Gastrointestinal Melatonin Secretion and Its Physiological Functions Postprint

Authors: Tan Bi' e, Ren Wenkai, Yin Yulong

Date: 2018-12-24T00:00:00+00:00

Abstract

Melatonin (N-acetyl-5-methoxytryptamine) is a physiological hormone that regulates biological rhythms, metabolism, and reproduction. Both intestinal microbiota and gastrointestinal endocrine cells can synthesize melatonin, which in the intestine exerts regulatory effects on gastrointestinal motility and secretion, and possesses antioxidant, anti-apoptotic, and immunomodulatory functions, demonstrating beneficial effects in various animal models of intestinal inflammation and clinical studies. This review summarizes the synthesis and secretion of melatonin in the gastrointestinal tract, its physiological functions, and its applications in intestinal inflammatory diseases.

Full Text

The Secretion and Physiological Functions of Melatonin in the Gastrointestinal Tract

Tan Bi' e, Ren Wenkai, Yin Yulong*

(Laboratory of Animal Nutritional Physiology and Metabolic Process, National Engineering Laboratory for Pollution Control and Resource Technology of Livestock and Poultry, Key Laboratory of Agro-Ecological Processes in Subtropical Region, Institute of Subtropical Agriculture, Chinese Academy of Sciences, Changsha 410125, China)

Abstract: Melatonin (N-acetyl-5-methoxytryptamine) is a physiological hormone that regulates biological rhythms, metabolism, and reproduction. Both intestinal microorganisms and gastrointestinal endocrine cells can synthesize melatonin, which plays important roles in the gut by regulating gastrointestinal motility and secretion, exerting antioxidant and anti-apoptotic effects, and modulating immune function. Melatonin has demonstrated beneficial effects in various animal models of intestinal inflammation and clinical studies. This

review summarizes the synthesis and secretion of melatonin in the gastrointestinal tract, its physiological functions, and applications in intestinal inflammatory diseases.

Keywords: melatonin; melatonin receptor; physiological function; gastrointestinal tract; intestinal diseases

Melatonin (N-acetyl-5-methoxytryptamine) is primarily produced in the pineal gland of the brain and serves as a regulator of the sleep-wake cycle, participating in physiological processes including biological rhythm, metabolism, and reproduction [1]. Recent research has confirmed that melatonin plays an even more important regulatory role in the digestive system. The gastrointestinal tract represents the most significant source of melatonin outside the pineal gland, with melatonin being produced by intestinal endocrine cells within the gut. Melatonin possesses strong free radical scavenging and antioxidant capacities and serves as an important regulator of gastrointestinal inflammation and motility, suggesting it may play a positive role in controlling many gut-related diseases, particularly intestinal inflammation [2-4]. This review aims to summarize the synthesis and secretion of melatonin in the gastrointestinal tract and its physiological functions, providing a reference for its application in regulating intestinal health and disease control.

1 Synthesis and Secretion of Melatonin in the Gastrointestinal Tract

The intestine is the primary site of melatonin production outside the pineal gland. Melatonin and its receptors are widely distributed throughout the gastrointestinal tract [5], with intestinal concentrations 400 times higher than those in the pineal gland and 10-100 times higher than plasma levels [6]. Melatonin distribution varies regionally along the gastrointestinal tract, with the highest concentrations found in the rectum and colon and the lowest in the jejunum and ileum. Following exogenous melatonin administration, the most pronounced accumulation is observed in the colon and rectum. Furthermore, intestinal melatonin concentrations change with age. In postnatal rats, gastrointestinal melatonin levels peak at birth and then decline to stable levels by day 21. However, melatonin levels increase later in life, with melatonin concentrations in the mucosa of the ileum and posterior colon being 126% higher in 22-24-month-old aged mice compared to 2-5-month-old mice [7].

