Review

Enterochromaffin cells as the source of melatonin: key findings and functional relevance in mammals

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ABSTRACT

The enteroendocrine cells in gastrointestinal (GI) tract synthesize more than thirty hormones in mammals. Among these cells, the enterochromaffin (EC) cells are probably the most important one due to the fact that they produce melatonin. The rate-limiting enzymes for melatonin synthesis including arylalkylamine-*N*-acetyltransferase (AANAT, currently the SNAT) and hydroxyindole-O-methyltransferase (HIOMT, currently the ASMT) have been identified in EC cells and this has confirmed the local melatonin production in GI tract by these cells. EC cells play a critical role in regulation of gastrointestinal physiology, particularly, in protection of the GI tract from free radical attack and inflammatory reaction. GI tract is the major site exposed to the oxidative stress and inflammation because of the food residue metabolism and the presence of trillions of microbes including the pathological bacteria. Thus, it requires strong protection. Melatonin synthesized by the EC cells provides the onsite protection in GI tract since this molecule is the potent free radical scavenger and effective ant-inflammatory agent. In this review we summarize the available information regarding the structural and functional variability of the EC cells as well as their pathophysiological roles in the GI tract. The focus is given to the protective effects of melatonin produced by the EC cells on the oxidative stress, inflammation and microbiota balance in GI tract.

Keywords: Gastrointestinal (GI) tract, enterochromaffin (EC) cells, oxidative stress, melatonin, inflammation, enteric microbiota.

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1. INTRODUCTION

Enterochromaffin (EC) cells are the most abundant enteroendocrine cells in gastrointestinal (GI) tract and they synthesize more than thirty hormones, hence they are referred as ‘the largest endocrine organ in the body’ of mammals (1). Melatonin is one of

these secretory products. Originally, serotonin was believed to be the prime hormone secreted by EC cells (2) However, further studies by use of immunohistochemical assay have identified that melatonin is the primary product of EC cells. Identification of melatonin synthetic system is the hallmark event in EC cell research (3-6). This observation raises a question as to what is the contribution of the GI melatonin on the circadian rhythm since the amounts of melatonin generated in the GI tract surpasses pineal melatonin by 10-100 folds (7-12). It was speculated that majority of circulatory melatonin during the day was derived from the GI tract since pinealectomy does not alter the daytime serum melatonin level (13-14). In addition, even though pinealectomy caused a decrease in night time circulatory melatonin level but it was unable to alter the melatonin concentration in the GI tract (10). Administration of L-tryptophan (Trp), the precursor of melatonin synthesis, in pinealectomized rats enhanced the circulatory melatonin level (15-16). The evidence mentioned above strongly supports melatonin synthesis in GI tract. A final proving of GI melatonin synthesis came from the identification of its rate-limiting enzyme, arylalkylamine-N-acetyltransferase (AANAT or SNAT), (12, 17-20) and hydroxyindole-O-methyltransferase (HIOMT or ASMT) (21) in GI tract, particularly in the EC cells of the digestive mucosa. Considering the large surface area of the GI tract and the relatively high concentrations of melatonin per gram of GI tissue it was calculated that the amounts of melatonin generated in GI tract of mammals would exceed the amounts of melatonin generated in pineal gland by roughly 400 times (22). This number may vary among the different species (23). Currently, the regulatory mechanisms on melatonin synthesis in GI tract have not been fully elucidated, but feeding regimen (meal frequency and timing of meals) seems to be the key environmental cue to synchronize the daily levels of GI melatonin in mammals (24-27).

Melatonin released from the EC cells seemed to act on a paracrine manner (12, 28-30) since the submucosa and muscularis tissue layer of the gastrointestinal wall possessed relatively low melatonin binding sites (28, 31-32). The GI melatonin can be transported into lamina propria and submucosa via blood vessels and then acts on the muscularis, where a substantial amount of melatonin was found (33). Physiologically, melatonin can either directly act on the intestinal muscles (6) or, produces its activities via myenteric nervous system (34). The presence of melatonin receptors and/or binding sites in the GI tissues supported the conjecture mentioned above (31, 34-36). All these clearly indicate the pleiotropic roles of melatonin played in the GI tract (20, 37-38). For example, as a signal molecule of photoperiodic clue melatonin has significant effect on the digestive physiology in mammals (12, 37). The constant light and constant darkness affected the activity of the digestive enzymes probably mediated by alterations in the levels of melatonin (39). Thus, the present review will summarize the functional relationships among EC cells, its melatonin production and the effects of melatonin on GI heath in mammals.

