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Review article

Melatonin's role as a co-adjuvant treatment in colonic diseases: A review☆

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ABSTRACT

Melatonin is produced in the pineal gland as well as many other organs, including the enterochromaffin cells of the digestive mucosa. Melatonin is a powerful antioxidant that resists oxidative stress due to its capacity to directly scavenge reactive species, to modulate the antioxidant defense system by increasing the activities of antioxidant enzymes, and to stimulate the innate immune response through its direct and indirect actions. In addition, the dysregulation of the circadian system is observed to be related with alterations in colonic motility and cell disruptions due to the modifications of clock genes expression. In the gastrointestinal tract, the activities of melatonin are mediated by melatonin receptors (MT2), serotonin (5-HT), and cholecystokinin B (CCK2) receptors and via receptor-independent processes. The levels of melatonin in the gastrointestinal tract exceed by 10–100 times the blood concentrations. Also, there is an estimated 400 times more melatonin in the gut than in the pineal gland. Gut melatonin secretion is suggested to be influenced by the food intake. Low dose melatonin treatment accelerates intestinal transit time whereas high doses may decrease gut motility. Melatonin has been studied as a co-adjuvant treatment in several gastrointestinal diseases including irritable bowel syndrome (IBS), constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D), Crohn's disease, ulcerative colitis, and necrotizing enterocolitis. The purpose of this review is to provide information regarding the potential benefits of melatonin as a co-adjuvant treatment in gastrointestinal diseases, especially IBS, Crohn's disease, ulcerative colitis, and necrotizing enterocolitis.

Contents

Abbreviations: MT2, melatonin receptors; 5-HT, serotonin; CCK2, cholecystokinin B; IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS; EC, enterochromaffin cells; GIT, gastrointestinal; NOS, nitric oxide synthase; NF-κB, nuclear factor kappaB; iNOS, inducible NOS; IL, interleukins; TNF-α, tumor necrosis factor alpha; RNS, reactive nitrogen species; SOD, superoxide dismutase; GPx, glutathione peroxidase; GRd, glutathione reductase; CAT, catalase; GSH, glutathione; CRF, corticotropin releasing factor; 6-OHMs, 6-hydroxymelatonin sulphate; CD, Crohn's disease; UC, ulcerative colitis; CACC, colitis-associated colon carcinogenesis; Nrf2, Nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; NQO-1, quinone oxidoreductase; Keap1, Kelch-like ECH-associated protein 1; HIOMT, hydroxyindole-*O*-methyltransferase; HCY, homocysteine; LPO, lipid peroxidation; MPO, myeloperoxidase activity; MEL, melatonin; MDA, malondialdehyde; PGE_2, prostaglandin E2; MMP, matrix metallopeptidase; PTX-3, pentraxin-3.

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1. Introduction

Gastrointestinal melatonin is produced by enterochromaffin cells (EC) of the digestive mucosa where its concentrations may exceed those in the blood [1]. One of melatonin's characteristics is its high lipophilicity allowing it to diffuse into deeper layers through the mucosa and submucosa, to act on the muscularis mucosae or the myenteric plexus. The amount of gastrointestinal (GIT) melatonin is estimated to be at least 400 times greater than in the pineal gland [2]. Its secretion from the EC cells may be influenced by food intake [3], its actions in the GIT are mediated by membrane receptors including (MT2), serotonin (5-HT) receptors, and its capacity of activate sympathetic neurons through the brain-gut connection system, and its antioxidant actions [4–8]. Melatonin produces smooth muscle relaxation by stimulating 5-HT4 receptors, whereas it may also cause smooth muscle contraction by acting on 5-HT3 receptors. 5-HT also modulates visceral sensation [6,9]. Moreover, it was observed recently that melatonin may inhibit the activity of the serotonin transporter, which controls the reuptake of 5-HT by intestinal epithelial cells, and inhibits NK2 receptor-triggered 5-HT release by acting at a MT3 melatonin receptor located in the cells of the mucosal layer [10]. Low dose melatonin is also observed to accelerate intestinal transit time while high doses may decrease GIT motility by interacting with cholecystokinin B receptor (CCK2) and 5-HT3 receptors, present on the vagal afferent fibers inducing, via this means, vago-vagal inhibitory reflexes [3,4]. Those findings are supported by melatonin's modulatory role on gastric emptying due to its capacity to alleviate the inhibitory effect of the lipid related ileal break [11].

Other roles related to motility regulation by melatonin have been suggested. The indoleamine reduces the nitrergic component of the smooth muscle inhibitory junction potential through a direct inhibition of nitric oxide synthase (NOS) activity at enteric synapses. Melatonin may also block nicotinic channels, or interact with Ca^{2+}-activated K^+ channels generating an inhibitory effect through an apamin-sensitive reaction [12,13]. Melatonin also modulates acetylcholine-induced contractions of intestinal strips by an extracellular calcium dependent pathway [14]. In addition, melatonin may reverse lipopolysaccharide-induced motility disturbances, which involves a reduction in lipid peroxidation and an increase of mitogen-activated protein kinase activation, nuclear factor kappaB (NF-κB) activation, inducible NOS (iNOS) expression, and finally nitrite production [15]. Finally, melatonin regulates myoelectric activity by relaxing the bowel during phasic contractions [16].