Studies have shown that melatonin release in the gastrointestinal tract follows a circadian rhythm, but differs from the typical secretion pattern of pineal melatonin [1,8]. Recent research in rainbow trout demonstrated rhythmic synthesis of melatonin in the gastrointestinal tract, with mRNA of key enzymes involved in melatonin synthesis also showing rhythmic expression [9]. Circadian variations in melatonin concentration have been detected in the pancreas, kidneys, spleen, and duodenum of rats, though colonic melatonin levels do not show characteristic nocturnal increases [10].

Enterochromaffin cells are the primary source of gastrointestinal melatonin [11], and melatonin distribution correlates with enterochromaffin cell density. L-tryptophan is the key precursor for intestinal melatonin synthesis. Tryptophan is sequentially catalyzed by four enzymes—tryptophan hydroxylase (TPH), aromatic L-amino acid decarboxylase (AADC), serotonin N-acetyltransferase (SNAT), and N-acetylserotonin O-methyltransferase (ASMT)—to generate 5-hydroxytryptophan, serotonin (5-hydroxytryptamine, 5-HT), N-acetylserotonin, and melatonin (Figure 1 [Figure 1: see original paper]) [12].

Some melatonin detected in the intestine originates from the pineal gland, but its levels are independent of pineal production, as pinealectomy in rats does not affect intestinal melatonin concentrations. Melatonin synthesis and secretion in gastrointestinal tissues are regulated by feeding and food composition. After feeding, melatonin levels in both the gastrointestinal tract and blood circulation increase sharply [13]. In human and animal studies, oral administration of pharmacological doses of L-tryptophan significantly increased blood melatonin concentrations comparable to nocturnal melatonin peaks [7,13]. Gastrointestinal melatonin synthesis is centrally regulated, as adding L-tryptophan or its metabolites to in vitro perfusion solutions does not promote gastrointestinal melatonin synthesis [13]. Intestinal flora can also regulate 5-HT release from enterochromaffin cells and metabolically produce melatonin [14].

2 Melatonin Receptors in the Gastrointestinal Tract

Based on their pharmacological properties, melatonin membrane receptors can be classified as melatonin receptor (MT) 1, MT2, and MT3. All three receptor types are expressed in the gastrointestinal tract, with the highest subcellular distribution in the nucleus, followed by microsomes and mitochondria, and the lowest in the cytoplasm [15]. Both MT1 and MT2 receptors belong to the G protein-coupled receptor family, sharing seven transmembrane structures and showing high homology at the amino acid level, with 55% overall homology and 70% homology within transmembrane domains [5]. Luzindole serves as an antagonist for both MT1 and MT2 receptors and is used in many studies; 4-P-PDOT is a selective MT2 antagonist, while no highly selective MT1 receptor antagonist has been reported. MT3 belongs to the quinone reductase family, possesses strong antioxidant properties, and can be blocked by prazosin [16].

Melatonin receptor expression shows tissue and cellular heterogeneity. In rats, MT1 mRNA expression is highest in the duodenum and lower in the jejunum and ileum, while the highest abundance of MT2 protein is found in the colon, primarily in the smooth muscle layer [17-18]. In duck intestine, radioligand binding assays detected 2-[125I]iodomelatonin binding sites with densities in different intestinal regions in the following order: ileum, jejunum > duodenum, colon > cecum > esophagus [15]. In the human gastrointestinal tract, MT1 and MT2 are expressed in intestinal epithelium, submucosa, myenteric plexus, and gastrointestinal blood vessels, with the highest expression in large intestinal epithelium. MT2 expression levels are significantly higher than MT1 in other

cell types, with high levels of MT2 expressed in enterochromaffin cells [19].

Studies have reported circadian variations in MT expression in the central nervous system, but no obvious rhythmic changes in the intestine [20]. Under a 12 h:12 h light-dark cycle, MT1 expression in the epithelial layer of the rat distal colon shows no significant circadian rhythm [20], and 2-[125I]iodomelatonin binding in duck intestine also displays no daily rhythm [15]. Nutritional status appears to control melatonin release. Short-term fasting increases MT1 expression in the epithelial layers of rat small and large intestine, while during long-term fasting, MT1 expression remains elevated only in the distal colon and returns to normal levels in the small intestine [20]. MT2 expression also does not change with food intake [18].