2. EC CELLS

The gastrointestinal mucosa is comprised of numerous types of endocrine cells with distinct appearances, localizations and functional characteristics. EC cells (or Type I cells) are one of the five enteroendocrine cell types (40). EC cell is designated its name by its occurrence in the intestinal epithelium and its ability to bind with chromium salts. It was first identified in the stomach of dog and rabbit (41) and then in many species. Erspamer classified EC cell as a collection of cells containing chromaffin and argentaffin granules that can bind with diazonium salts and exhibit fluorescence under Wood's light. EC cells are found in the GI tract of different vertebrate and non-vertebrate species including Amphioxus, Ascidia, Octopoda, Muricidae and Amphibia (42).

2.1. Structural features of EC cells.

Up to 1969, there are different opinions as to the classification and categorization of endocrine cells in the gut. The opinion of only single type of endocrine cell in gut was rejected following the identification of different endocrine cells in the digestive tract of rats (40). Morphologically, epithelium of the GI mucosa has, at least, five different types of endocrine cells and the EC cell is one of them (40). However, EC cells are the major type of endocrine cells and they are structurally characterized by the presence of tapering end with numerous microvilli similar to intestinal columnar epithelial cells (40). The junctional proteins, including zonula adherens, zonula occludens and macula adherens, connect the apical region of the EC cells to the adjacent epithelial cells (40, 43). The rough endoplasmic reticulum is around the nuclei, whereas mitochondria are in the perinuclear as well as in the basal region of cytoplasm. Golgi apparatus occupy the cytoplasm of the apical zone, while the secretory granules are distributed in the wide basal end. Secretory granules are membrane bound molecules with slender, spherical, oval or bean shaped appearances (40, 43). These granules contain uniform opaque substance which can be stained with simple and fluorescent dyes or has ninhydrin vapour and alkallinethionidoxyl reactions. The presence of 5-hydroxytrypatamine (serotonin, 5-HT) in these granules was confirmed by auto-radiographic assay. In fact, about 95% of serotonin in the body are produced by EC cells (44-48). Motilin (49), substance P (50), and enkephalin (51) were also identified in the secretory granules. The lamina propria beneath the basement membrane has rich supply of fenestrated blood capillaries and lymphatic vessels. EC cells have the capacity to make direct anatomical connections with afferent and efferent nerve fibres involving both extrinsic neural pathways and the enteric nervous system of the GI tract (43).

2.2. Functional variability of the EC cells.

EC cells play pivotal roles in gastric secretion and motility and both are mainly mediated by serotonin and melatonin released from EC cells. Activations of specific EC cell receptors and signalling pathways orchestrate a variety of functions including propulsion, mixing and digestion of food, host-microbial signalling and modulating the gut immunity (52-54). A variety of membrane receptors of EC cells have been identified and these include 5HT receptors, cholinergic receptors, γ-amino butyric acid receptors, adrenoceptors (both α and β), corticotrophin releasing hormone receptors, irritant receptors (transient receptor potential A1) and pituitary adenylate cyclase-activating polypeptide receptors (55-57). Additionally, it has been observed that serotonin release is stimulated by addition of odorants and tastants to the EC cell cultures indicating the presence of olfactory and gustatory receptors too on the EC cells (58).

2.2.1. Role of EC cells in modulating gut motility in response to chemical and mechanical stimuli.

Mechanical and chemical stimulations of the gut luminal wall increase serotonin secretion and this reaction is, at least partially, mediated by neural reflexes (54, 57). The afferent vagal nerve does not make direct contact with the luminal contents of the gut. Instead, many bioactive substances in the intestinal lumen activate the EC cells to release serotonin as response to the chemical stimulation. These stimuli include glucose, oxygen, short-chain fatty acids, amino acids, peptides, purines, change in osmolarity and pH, certain drugs and even the products released by the enteric microbiota (57, 59-62). Besides, the mechanical forces generated during mixing and propulsion of food, defecation, increased stretch or, distension

also lead to the release of serotonin from EC cells (54). Serotonin binds to 5HT3R receptors at the nerve endings of vagal sensory neurons, thereby activating the vagal afferents (52). Serotonin binding to 5HT4 receptors at the nerve terminals of the intrinsic afferents has also been observed. The stimulation of the enteric nervous system triggers excitation of the cholinergic neurons that makes efferent connections with the GI smooth muscles, finally leading to the smooth muscle contraction (63-64). Serotonin released from the EC cells also directly communicates with the serotonin receptors on smooth muscle cells of the GI tract to induce relaxation of the smooth muscles (65). Hence, serotonin released from EC cells is responsible for both contraction and relaxation of intestinal smooth muscle depending on the action positions. This makes the alternative intestinal segments to form peristaltic wave pattern (1).

