Editorial

Basic and Clinical Aspects of Melatonin in the Gastrointestinal Tract. New Advancements and Future Perspectives

This special issue of Current Pharmaceutical Design is intended to provide an update on the role of melatonin, originally discovered as the major secretory product of the pineal gland, in the treatment of upper and lower of the gastrointestinal (GI) tract disorders. It has become evident that melatonin is a widely-produced and ubiquitously-distributed molecule with multiple critical functions in all organs and in all organisms but its involvement in the function and integrity of GI-tract has only recently been reviewed [1]. With this volume we decided to provide an overview of the recent advances in experimental research and clinical studies on the efficacy of endogenously secreted melatonin and exogenously applied melatonin to prevent GI injury and the contribution of this hormone to the protection of major GI-tract organs including the esophagus, stomach, intestine, pancreas and liver.

In this issue, Reiter and colleagues [2] review the potential sources of melatonin in the human body with focus to the local production of this indoleamine in the enterohepatic system, which seems to be independent from pineal synthesis of this indole. They conclude that the high concentration of melatonin in the bile and enterohepatic circulation plays an important role in the mechanism of protection of the liver and biliary tract [2]. All these information's seem to be of great importance for the understanding of mechanism of hepatic and biliary protection from oxidative stress and damaging action of various chemicals. Reiter et al. [2] have also provided the recent advances on GI microbiome and transplantations of abdominal organs with relation to melatonin synthesis. This review is essential in our understanding of prophylactic and therapeutic efficacies of melatonin providing the reader with an insight into clinical usefulness of this indole [2].

Extensive research in the last decade has revealed that melatonin, in addition to being the major sleep hormone which exhibits a circadian rhythm with maximal release during the night hours, exerts protective functions in the upper and lower GI-tract and the hepatobiliary system [3]. High concentrations of melatonin in the GI epithelium reflecting the abundant activity of key enzymes of the melatonin biosynthetic pathway arylalkylamine-N-acetyltransferase (NAT) and hydroxy indole O-methyltransferase (HIOMT) and the presence of enterochromaffin cells (EC) which synthesize the melatonin precursor, serotonin, appear to be critical for the local activity of this indoleamine in the gut [2, 3]. The published data has documented the exceptionally high concentrations of melatonin in the hepatocytes, bile and enterohepatic circulation which can influence the function of the biliary tree and the liver independently of pineal-derived melatonin [2, 3].

The concentration of melatonin is decreased with age and the ratio of 5-hydroxy tryptamine (5-HT) to melatonin has been shown to be altered during aging along with a rise in the incidence of GI-tract disorders due to the aging-related decrease in the efficiency of natural protective factors which maintain the mucosal barrier [4]. In this issue, Bertrand and colleagues [5] have concentrated in their expert review on functions of melatonin as a product of serotonin metabolic pathway in physiology of the upper and the lower gut with a major attention addressed to pioneered author's method of detection of melatonin released from GI endothelium. The method of this measurement available so far include the determination of kinetics of this indoleamine and the ratio of 5-HT to melatonin in particular regions of GI-tract [5]. This local excessive release of melatonin could serve as explanatory for the protective effects of melatonin against the intestinal damage [5]. Interestingly, the impairment of aged GI-mucosa is restored by supplementation with melatonin thus accounting for some of the therapeutic efficacy of this hormone [4, 5]. Membrane bound melatonin receptors (MT_1 and MT_2) are present on some smooth muscles, neurons, and epithelial cells. Melatonin also acts as a potent free radical scavenger (a receptor - independent action) and provides GI cell protection against reactive oxygen metabolite-induced organ damage. These actions of this indole are best documented in the stomach, liver and biliary system [4-6].