Melatonin exerts its physiological effects by activating specific receptors. Membrane receptors mediate their functions through G protein-coupled second messengers. MT1 couples with G proteins that mediate adenylate cyclase inhibition and phospholipase C activation, while MT2 couples with transduction pathways including phosphoinositide production, adenylate cyclase inhibition, and soluble guanylate cyclase pathway inhibition [1]. Nuclear melatonin signaling is mediated by the transcription factor retinoid Z receptor/retinoid acid receptor-related orphan receptor (RZR/ROR) (Figure 2 [Figure 2: see original paper]) [1,21]. The RZR/ROR isoform is widely distributed, and its expression determines melatonin' s effects on transcriptional regulation. RZR/ROR has been confirmed to be involved in melatonin' s immunomodulatory effects [21].

3.1 Regulation of Gastrointestinal Motility and Secretion

Melatonin is highly lipophilic and may diffuse through the mucosa and submucosa to deeper layers, ultimately acting on the muscularis mucosa or myenteric plexus to regulate gastrointestinal motility. Both in vitro and in vivo studies have shown that melatonin can inhibit muscle activity in the gastrointestinal tract, with the degree of inhibition proportional to the contraction intensity of the stomach, duodenum, small intestine, and large intestine [1]. Pineal gland removal inhibits the regular phase of the migrating myoelectric complex, while exogenous melatonin treatment can restore normal migrating myoelectric complex activity in rat ileum [22]. These changes may depend on melatonin' s effects on gastrointestinal neurons. In the stomach, melatonin partially inhibits gastric motility by activating sympathetic neurons [3].

Melatonin produces both excitatory and inhibitory effects on the intestine depending on dosage. High concentrations of melatonin show inhibitory effects on spontaneous and 5-HT-induced peristalsis in gastric, ileal, jejunal, and colonic muscles. Conversely, low doses of melatonin produce stimulatory effects on intestinal muscle tissue, accelerating intestinal peristalsis [22-23]. Melatonin inhibits the motility activity of the gastrointestinal tract stimulated by various agents including 5-HT, potassium chloride, and carbachol (a cholinergic receptor agonist) [13]. Therefore, the inhibitory effect of melatonin on muscle

contraction involves multiple mechanisms. The most likely site of melatonin action in gastrointestinal smooth muscle cells is membrane-bound melatonin receptors. Studies have found MT2 immunoreactivity in the muscularis mucosa and circular and longitudinal muscle layers of rat stomach, colon, and duodenum [18], indicating that MT2 receptors are involved in melatonin' s regulation of gastrointestinal motility.

Other possible sites of melatonin action are 5-HT receptors. Kasimay et al. [3] demonstrated that melatonin' s delaying effect on gastric emptying is mediated by 5-HT3 and cholecystokinin (CCK2) receptors. Pretreatment with 5-HT3 receptor (ramosetron, 50 g/kg) or CCK2 (L-365,260; 1 mg/kg) blockers 15 minutes before melatonin injection eliminated the melatonin-induced delay in gastric emptying, while blockade of sympathetic ganglia (benzyl benzoate tosylate, 15 mg/kg) significantly reduced the delay in gastric emptying rate. Melatonin' s effects may be related to its blockade of nicotinic acetylcholine receptors or its modulation of calcium ion (Ca2+) channels and Ca2+-activated potassium ion (K+) channel activity in cell membranes [24-25].