EC cells are electrically excitable due to the presence of voltage-gated sodium and calcium channels in their membrane. This has been confirmed with the whole cell patch clamp study in transgenic mice. This feature seems to be partially responsible for signal transduction in EC cells (57). Mechanical stimulation also leads to intestinal mechano-sensory transduction. This is mediated by the activation of Piezo-2 mechano-gated channel in EC cells and the adjacent epithelial cells to cause purine release. The elevated purine level further triggers the release of serotonin from EC cells to perform its autocrine and paracrine functions, respectively. The purines, including ATP and UTP, activate IP3-DAG signalling pathway and consequently promote the release of calcium from endoplasmic reticulum. The calcium levels are responsible for peristalsis, mixing and propulsion of gastrointestinal contents (54, 66).

2.2.2. EC cell as the gut immunomodulator.

The role of EC cells in modulating immune functions has been well documented (67). A variety of toll-like receptors have been identified in mouse derived EC cell line (STC-1). The toll-like receptors can detect different microbial components and facilitate EC cell to participate in host-pathogen interaction (68). The severe combined immunodeficiency (SCID) mice without T-cell receptors are suffered from lack of EC cells and have low circulating level of serotonin (69-71). Similar situations have been observed in the inflammatory bowel disease and constipation-predominant irritable bowel syndrome (C-IBS) (69, 71-72). Conversely, diarrhoea-predominant irritable bowel syndrome (D-IBS) is characterized by rise in plasma serotonin levels. D-IBS can be attenuated by 5-HT3 receptor antagonist or, inhibitor of tryptophan hydroxylase-1 (the rate-limiting enzyme in the synthesis of serotonin) (69). All evidence points out to the fact that EC cells contribute to the patho-physiological mechanisms of these inflammatory disorders in the GI tract (69, 71-72). In addition to serotonin, melatonin is another important tryptophan derivative found in the EC cells. Discovery of melatonin being a potent antioxidant and an immunomodulatory molecule is a major breakthrough in understanding the functional diversity of the EC cells in GI tract. The importance is discussed in the following sections.

3. EC CELLS ARE THE PRIME SOURCE OF MELATONIN PRODUCTION IN THE GI TRACT

The presence of melatonin in GI tract is well documented without debate (4, 20, 73-75). By the use of different methodologies including immunohistology, radioimmunoassay and high performance liquid chromatography, it is confirmed that the abundance of melatonin primarily localizes in the EC cells (3, 22, 28, 76).The result from autoradiographic studies indicated that melatonin utmost bound to the mucosa and villi of the GI tract (32). At the sub-

cellular distributions, the maximum binding of melatonin was detected in the nuclear fraction followed by microsomal, mitochondrial and cytosolic fractions, respectively (28, 77). The EC cells are the active melatonin synthetic cells among other cells in GI tract (4). The immunohistochemical assay has identified that the antibodies of melatonin and its immediate precursors (serotonin and N-acetylserotonin) all are present in the EC cells (78-79). The different methodologies including Coon's indirect immunofluorescent and immunoperoxidase further detected the large quantity of melatonin and its precursors in the GI tract of mammals and humans (80). A question raised is whether the melatonin is synthesized by the EC cells, or it is taken up from the other sources by these cells? To answer this question, it requires to identify whether the melatonin synthetic machinery is also present in these cells. Not surprisingly, the melatonin synthetic rate-limiting enzymes, HIOMT (or SAMT) and AANAT (or SNAT), have been found in EC cells (12, 20, 38, 81-82). These observations have unambiguously proven that EC cells *de novo* synthesize melatonin. Since the total number of EC cells greatly surpasses the number of the pinealocytes and EC cells are responsible for 95% of serotonin synthesis (precursor of melatonin) in mammals (83), a mathematical calculation indicated that the amounts of melatonin produced by the EC cells might be several hundred-fold higher that that produced by pineal gland.