The accumulated evidence indicates that melatonin is effective against the damage induced by experimental reflux esophagitis and prevents the incidence of GERD in humans [7, 8]. In this issue, Brzozowska *et al*. [9] has focused on various aspects of protective and ulcer healing activities of melatonin in the upper gut. This review was designed to summarize the involvement of melatonin, conventionally considered as a major hormone of the pineal gland, in the maintenance of gastric mucosal integrity, gastroprotection, ulcer healing and intestinal disorders [9]. Authors emphasized that the protective functions of melatonin in the esophagus and stomach are mediated by both receptor-mediated and receptor-independent actions of this indole affecting the release of protective mediators such as nitric oxide (NO), prostaglandins and vasodilatory neuropeptides such as calcitonin gene related peptide (CGRP) [7-10]. These Authors also provide the evidence that treatment with melatonin accelerates the healing of chronic gastric ulcers *via* a rise in gastric blood flow at the ulcer edge mediated by NO and PG, and the scavenging of reactive oxygen metabolites and the inhibition of gastric acid secretion by this indoleamine [7, 11].

Melatonin has also been implicated in the protection of lower GI-tract disorders, e.g., inflammatory bowel disease (IBD) in experimental models of ulcerative colitis and in Crohn's disease in human subjects [12]. This topic has been reviewed in this issue of the journal by Talero *et al*. [13] who focused on the pathophysiology of IBD in experimental animals and human subjects. According to the evidence accumulated in this review [13], IBD is a complex process mediated by cytokines, chemokines, adhesion molecules, cytoplasm nuclear receptors, among others. Recent data also support a participation of the endoplasmic reticulum (ER) stress, process of autophagy and mitochondrial dysfunctions in pathogenesis of IBD [13, 14]. Authors have concentrated on the intriguing mechanism of autophagy reflecting duality of effect of melatonin on this process, which could be either beneficial or detrimental [13]. In this issue, Talero *et al*. [13] presented recent advances in the understanding of the process of autophagy that could be linked with the development and progression of IBD and the modulation of the process of fatty liver graft preservation. Although autophagy is actually considered more a pro-survival than a pro-death pathway, these two features of this process are relevant in human diseases and there is therapeutic potential for both activators and inhibitors of autophagy [13]. Melatonin can act as a potential activator or sometimes as the inhibitor of this process demonstrating a duality in action thus affording the protection against development of chronic inflammation, the damage to intestinal mucosa, the pancreatic tissue and even colon cancer [13, 14]. The mechanism of this protective action of melatonin against colonic damage may involve the immunoregulatory reduction of T cell, modulation of macrophage activity, suppression of NFκB activity, inhibition of proinflammatory cytokines and cell adhesion molecules, attenuation of COX-2 and iNOS expression and the subsequent production of PGE_2 and NO, the reduction of matrix metalloproteinase (MMP) -2 and -9 activity, and modulation of apoptosis [13, 14].

Recently, there has been an increased interest in the roles of sleep, circadian rhythms and melatonin regulators of inflammation in the GI tract [3, 15]. Undoubtedly, the advances in our understanding of the molecular machinery of the circadian clock, and the discovery of clock genes in the GI tract are opening up new avenues of research for a role of sleep in IBD [15]. Of note, chronodisruption significantly worsens the development of colitis in animal models, and preliminary human studies have shown that patients with IBD are at increased risk for altered sleep patterns [3, 15]. Regarding other abdominal organs, the results of numerous experimental studies using animal models of liver damage have confirmed the hepatoprotective role of melatonin [6]. Preliminary trials in human subjects have revealed that the beneficial effect of

exogenous melatonin as well as that converted from its precursor, L-tryptophan, are effective in the prevention of ulcerative colitis, colon cancer, and the amelioration of non-alcoholic fatty liver disease (NAFLD) and the complications associated with partial resection of the liver in human subjects [16-19].

In this issue, Chojnacki *et al.* [20] has provided an updated review on the beneficial effect of melatonin on the liver and the potential usefulness of this indoleamine as the preventive and therapeutic strategy in the treatment of liver disorders such as non-alcoholic steatohepatitis (NASH) and the NAFLD. They emphasized that melatonin protects the hepatocytes from free radical damage by means of its direct free radical scavenging activity, a process which is receptor independent, and via receptor mediated action which involve the stimulation of antioxidant enzymes [20]. These authors pioneered and confirmed the effectiveness of melatonin and its biological precursor, L-tryptophan in the treatment of human NAFLD and during surgical procedure of partial liver resection in human subjects [20].