Melatonin' s regulation of gastrointestinal secretion primarily involves secretory responses in the duodenum. Central nervous system stimulation by the 1-adrenergic receptor agonist phenylephrine induces melatonin release from intestinal mucosa, which exerts paracrine effects in adjacent duodenal enterocytes and can also activate secretomotor neurons in the enteric nervous system, leading to bicarbonate secretion. Melatonin can also induce increased intracellular calcium concentration in duodenal enterocytes, thereby activating electroneutral bicarbonate/chloride (HCO3-/Cl-) exchangers. The melatonin antagonist luzindole eliminates duodenal secretory responses induced by both melatonin treatment and central phenylephrine administration, but does not affect intestinal melatonin release [26]. Additionally, melatonin is a physiological regulator of ion transport in the lower gut and is thought to play a role in regulating secretions. Melatonin can affect the expression of cyclooxygenase 2 (COX-2) and inducible nitric oxide synthase (iNOS), modulating prostaglandin (PG) E2- and sodium nitroprusside-induced secretion in rat distal colon. Its secretory effects appear to be limited to colonic epithelium and involve the cyclic adenosine monophosphate (cAMP) pathway [1].

3.2 Antioxidant Effects

The antioxidant effects of melatonin have been demonstrated in numerous in vivo and in vitro studies, and its protective effects against gastrointestinal injury are largely attributed to its antioxidant functions [27-28]. Melatonin possesses both lipid and water solubility, enabling it to freely cross any physiological barrier, giving it advantages over other antioxidants and allowing direct access to mitochondria. Melatonin can directly scavenge free radicals by utilizing the 5-methoxy group on its indole ring to directly scavenge oxygen free radicals and reactive species including hydroxyl radicals (• OH), lipid peroxides, hydrogen peroxide, and superoxide anions (O2 • -). After quenching one • OH molecule,

melatonin loses an electron and becomes a low-toxicity indole cation, which subsequently scavenges one $O2\bullet-$ molecule. Through a cascade reaction, it transforms into N1-acetyl-N2-formyl-5-methoxyknuramine (AFMK), N-acetyl-5-methoxyknuramine (AMK), and other metabolites, all of which can effectively scavenge free radicals and synergize with melatonin (Figure 3 [Figure 3: see original paper]). In this manner, one melatonin molecule can scavenge up to 10 reactive oxygen species (ROS) [2,9,29]. The cascade reaction of melatonin interacting with ROS amplifies its capacity as a potent antioxidant. The products (or metabolites) after interaction with ROS and nitric oxide synthase (NOS) retain free radical scavenging ability, and melatonin' s capacity to neutralize $\bullet OH$ is five times that of glutathione (GSH) [29].

Beyond the antioxidant scavenging cascade, another important characteristic of melatonin as an antioxidant is its induction by moderate oxidative stress or adverse environmental conditions [9]. Oxidative stress can alter the ratio of melatonin to its oxidative metabolites, and the resulting signal may lead to gene expression causing positive induction of N-acetyltransferase (NAT) and/or hydroxyindole-O-methyltransferase (HIOMT), thereby promoting melatonin production. Melatonin may also be depleted by severe oxidative stress, as free radical-induced melatonin degradation may occur much faster than its production. Consequently, melatonin levels are lower in oxidative stress-related diseases compared to healthy individuals [2,29].

Melatonin can rapidly enter the mitochondrial intermembrane space and matrix and can also be synthesized in mitochondria, acting as a mitochondria-targeted antioxidant. Melatonin' s antioxidant properties are related to mitochondrial physiology, with an important feature being the inhibition of mitochondrial iNOS activity. Its metabolite AMK has stronger inhibitory effects on mitochondrial iNOS activity and nitric oxide (NO) scavenging properties than melatonin itself [30]. Melatonin improves the efficiency of the electron transport chain (mitochondrial complexes I, II, III, and IV) and enhances adenosine triphosphate (ATP) production. Mei et al. [31] found that melatonin treatment significantly reduced diclofenac-induced intestinal mucosal permeability, pathological scores, malondialdehyde and myeloperoxidase (MPO) levels, and intestinal mucosal ulcers, while restoring ATPase and succinate dehydrogenase activities at the mitochondrial level.

Furthermore, melatonin can exert indirect antioxidant effects by enhancing antioxidant enzyme activity and gene expression. Studies have confirmed that melatonin can increase the activities of antioxidant enzymes including glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT) [9,28-29,32]. Melatonin stimulates -glutamylcysteine synthetase, thereby increasing GSH levels and enhancing glutathione reductase (GSR) activity to convert oxidized glutathione (GSSG) to its reduced form GSH [32]. Melatonin can also inhibit NOS activity in vivo through calmodulin, thereby suppressing excessive NO production and generation of other reactive nitrogen species [33].