4. BIOSYNTHESIS OF MELATONIN IN EC CELLS

The melatonin synthetic pathway in the EC cells should be as same as in pinealocytes since they share the same enzymes. This pathway is illustrated in the Figure 1. Briefly, EC cells take up L-tryptophan from the circulation. Tryptophan-5-hydroxylase or, monooxygenase converts L-tryptophan to 5-hydroxy-tryptophan (5-HTP) (84). L-aromatic amino acid decarboxylase then decarboxlates 5-HTP to form serotonin or, 5-hydroxy tryptamine (5-HT) (85). AANAT (or SNAT) acetylates serotonin to form *N*-acetyl serotonin (NAS) (86) which is further o-methylated by HIOMT (or ASMT) to form melatonin (87). The melatonin synthetic sites in EC cells probably occur in mitochondria as it occurs in pinealocytes (88-90). The regulatory mechanism of melatonin synthesis in EC cells is not available currently, but it is not regulated by light as in the pineal gland. It seems that its synthesis is under central regulation triggered by intestinal contents (80).

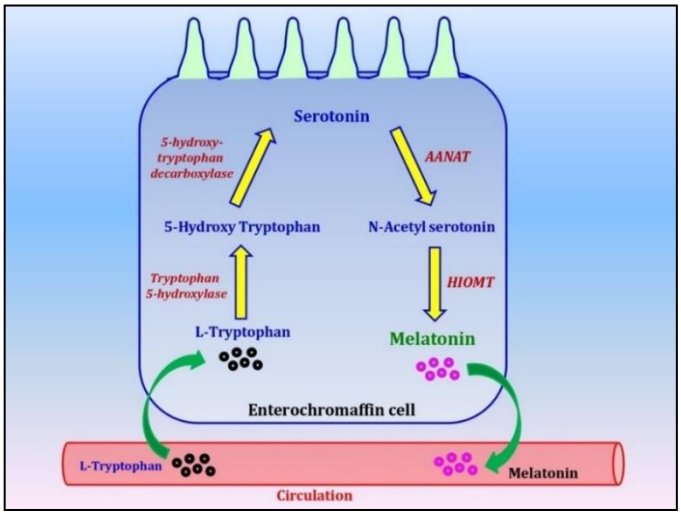

Fig. 1. Biosynthetic pathway of melatonin in the EC cells in mammals.
AANAT:arylalkylamine-N-acetyl transferase, HIOMT:hydroxyindole-O-methyltransferase, arrows indicated the direction of the reactions.

5. RECEPTORS OF MELATONIN IN THE GI TRACT

Identification of melatonin receptors and/or their binding sites in the gastrointestinal cells suggests the paracrine actions of melatonin generated by EC cells locally (76, 91). Melatonin acts on its two primary membrane receptors MT1 and MT2 to produce different biological consequences in GI tissues. For example, activation of MT1 triggers G-protein mediated signalling, but inhibits cAMP signalling (92). On the other hand, activation of MT2 regulates phosphoinositol signalling pathway, but suppresses adenylyl cyclase and guanylyl cyclase mediated signalling pathways (92). Both MT1 and MT2 act synergistically to mediate melatonin's signal. MT3 receptor, which is actually human quinone reductase-2, is also thought to be involved in melatonin mediated signalling (38, 93). Apart from its membrane receptors, melatonin also can bind to several nuclear receptors including RZR/RORγ (94) to mediate some of its biological activities (95-96). Currently, MT1 and MT2 receptors have been identified in the mitochondrial membrane of gastric endothelial cells (97). The authors speculated that some physiological effects of melatonin on GI tract, for example, angiogenesis, might be mediated by its mitochondrial melatonin receptors rather than the membrane receptors. This observation remains to be confirmed.

6. FUNCTIONAL DIVERSITY OF MELATONIN IN THE GI TRACT

Being an amphiphilic molecule melatonin can diffuse through any biological membrane to reach its targets inside and outside of the cells. Presence of its specific transporters in cellular and mitochondrial membranes (98-101) facilitates melatonin's transportation against its concentration gradient. In this way, melatonin can accumulate in extremely high concentrations in some sub-cellular sites such as in mitochondria. Additionally, its wide presence in the inside/outside of the cells and its variety of receptors render this molecule to have pleiotropic physiological as well as pharmacological effects in GI tract (20, 37-38, 102-103).