The pancreas regulates the process of digestion and intestinal absorption of nutrients from ingested food but this organ is susceptible to damage induced by the activation of pancreatic enzyme cascades that may lead to the development of acute pancreatitis which is considered as a critical risk for the patient [21]. In this issue, Jaworek *et al.* [22] review the role of endogenous melatonin produced both, the pineal gland and the GI-tract in the mechanism of pancreatic protection against caerulein- and taurocholate-induced pancreatic damage thus preventing the development of pancreatitis. These studies can be of potential interest for clinical gastroenterologists since there is no effective therapy against this disorder currently available. Jaworek *et al.* [22] provided an evidence that both melatonin and its precursor L-tryptophan have been shown to protect the isolated pancreatic cells *in vitro* and the pancreas *in vivo* against acute pancreatitis and to attenuate pancreatic tissue damage through an increase in the pancreatic microcirculation and the attenuation of the oxidative stress possibly mediated by an activation of pro-apoptotic signaling pathways . The mechanism of melatonin-induced pancreatic protection involves a direct scavenging effect against radical oxygen and nitrogen species, the activation of antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase), and stimulation of apoptosis and heat shock protein (mainly HSP70), while increasing pancreatic regeneration [22, 23]. In line with observations originally accumulated in studies on the gastric mucosa, the removal of the pineal gland markedly lowered the plasma levels of this indoleamine and exacerbated the incidence and severity of experimental pancreatitis [22]. Moreover, Jaworek *et al*. [22] documented in their review that the low plasma levels of melatonin are associated with an increased risk of severe acute pancreatitis which is consistent with the observation that the blockade of MT_2 receptors by luzindole aggravated pancreatitis. There is considerable agreement that endogenous melatonin produced in the GI system could contribute to the natural defense system thereby protecting the gastrointestinal mucosa and pancreatic tissue against acute aggressive factors such as ethanol, bile and pancreatic proteases.

Melatonin also influences many metabolic processes in the human body affecting e.g. insulin secretion both *in vivo* and *in vitro* [24, 25]. Lardone *et al*. [26] reported in this issue that the night-time melatonin levels are related to night-time insulin concentrations in patients with diabetes and this is linked with a single nucleotide polymorphism of the human melatonin receptors which is linked to an increased risk of type 2 diabetes development. This review is important since melatonin may yet play a role in diabetes and associated metabolic disturbances affecting insulin secretion but at the same time this anti-inflammatory indoleamine provides protection against reactive oxygen species [26]. These notion is based on the fact that pancreatic β-cells are particularly susceptible to oxidative stress because they possess only low anti-oxidative capacity [26].

Novel conformationally restricted analogues of agomelatine were recently synthesized and pharmacologically evaluated at MT_1 and MT_2 melatoninergic receptors [27]. Great interest has developed in the search for new molecules capable of mimicking or antagonizing the responses to melatonin. These novel compounds have been derived from the indole ring or its bioisosteres such as naphthalene [28]. The development of high-affinity conformational-locked compounds appear to be an interesting and rational approach to obtain a clear insight into the structural parameters involved in the binding to the receptor site, as well as information about the selectivity for both receptor subtypes. The non-selective naphthalene strict structural analogue of melatonin, agomelatine (Valdoxan), was the first found to control circadian rhythm disorders and is now marketed for the treatment of depression due to its antagonist activity at the 5-HT2C receptor subtype [28, 29]. This is of particular importance since the stress plays a predominant role in the development and progression of GI-tract disorders, for instance, irritable bowel syndrome (IBS) patients most frequently suffer from psychosomatic symptoms [30]. This promising new chemical design result opens new perspectives on the development of agonists of melatonin MT_1 and MT_2 receptors that could mimic some of the beneficial effects of melatonin's in clinical practice.

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