3.3 Anti-apoptotic Effects

The ability of melatonin to modulate apoptosis has been demonstrated both in vivo and in vitro, with its anti-apoptotic effects attributed to its antioxidant and free radical scavenging activities [34-35]. Melatonin can prevent the development of mitochondrial oxidative stress and activation of the mitochondrial apoptotic pathway. Hydroxyl radicals ($\bullet$OH) generated during oxidative stress and disease infection promote apoptosis through the mitochondrial death pathway, while melatonin can effectively scavenge $\bullet$OH, protecting cells and tissues from oxidative damage [36]. Both pro-apoptotic and anti-apoptotic factors can be modulated by melatonin, which upregulates anti-apoptotic proteins and downregulates pro-apoptotic proteins in mitochondria, reducing oxidative damage to lipids, proteins, and DNA [32].

Melatonin inhibits the upregulation of B-cell lymphoma-2 associated protein X (Bax) and Bak expression and the downregulation of B-cell lymphoma-2 (Bcl-2) and Bcl-xL expression, preventing indomethacin-induced mitochondrial Bax translocation and mitochondrial membrane potential collapse, and reducing indomethacin-induced activation of caspase-9 and caspase-3 by preventing cytochrome C release [4]. In C2C12 cells, melatonin increased Bcl-2 expression, decreased Bax expression and the Bax/Bcl-2 ratio, protecting cells from apoptosis and autophagy [37]. Melatonin can also inhibit NO-induced apoptosis through increased expression of phosphorylated Protein kinase B (p-Akt), Bcl-2, CAT, and manganese superoxide dismutase (Mn-SOD) [36]. Additionally, melatonin can directly inhibit the mitochondrial permeability transition pore (mtPTP) to exert anti-apoptotic effects [38]. Melatonin modulates uncoupling proteins to maintain optimal mitochondrial inner membrane potential, preventing mtPTP opening and limiting cytochrome C escape when mitochondria are damaged by ROS [32].

3.4 Immunomodulatory Effects

The immunomodulatory properties of melatonin are well established. T cells express both membrane-bound and nuclear binding sites for melatonin, and therefore melatonin affects T cell development, activation, differentiation, and memory [39]. Under immunosuppressive conditions, melatonin exerts stimulatory functions by promoting effector T cell function. Haldar et al. [40] found that melatonin treatment increased thymocyte density in the thymic cortex and resisted dexamethasone-induced immunosuppression. Conversely, melatonin suppresses immune stress by reducing effector T cell responses and enhancing regulatory T cell (Treg) responses [39]. Capelli et al. [41] observed anti-proliferative effects of melatonin in phytohemagglutinin-stimulated human lymphocytes.

Melatonin can increase T helper cell 2 (Th2)-mediated immune responses [42]. Treatment of antigen-sensitized mice with melatonin for 5 days induced a Th2 cell response by increasing interleukin (IL)-10 and decreasing tumor necrosis factor (TNF)- production [43]. Melatonin participates in the regulation of

apoptosis in T cells and B cells. It protects CD4+ T cells from apoptosis by inhibiting upregulation of cluster of differentiation (CD)95 ligand mRNA and protein in response to T cell receptor (TCR)/CD3 stimulation [40]. Yu et al. [44] found that oral melatonin inhibited apoptosis of mouse bone marrow precursor B cells and promoted survival of newly formed B cells.