6.1. Melatonin as an antioxidant against gastrointestinal injuries induced by oxidative stress.

The advantage of melatonin as an antioxidant over other antioxidants is its ubiquitously protective effects on GI injuries caused by a variety of etiologies (Figure 2) (12, 20, 38, 104). Melatonin not only directly scavenges a broad spectrum of reactive oxygen species (ROS), but it also upregulates different antioxidative enzymes and downregulates prooxiative enzymes. These are classified as its receptor-independent or dependent antioxidant activities (103, 105-112).

As to its receptor-independent activity, melatonin interacts with highly toxic ROS including hydroxyl radical, peroxynitrite anion, peroxinitrite, peroxyl radicals and singlet oxygen (106-110). This direct antioxidant property of melatonin has been confirmed not only through *in vitro* but also in many animal studies (109, 113). A protective role of melatonin has been frequently reported in ischemia-reperfusion induced GI injuries by caused by diverse stressors including bacteria (114-120). In addition, melatonin treatment upregulates matrix-metalloproteinase-2 (MMP-2) but downregulates MMP-9 levels which is mediated by MT2 receptor in GI tract, finally suppressing the tissue ROS level (121-122). The interactions of melatonin with ROS generate several products which also exhibit profound antioxidant capacity (107-108, 123-124). The continuously free radical scavenging activity of melatonin with its metabolites has been classified as the antioxidant cascade reaction. From this reaction one melatonin molecule can scavenge up to 10 ROS (125).

The indirect antioxidant activity of melatonin is mediated by its membrane and nuclear receptors (126-127). In this pathway, melatonin upregulates a serial of stress responsive genes including *AMPK, HIFα, Sirt*, etc. (128-129). Activations of these pathways lead to upregulation of variety of antioxidant enzymes including SODs, catalase, glutathione peroxidase and glutathione reductase (103, 127, 129-131), thus, further reduces the oxidative stress and protect the tissue injuries in GI tact.

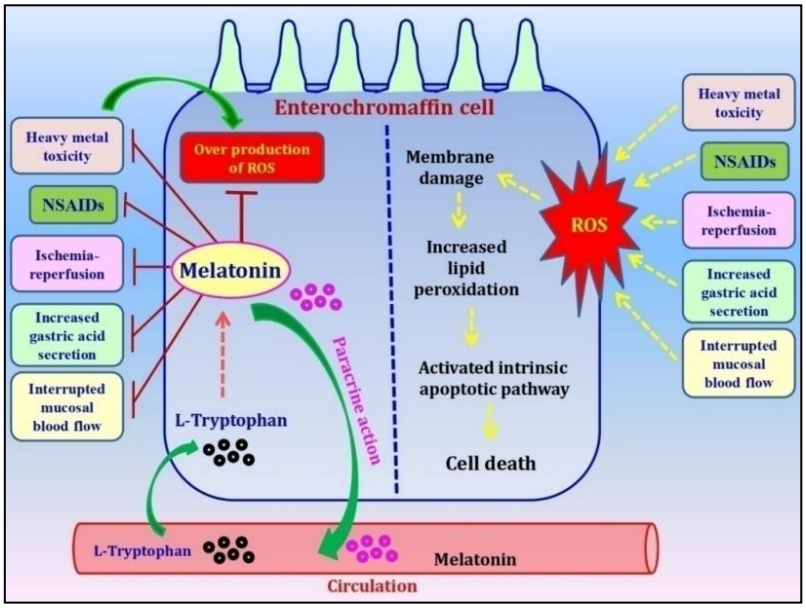

Fig. 2. Effects of melatonin produced by the EC cells on multiple oxidative stresses in the GI tract.

NSAIDs: Non-steroidal anti-inflammatory drugs; ROS: reactive oxygen species; Arrows: indicated the direction of the reaction, Bars: blocking activity.

6.2. Effects of melatonin on GI tissue injury induced by heavy metal toxicity.

Heavy metal pollution is a serious global problem. It not only destroys the ecosystem but also is a major hazard for human health. Usually, the GI tract is the primary site to first contact with heavy metals. Heavy metals can be extracted in GI system by contaminated food and water. If not properly treated, it will damage the GI tissues via oxidative stress (132-133). For example, cadmium (Cd)-induced GI injury is mediated through two possible pathways by disturbing mitochondrial fusion and fission process (134-137) and by activating transcription factor EB mediated autophagy (135). The alterations induced by Cd in GI tract can be protected by melatonin (138-140). In addition to Cd, melatonin also protects GI from injuries associated with the toxicity of mercury (138), arsenic (139) and lead (140). One of the protective mechanisms is its antioxidant capacity. For example, in lead-induced GI toxicity, pre-treatment with melatonin efficiently reduced the tissue level of lipid peroxidation and protein carbonyl content, possibly by restoring the activities/levels of different enzymatic and non-enzymatic antioxidants in the GI tract of rats (140).