Antinociceptive effects of melatonin have been reported, but the mechanisms are not well defined. A recent study suggested that these actions of melatonin were probably not directly at the level of the GIT since luzindole (a non-specific MT1 and MT2 receptor antagonist), or naltrexone (a non-specific opioid receptor antagonist), blocked the antinociceptive actions; this suggested viscero-motor response and modulation of lumbosacral spinal neuronal activity [17].

Gastrointestinal melatonin may also modulate the immune response by inhibiting macrophage activity through the reduction of NF-κB levels, COX-2 and iNOS activity; also, it modulates secretion elicited by prostaglandin E2 and regulates gene expression of proinflammatory cytokine levels including interleukins (IL-1), tumor necrosis factor alpha (TNF-α) and IFN-γ [18–21]. In addition, gastrointestinal melatonin has antioxidant effects [22,23], reduces prostaglandin degradation by prostaglandin reductase and limits gastric lesions and hydrochloric acid secretion [22–24]; it also antagonizes 5-HT actions, which are related to gastric ulcer formation [3].

Melatonin and its metabolites function as free radical scavengers and neutralize superoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and the hydroxyl radical (·OH) [25–29], a highly reactive oxygen species (ROS) [30], as well as nitric oxide (NO•) and the peroxynitrite anion ($ONOO^{\bullet -}$) [31,32], which are reactive nitrogen species (RNS) [33]. In addition, the indoleamine stimulates the cellular antioxidant defense system increasing mRNA levels and the activities of several important antioxidant enzymes including superoxide dismutase (SOD, which catalyzes the conversion of $O_2^{\bullet -}$ to H_2O_2) and glutathione peroxidase (GPx) and glutathione reductase (GRd) [34–36]. Catalase (CAT) is also stimulated by melatonin and causes direct breakdown of H_2O_2 to O_2 and H_2O [37,38]. Moreover, the indoleamine inhibits iNOS, an enzyme involved in NO• generation [39]. Melatonin also promotes the synthesis of another important antioxidant, glutathione (GSH) [40] and it synergizes with other classic antioxidants to reduce oxidative damage [41]. Finally, melatonin chelates transition metals thereby reducing the formation of the highly toxic ·OH which significantly limits the number of essential molecules that are oxidatively mutilated [42,43].

Herein, we summarize the protective actions of melatonin against several gastrointestinal diseases, including irritable bowel syndrome, Crohn's disease, ulcerative colitis, and necrotizing enterocolitis. To the authors' knowledge, this is the first review related to these subjects.

2. Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a common disorder (prevalence reported between 10 and 20%) characterized by recurrent abdominal pain or discomfort, in combination with disturbed bowel habits in the absence of identifiable organic cause [44]. IBS is 3-fold more prevalent in women than in men, and in the postmenopausal period this number increases to 6-fold. This may be a consequence of drop in melatonin secretion preceded by the rise in follicle-stimulating hormone (FSH) concentration in postmenopausal women [45,46]. Its pathophysiology has been associated with abnormal gastrointestinal motor functions, visceral hypersensitivity, psychosocial factors, autonomic dysfunction, mucosal inflammation, and intestinal microbiota imbalance [47,48]. Moreover, corticotropin releasing factor (CRF) is released during stress, and stimulates colonic motor activity via either central [49,50] or peripheral CRF receptors [51] resulting in colon hyperkinesis. Depending of the IBS predominant symptoms, there are two clinical types: constipation predominant IBS (IBS-C) and diarrhea-predominant IBS (IBS-D). IBS-D is associated with reduced 5-HT reuptake, while IBS-C is related with lack of 5-HT release [9].

Sleep disorders are also present in 26–55% of IBS patients [52] and are related to rapid eye movement (REM) sleep modifications [53]. In addition, the severity of IBS symptoms is observed to vary with the quality of the previous night's sleep [54]. It is suggested that sleep disorders are a result of an increase in the activity of the kynurenine pathway (a tryptophan metabolite) (Fig. 1) with a reduction in the serotonin/melatonin pathway [55–57]. This theory was considered since some studies reported reduced ratios of kynurenine/tryptophan in IBS patients [58]. One human study observed increased cortisol levels with a reduced melatonin/tryptophan ratio in IBS [58]. The mechanisms responsible for the sleep disorders in IBS patients remain unexplained.

6-Hydroxymelatonin sulphate (6-OHMs) is a hepatic metabolite of melatonin that is excreted in the urine. Urinary levels of 6-OHMs over a 24-h period correlate well with plasma melatonin levels [59]. Human studies reported increased levels of 6-OHMs in premenopausal and postmenopausal women afflicted with IBS-C or IBS-D [60]. The authors did not observed significant statistical differences between IBS-C