Another effect of melatonin on the immune system is through regulation of immunomodulatory factor gene expression and cytokine production. Melatonin can enhance antigen presentation from mouse splenic macrophages to T cells and promote expression of major histocompatibility complex (MHC) class II molecules and IL-1 [45]. It regulates gene expression of several cytokines released by human CD4+ T cells, including IL-2, IL-2R, and interferon (IFN)- [46]. Liu et al. [47] found that melatonin upregulated gene expression levels of transforming growth factor (TGF)- , macrophage colony-stimulating factor (M-CSF), TNF- , and stem cell factor (SCF) in peritoneal plasma cells, and IL-1 , M-CSF, TNF- , IFN- , and SCF in splenocytes. Additionally, melatonin affects non-specific immune responses. Currier et al. [48] found that melatonin administration increased natural killer (NK) cell and monocyte numbers in mouse bone marrow and enhanced NK cell activity.

Melatonin plays a key role in immunomodulation in animal models, though research results are not entirely consistent. In rats infected with Trypanosoma cruzi, melatonin promoted Th1 lymphocyte immune responses, inhibited splenocyte proliferation, and decreased serum IL-4, IL-10, and TGF- 1 levels [49]. However, Brazão et al. [50] found that melatonin treatment had no significant effect on the percentages of CD4+ and CD8+ T lymphocyte subsets in chronically Trypanosoma cruzi-infected rats, but promoted thymocyte proliferation and increased serum IL-2 and IL-10 levels. Although melatonin has been shown to interfere with several regulatory pathways of the immune system, it does not produce a unique immunological pathway, and different regulatory pathways may be involved under different doses or antigen stimulation conditions [51].

The immunomodulatory effects of melatonin are mediated by melatonin receptors located on immunocompetent cells. Carrillo-Vico et al. [52] found that MT2 receptor antagonists reduced IL-2 production in human lymphocytes, demonstrating that MT2 binding sites are involved in IL-2 production. Recent studies indicate that melatonin' s regulatory role in the intestine may also be mediated by its induction of the 7 nicotinic acetylcholine receptor (7nAChR). Melatonin is an important positive regulator of 7nAChR, which inhibits NOD-like receptor 3 (NLRP3) activation through oxidized mitochondrial DNA (mtDNA) [53].

4 Application of Melatonin in Anti-Intestinal Inflammation Research

Melatonin has demonstrated important regulatory effects in various intestinal inflammatory animal models and clinical studies, reducing inflammatory lesions, improving colitis symptoms, and decreasing pro-inflammatory cytokine secre-

tion [30,54-60]. Pharmacological doses of melatonin exert clear dose-dependent anti-inflammatory activity in chronic inflammation models, with effects comparable to the standard anti-inflammatory agent piroxicam [57]. Clinical reports on melatonin dosage and administration duration for colitis treatment vary considerably, with doses ranging from 0.15 to 100.00 mg/kg body weight and treatment durations from 4 days to 7 weeks.

The anti-inflammatory effects of melatonin are associated with regulation of many transcription factors, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF- B), hypoxia-inducible factor (HIF), and nuclear factor-erythroid 2-related factor-2 (Nrf2). NF- B is a key transcription factor for iNOS gene expression, and melatonin' s therapeutic effects on intestinal inflammation depend at least partially on inhibition of NF- B activation, leading to suppression of pro-inflammatory cytokine gene expression. Melatonin has been shown to inhibit iNOS and COX-2 expression [61-62]. In rats with colitis induced by acetic acid and dinitro-benzene-sulfonic acid (DNBS) enemas, colonic iNOS and COX-2 expression and NO and PGE2 content were significantly elevated, while treatment with 5.0 and 10.0 mg/kg melatonin significantly downregulated colonic iNOS and COX-2 expression [54]. Similarly, in a rat colitis model induced by trinitro-benzene-sulfonic acid (TNBS) enema, melatonin reduced inflammatory colonic injury by downregulating pro-inflammatory factors mediated by NF- B inhibition and blocking degradation of nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor alpha (I B) [56]. Inhibition of iNOS and downregulation of NF- B lead to changes in inflammatory markers. Experimental and clinical data show that melatonin can limit NO, prostaglandins, leukotrienes, and other inflammatory mediators such as cytokines, chemokines, and adhesion molecules [30,61-62]. Blocking the effects of these cytokines can alleviate the development of intestinal inflammation and suppress inflammation and intestinal damage. Melatonin reduces lipopolysaccharide-induced pro-inflammatory cytokines, chemokines, and positive acute-phase proteins including TNF- , IL-1 , IL-6, GM-CSF, and C-reactive protein, while increasing expression of the anti-inflammatory cytokine interleukin-1 receptor antagonist (IL-1Ra) and negative acute-phase protein fibrinogen [63]. In TNBS- and ethanol-induced colitis in rats, melatonin modulated macrophage activity, thereby reducing IL-1, TNF- , and NO activity [64].