6.3. Effects of melatonin on non-steroidal anti-inflammatory drug (NSAID) induced GI damages.

NSAIDs cause severe GI injuries including bleeding, ulceration and apoptosis. The protective roles of melatonin on NSAID-induced GI tissue damage are frequently reported.

These include the beneficial effects of melatonin on indomethacin, aspirin and piroxicam induced GI injuries (114, 141-147). Melatonin not only protects the GI tissues from the adverse effects of these drugs, but also accelerates healing process of the ulcer induced by NSAID (141). Orally application of both melatonin and its precursor (L-tryptophan) accelerated the healing process of the GI mucosal damages caused by unregulated aspirin intake in patients (142, 146). Importantly, the data showed that the endogenously produced melatonin also significantly elevated in these patients. This is probably the auto-response of the oxidatively stressed GI tissues to increase their melatonin against the oxidative stress. This stress-stimulated and stress-released melatonin phenomenon has been reported previously (127). Melatonin treatment effectively reduced diclofenac induced intestinal damage with the mechanism to restore the intestinal permeability and mucosal integrity (143-144). To increase the activities of antioxidant enzymes including peroxidase, superoxide dismutase and catalase in GI tract is another mechanism of melatonin protect against NSAIDS-induced GI damages (145). In addition, other mechanisms of melatonin also enhance its protective effects on the NSAIDS-induced GI damages. These include that melatonin inhibits gastric acid secretion, suppresses infiltration of neutrophils, increases mucosal blood flow in the inflamed tissues, enhances bicarbonate secretion in the duodenum and promotes synthesis of prostaglandins (142, 146-147).

6.4. Melatonin as an anti-inflammatory agent in the GI tract.

Among the diverse pathophysiological conditions, inflammation plays an important role in GI disorders. Actually, melatonin is a profound anti-inflammatory molecule in the GI tract (102, 148-153). A major signal transduction pathway of inflammation in GI is possibly mediated by necrosis factor kappa β (NFkβ) (154-157). Melatonin inhibits the translocation of NFkβ to the nucleus, hence reduces its binding to DNA (158). The NFkβ mediated inflammatory pathway is primarily triggered by TLR4 and TLR5. Melatonin downregulates the expression of *TLR4* and its signal associated genes, such as *MyD88* (159). Melatonin also enhances the levels of Ikβ, eventually suppressing the expression of NFkβ (159). The multiple blocking of NFkβ pathway by melatonin lead to the suppression of overproduction of leukocytes, the adhesion agents and the implementation of different inflammatory cells (158) and all these result in the reduced inflammatory reaction in the GI tissue. On the other hand, aflatoxin B1 mediated intestinal lesions in rat is known to increase circulating level of proinflammatory cytokine IL-1β and melatonin administration profoundly reduces its level (160). Presence of melatonin receptors in mast cells plays a key role in modulation of anti-inflammatory pathway and activation of these receptors by melatonin inhibits the release of TNF-α in the circulation or, tissue (161). In addition, metabolites of melatonin, AFMK and AMK, are also known to exert similar anti-inflammatory functions as melatonin (162). Other mechanisms also involve the anti-inflammatory activity of melatonin including suppression of synthesis of prostaglandins and adhesion molecules (109), inhibition of leukocyte transendothelial cell migration (102) and cyclooxygenase 2 expressions in the macrophages (163) as well as reduction of the recruitment of different pro-inflammatory cells to the sites of inflammation (109, 162). Similarly, melatonin administration reduced the circulating levels of different pro-inflammatory cytokines including IL-1β, IL-6, IL-17, interferon-γ and TNF-α and downregulated the expressions of protein kinase Cζ (PKCζ) and calmodulin 3 (CALM3) (164). In an animal study, melatonin treatment significantly reversed the colonic mucosal injury induced by acetic acid (AA) and further confirmed its anti-inflammatory function in GI tract (165).

