such as superoxide anion and NO. Oxidative stress appears to be associated with inflammation and the pathogenesis of IBD. As mentioned in the introduction, clinical findings indicate the presence of oxidative stress in IBD patients. Increased levels of MDA, which is an indicator of lipid peroxidation, have been reported in patients with IBD, which may indicate oxidative stress in these patients [198,199]. The increase in MDA may be in relation with disease activity in IBD patients [9,200], which further reinforces the hypothesis of the importance of oxidative stress in IBD pathogenesis.

NO levels and nitric oxide synthase activity appear to increase in the colon tissue of patients with IBD [201,202]. In addition, the activity of inducible nitric oxide synthase in colon tissue has a significant correlation with endoscopic and histological grade of inflammation in patients with IBD [202]. Inducible nitric oxide synthase expression appears to be increased in the leukocytes of patients with active IBD, as well [203]. NO seems to be able to enhance the production of TNF-α in the mice colon tissue [204], which has previously been shown to play a destructive role in IBD pathogenesis.

Some studies indicated that immune cells in patients with active IBD may have increased SOD activity, increased H2O2 production, increased lipid peroxidation, and decreased catalase activity. Interestingly SOD activity and H2O2 production appear to be reduced during disease remission [205]. It appears that H2O2 may potentiate NF-κB activation in Jurkat T cells [206].

As mentioned in previous sections, NF-κB plays a very important role in the production of pro-inflammatory cytokines and the enhancement of inflammation in IBD. In addition, NF-κB appears to increase NADPH oxidase expression, which may lead to increased production of oxidizing agents and enhanced oxidative stress. In fact, there may be a positive feedback mechanism in which oxidative stress enhances NF-κB activation, and NF-κB exacerbates

oxidative stress by enhancing the production of oxidizing agents [207].

Reduced glutathione levels also appear to be significantly decreased in the intestinal tissue of IBD patients [208]. The results of a study on piglets with colitis have shown that cysteine and γ-glutamylcysteine levels in the distal colon decreased and glutathione synthesis is attenuated [209]. It seems that the total antioxidant capacity also decreases in patients with IBD, and this decrease maybe inversely correlated with the severity of intestinal inflammation [210].

In addition, some studies have shown that glutathione peroxidase activity decreases in IBD, and this decrease corresponded with disease activity. However, some other studies have shown that the combined knockout of catalase and glutathione peroxidase genes may attenuate colitis in IBD mouse models by enhancing the function of Treg cells [211,212]. Some studies have also reported that the levels of glutathione peroxidase is increased in IBD patients compared to controls [8,10], as well as, significant correlation was also observed between the levels of glutathione peroxidase and fecal calprotectin in IBD patients, which may indicate a compensatory mechanism for the neutralization of oxidative stress following inflammation [8].

Some studies on mouse models of IBD have shown that myeloperoxidase (MPO) activity is increased in the colon tissue of these mice [213]. MPO is one of the enzymes involved in the production of oxidizing agents. All of the above findings could indicate oxidative stress in IBD, which may also play a destructive role in the pathogenesis of this disease.

The relationship between sleep disorders and melatonin with oxidative stress is one of the most interesting topics. Sleep deprivation appears to increase MDA levels and decrease levels of catalase, glutathione peroxidase, superoxide dismutase, and total antioxidant capacity in the intestine of mice [56,80]. In addition, sleep deprivation can increase tissue MPO activity in IBD mouse models [214]. Considering the importance of oxidative stress in IBD pathogenesis, these results may also justify the relationship between sleep disorders and IBD.