Melatonin may combat intestinal inflammation through pleiotropic effects involving antioxidant, anti-apoptotic, and immunomodulatory actions (Figure 4 [Figure 4: see original paper]). Melatonin can reduce the degree of colonic damage by maintaining endogenous antioxidant GSH reserves, inhibiting MPO activity, and preventing destruction and release of lysosomal enzymes [59]. Melatonin can alleviate TNBS-induced colonic injury and lipid peroxidation, with its ability to reduce colonic damage associated with decreased activity and expression of matrix metalloproteinase (MMP)-9 and MMP-2 [55]. Melatonin can also reduce inflammation by inhibiting endoplasmic reticulum stress, significantly suppressing expression of inflammatory cytokines and endoplasmic reticulum stress-related molecules [53]. In DNBS-induced rat colitis, colonic

injury is associated with increased pro-apoptotic protein Bax expression and decreased anti-apoptotic protein Bcl-2 expression, while melatonin inhibits apoptosis by suppressing NF- B, reducing Bax expression, and preventing loss of Bcl-2 protein [65]. Melatonin can also inhibit activation of apoptosis-related factor ligand (FasL) gene, thereby suppressing the pro-inflammatory response characterized by release of IL-1 , macrophage inflammatory protein (MIP)-1a, MIP-1b, and MIP-2 [65]. Additionally, melatonin can exert protective effects on colonic inflammation by reducing bacterial translocation, decreasing bacterial translocation and apoptosis [60,66].

5 Regulation of Melatonin Physiological Functions by Gut Microbiota

The role of gut microbiota in melatonin regulation of normal physiological functions and disease has gradually become a research hotspot. Melatonin may alter gut microbiota composition, including promoting a decreased Firmicutes to Bacteroidetes ratio and increasing the relative abundance of Akkermansia muciniphila, thereby helping prevent obesity, insulin resistance, hepatic steatosis, and low-grade inflammation [68]. Melatonin influences weight gain, intestinal morphological structure, and colonization of enterotoxigenic Escherichia coli (ETEC) in the intestine through the gut microbial population [69]. Gut microbiota can produce short-chain fatty acids such as acetate, propionate, and butyrate, as well as neurotransmitters including catecholamines, -aminobutyric acid, 5-HT, and melatonin to regulate intestinal endocrine function, acting on the immune and nervous systems and interacting with the host to regulate various physiological functions and disease development. Gut microbiota regulates secretion of gut-brain peptides and other hormones from intestinal endocrine cells, acting on the brain to achieve information exchange between the brain and gut [70].

6 Summary and Outlook

Gastrointestinal melatonin, produced by intestinal endocrine cells, possesses multiple functions including regulation of gastrointestinal motility and secretion, antioxidant activity, anti-apoptotic effects, and immunomodulation. Through these pleiotropic actions, melatonin reduces inflammatory lesions, improves colitis symptoms, decreases pro-inflammatory cytokine secretion, and plays positive roles in various intestinal inflammatory animal models and clinical studies. Future research on melatonin regulation of intestinal health can systematically investigate energy balance and feeding regulation, improvement of microcirculation throughout the intestine, and promotion of epithelial regeneration. Additionally, the interaction between gut microbiota and melatonin metabolism may mutually regulate intestinal physiological functions. Given the complexity of gut microbiota, the mechanisms by which microbiota mediate intestinal sensing of melatonin signals and their feedback regulation of intestinal physiological functions require further investigation.

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