6.5. Effect of melatonin on the balance of intestinal microbiota.

Roughly 1014 microbes belonging to nearly 500 diverse species exist in GI tract of animals (166). The normal microbial distribution defines the health and function of GI system. The disruptions of microbial signalling and their normal distribution pave the way for a number of gut related pathologies. The balance of gut microbial community with enteric microenvironment keeps GI healthy. A variety of factors contribute to the GI microbial balance. Melatonin generated by pineal gland and EC cells is one of the most important factors that maintain the GI healthy (167). An interesting correlation between melatonin and gut microbial profile was observed in high fat diet (HFD) fed mice, a model of lipid metabolism imbalance. Antibiotic treatment disturbed the gut microbiota and thus, promoted the metabolic impairment in HFD fed mice while melatonin supplementation significantly improved the metabolic disturbances. Further analysis indicated that melatonin had the capacity to re-establish the balance of GI microbiota by promoting the growth of *Alistipes* and *Bacteroides* which are beneficial bacteria in GI tract (168). It is speculated that disturbance of gut motility may lead to the development of irritable bowel syndrome (IBS) and gastroesophageal reflux disease (GERD) (169). Actually, these disorders may be associated with dysregulation of intestinal microflora. Melatonin treatment preserved the abundance and diversity of enteric microbiota in dextran sulfate sodium (DSS) induced murine collitis model (166). Besides restoring healthy gut microbial population, melatonin has the potency to regulate altered gut permeability and immune response initiated by *Escherichia coli* (170). On the other hand, *Helicobacter pylori* infection downregulated the expression of *AANAT* and *HIOMT* and reduced the production of melatonin in the GIT tissues. This may be one of the factors to promote the gastro ulceration associated with this bacterium. Once the infection subsides, melatonin production returns back to its normal level (171). Undoubtedly, the crosstalk between gut microbial population and the gastrointestinal melatonin is a fascinating area to be explored.

6.6. Effects of melatonin on GI physiology.

In addition to the protective effects of melatonin on the GI tissues, it also participates in diverse of GI physiologies. Melatonin exhibits inhibitory effect on the motor activity of GI tract. This inhibition is directly proportional to the tone and intensity of contractions in the different portions of the GI tract (172-173) possibly by blocking nicotinic acetylcholine receptors on the submucosal nervous plexus (33). Melatonin administration suppressed cell proliferation and gastrointestinal motor activity induced by gastrin (174). The structural similarity of melatonin with the gastrin receptor antagonist (benzotript) may render melatonin having this effect (80). It has been known that melatonin inhibits cAMP production which serves potent role in hydrochloric acid secretion by the parietal cells; therefore, melatonin is thought to suppress HCl production. In contrast, histamine usually enhances cAMP production and cAMP is crucial for melatonin secretion, thus melatonin secretion from the EC cells may be regulated by histamine (80). Interestingly, the effects of cholecystokinin on the motor activities in GI tract are also mediated by melatonin. Melatonin might be the utmost regulator of cell proliferation in the mucosa of the GI tract (80). There are many physiological functions of melatonin on the GI tract and those are not the focus of the current review.

7. CONCLUDING REMARK

EC cells are the important cell type in GI tract. The importance of these cells is not because of their specific morphology but they synthesize melatonin. Originally, melatonin was thought to be solely a pineal derived hormone, but the discovery of melatonin synthesis in EC cells has greatly expanded the spectrum of extra-pineal melatonin sources in mammals. Judging from the cell numbers, it was calculated that the amounts of melatonin generated by the EC cells are several hundred-fold greater than that produce by pineal gland. This melatonin may contribute to the day time circulatory melatonin level. The gastrointestinal melatonin mainly functions as autocrine and paracrine to participate in diverse pathophysiological activities in GI tract. It protects GI tissues against damage caused by oxidative stress and inflammation. Melatonin can bind to its membrane receptors and/or its intra- as well as extra-cellular signalling molecules in exerting its physiological activities in GI tract. These activities include regulation of the GI movement, HCl production, cell proliferation, microbiota balance and prostaglandin synthesis. Collectively, discovery of melatonin synthesis in the EC cells in GI tract of mammals can be considered as a hallmark event in the field of endocrine as well as melatonin researches.

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AUTHORSHIP

Dr. DB and Dr. AC contributed to conception, revised the manuscript critically and approved it. Dr. PKP prepared figures, drafted and edited the manuscript. SS contributed in drafting the manuscript and edited it. Dr. DXT edited the manuscript critically.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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