Melatonin appears to have the ability to attenuate the production of superoxide anion by neutrophils and reduce iNOS activity and NO production in macrophages (Fig. 3) [215–217]. In addition, it appears that melatonin can attenuate NF-κB activity and NO levels in intestinal epithelial cells following IL-1β stimulation [85]. These effects of melatonin may have a beneficial effect on intestinal pathology as several animal model studies have shown these beneficial effects. For example, a very interesting recent study has shown that melatonin loaded chitosan nanoparticle (Mel-CSNPs) can have a significant effect in attenuating neutrophilic infiltration and preventing crypt damage in mice with DSS-induced colitis. The findings of this study suggest that the significant anti-inflammatory effects of Mel-CSNPs are related to the reduction of NO, IL-1β and IL-6 levels and the attenuation of nuclear translocation of NF-κB p65 [218]. Besides, a study on rats with TNBS-induced colitis, showed that melatonin administration (intraperitoneally at doses of 5 and 10 mg/kg/day for 10 days after induction of colitis) can attenuate the expression of NF-κB p65 in colon tissue, improve colonic mucosal damage, reduce ulcer area, protect the crypt and goblet cell structure, and attenuate immune cells infiltration [219].

Some studies have shown that melatonin treatment can reduce MDA levels and increase levels of catalase, glutathione peroxidase, superoxide dismutase, and total antioxidant capacity in the intestines of sleep-deprived mice (Fig. 3) [56,80]. Studies have also shown that melatonin also increases reduced glutathione levels in the intestinal tissue of IBD mouse models and prevent its reduction following inflammation [213,220]. Besides, it has been demonstrated that melatonin treatment could reduce colonic MPO activity in rat models of IBD (Fig. 3) [213]. Interestingly, a meta-analysis on human studies also showed that melatonin supplementation could improve the function of antioxidant enzymes including superoxide dismutase and glutathione peroxidase, enhance total antioxidant capacity, and attenuate lipid peroxidation [221].

All the above findings indicate that melatonin can effectively reduce oxidative stress in IBD by attenuating the production of oxidants by immune cells, attenuating MPO activity in colon tissue, attenuating NF-κB expression and enhancing antioxidant power.

Therefore, melatonin may be able to neutralize the destructive effect of oxidative stress on the exacerbation of inflammation to some extent. Undoubtedly, more detailed studies will shed more light on the relationship between sleep disorders, melatonin, oxidative stress and IBD.

5. Clinical evidences regarding melatonin effects in IBD

According to what was discussed in the previous sections, it seems that melatonin can affect almost all of important events involved in IBD pathogenesis in favor of reducing inflammation. However, few clinical studies have been conducted with the aim of investigating the plasma and tissue levels of melatonin in IBD. Findings regarding the relationship between melatonin and disease activity in IBD patients are also very limited. A study of 112 patients with ulcerative colitis and 110 healthy controls showed that plasma melatonin levels in the first morning sample of patients with ulcerative colitis were lower than in healthy individual [55]. In another study of 30 patients with ulcerative colitis, a significant inverse correlation was observed between levels of 6-sulfatoxymelatonin, the urinary metabolite of melatonin, and fecal calprotectin [222]. Fecal calprotectin is a diagnostic indicator of IBD that has a direct and significant correlation with endoscopic and histological activity of the disease [3,8].

Another study on 24 patients with ulcerative colitis showed that the 24-h urinary levels of 6-hydroxymelatonin sulfate increased in patients with ulcerative colitis compared to healthy people and had an inverse relationship with the severity of the disease [223]. A study conducted on colon tissue biopsy samples of IBD patients also suggested that melatonin may be useful in weakening inflammatory infiltration and enhancing ultrastructural recovery of colonic mucus [224]. Therefore, there is a possibility of a relationship between melatonin levels and endoscopic and histological activity of IBD, which needs to be considered in future studies. These studies can be designed to investigate the correlation between plasma levels of melatonin or urinary levels of 6-sulfatoxymelatonin and numerical indexes of endoscopic and histological activity of the disease.

Above mentioned clinical findings along with what was discussed in the previous sections raise the question of whether melatonin supplementation can be effective in the treatment of IBD and have helpful effects on intestinal pathology in these patients.

Based on the clinical studies that have been done so far, it can be said that the answer is yes. Although the numbers of clinical these clinical studies are limited, the reported results are promising. In a study of 50 patients with IBD, 5 mg melatonin tablets were given once daily for eight weeks before bedtime. In this study, patients with ulcerative colitis were treated with infliximab at a dose of 5 mg/kg by intravenous infusion every eight weeks, azathioprine at a dose of 50 mg twice daily, and mesalamine at a dose of 1 g four times a day. Patients with Crohn's disease were treated according to the same protocol, except that mesalamine was not prescribed. Disease activity was calculated based on Harvey-Bradshaw index and simple clinical colitis activity index (SCCAI). The findings of this study showed that melatonin supplementation significantly enhances the effect of common treatment regimens in improving

disease activity indices and lowering the level of ESR, a well-known inflammatory marker, in patients with active IBD and can be considered as helpful adjuvant therapy [225]. Another study of 60 patients with ulcerative colitis in the remission phase of the disease showed that daily administration of 5 mg of melatonin at bedtime with mesalazine at a dose of 1 g twice daily had a significant effect on maintaining remission. In this study, it was shown that after a twelve-month period, all 30 patients who received melatonin remained in clinical remission and had significantly lower Mayo Clinic Disease Activity Index (MCDAI) levels than the placebo group [226]. These findings suggest that melatonin supplementation as an adjunctive therapy can have a significant effect in reducing the severity of the disease and maintaining remission in patients with IBD.

In another study that was conducted on 30 patients with mild to moderate ulcerative colitis, melatonin supplementation was performed at a dose of 3 mg for a three months period. The results of this study showed that melatonin supplementation can significantly reduce SCCAI and stool calprotectin levels. In addition, the results of this study showed that while before the start of the study there was no significant difference in the different parts of SF-36 between the melatonin and placebo groups, at the end of the study energy, role-emotional and general health in the melatonin group significantly improved [227]. The results of this study suggest the usefulness of melatonin supplementation in reducing disease activity and improving quality of life in patients with ulcerative colitis. However, more studies should be done to draw accurate conclusions. Another study that was conducted on 20 patients with sleep disorders who were in the clinical remission phase of IBD used the short inflammatory bowel disease questionnaire (SIBDQ) to evaluate health-related quality of life.

The results of this study suggest that melatonin supplement at a dose of 10 mg for two weeks can be useful in increasing the quality of sleep and improving the quality of life [228]. These results show that melatonin can be further studied as a useful compound both for improving sleep quality and relieving IBD symptoms. In addition to the fact that the clinical studies conducted so far regarding the effects of melatonin in the treatment of IBD are limited to the few studies reviewed in this section, the sample size in these studies is also small. Therefore, it is necessary to consider a larger sample size in future studies.

6. Conclusion and future direction

Sleep disorders, may play a role in weakening the intestinal mucosal barrier, exacerbating dysbiosis, enhancing inflammation, and exacerbating oxidative stress. Some clinical studies have also suggested that sleep disturbances are associated with IBD. On the other hand, melatonin affects most important aspects of the IBD pathogenesis. Melatonin strengthens the intestinal mucosal barrier, alters the composition of intestinal bacteria in favor of bacteria with anti-inflammatory properties, regulates the immune response and attenuates inflammation, enhances antioxidant defenses and attenuates oxidative stress. In addition, melatonin supplementation has been shown to improve intestinal ulcers and reduce inflammation in animal models of IBD. Clinical studies have also shown that melatonin supplementation can enhance the effectiveness of common IBD treatment regimens in reducing disease activity and maintaining clinical remission, and lowering levels of inflammatory markers. Therefore, it can be suggested as an adjuvant therapy for IBD treatment. However, a small number of clinical trials have been performed in this regard, which also had a relatively small sample size. Therefore, more clinical studies are needed. In addition, it can be very useful to investigate the relationship between melatonin supplementation and mucosal healing and endoscopic activity in patients with IBD. Further studies on the effect of melatonin on the most important aspects of the pathogenesis of IBD in human samples obtained from patients with IBD in both active and remission phases can also add a great deal of information to current knowledge. It is possible that clinical use of melatonin, in addition to relieving sleep disorders in patients with IBD, could extend the remission period and improve the effectiveness of conventional treatment regimens. However, there may be a long way to go before clinical use of melatonin as a common adjuvant therapy for IBD treatment and a large number of studies should be performed.

Acknowledgment

The authors would like to thank Shohada Clinical Research Development Unit, Shohada Hospital, Tabriz University of Medical Science, Tabriz, Iran.

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