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Review article

Melatonin as a multifunctional anti-cancer molecule: Implications in gastric cancer

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ABSTRACT

Gastric cancer (GC) is a predominant malignancy with a high mortality rate affecting a large population worldwide. The etiology of GC is multifactorial spanning from various genetic determinants to different environmental causes. Current tretaments of GC are not efficient enough and require improvements to minimize the adverse effects. Melatonin, a naturally occurring compound with known potent inhibitory effects on cancer cells is one of the major candidates which can be recruited herein. Here we reviewed the articles conducted on the therapeutic effects of melatonin in gastric cancer in various models. The results are classified according to different aspects of cancer pathogenesis and the molecular mechanisms by which melatonin exerts its effects. Melatonin could be used to combat GC exploiting its effects on multiple aspects of its pathogenesis, including formation of cancer cells, tumor growth and angiogenesis, differentiation and metastasis as well as enhancing the anti-tumor immunity. Melatonin is a pleiotropic anti-cancer molecule that affects malignant cells via multiple mechanisms. It has been shown to benefit cancer patients indirectly by reducing side effects of current therapies which have been discussed in this review. This field of research is still underdeveloped and may serve as an interesting subject for further studies aiming at the molecular mechanisms of melatonin and novel treatments.

Introduction

Gastric cancer (GC) comprises a diverse array of malignant lesions with multiple underlying etiologies and predisposing factors. Although declining, GC is the fourth most common cancer worldwide, accounting for approximately 10% of invasive cancers that makes it the third leading cause of cancer mortalities [1]. The treatment course of GC is burdensome and routinely combines surgical, radiotherapeutic, and chemotherapeutic methods. Moreover, treatment outcomes and the survival rate is poor and calls for more effective and safer therapies. In search of new therapeutic compounds, melatonin has been an interesting candidate due to its high efficacy, multimodal mechanism of action, and minimal toxicity.

Melatonin (*N*-acetyl-5-methoxy tryptamine) is a naturally occurring derivative of the amino acid tryptophan. An evolutionarily conserved molecule dating as far back as to earliest cyanobacteria, it was inherited by eukaryotes, as they engulfed endosymbiont bacteria which later became mitochondria and chloroplasts, and has since then evolved from a mere antioxidant to an influential molecule assuming a putative role in numerous biological functions [2].

Melatonin was first isolated from bovine pineal gland [3] and was believed to be produced exclusively in the pineal gland locally acting as a hormone regulating the circadian and circannual cycles [4]. Further studies have discovered melatonin-related enzymes in various other tissues [5] and the expression of melatonin receptors in numerous cells. These facts, coupled with the discovery of melatonin's potent antioxidant and cell-modulating properties [6], promoted the status of melatonin from a hormone limited to the brain, to a ubiquitous molecule involved in the regulation of many biological functions uch as the circadian rhythm, seasonal breeding [7], the cardiovascular system [8], immune system [9,10], nervous system [11], energy balance [12] and aging [13]. In addition, recent studies have uncovered the involvement of melatonin in the protection against a spectra of diseases including but not limited to diabetes, obesity, gastrointestinal disorders such as

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IBD and IBS, immune disorders, cardiovascular diseases, neurodegenerative diseases [14–16], numerous cancers such as pancreatic cancer [17], liver cancer [18], breast cancer [19], prostate cancer [20], and oral cancer [21] and toxicant-induced disorders [22,23] via its pleiotropic effects on cell functions.

The gastrointestinal (GI) tract is a major source of melatonin production and its storage as it contains up to 400 times more melatonin that the pineal gland [24,25] with levels exceeding 100 times as much as the serum levels [26]. This indicates a definitive involvement of melatonin in the maintenance of gastrointestinal tract health and function. The melatonin content of GI originates from numerous sources such as: (a) endogenous production in the mitochondria of gastrointestinnal cells such as enterochromaffin cells [27], (b) production by microbial flora of the gut [28], (c) dietary intake of foods rich in melatonin [29] and (d) melatonin uptake from other tissues [30]. Physiologic functions of melatonin in GI include the inhibition of smooth muscle contraction, regulation of ions and water transport and secretion, mediating gastric acid neutralization by bicarbonate, controlling proliferation of cells, augmentation of the immune system [31], and modulation of the myenteric nervous system [32].

Melatonin takes on protective roles in the course of pathological conditions such as cancer. This is perhaps attested by observations linking abnormal circadian cycle disruption, as happens during night shift work, to increased incidence of colorectal cancers [33,34].

In the context of GI cancers, melatonin supplementation has proven to be beneficial in numerous studies [17,21,35]. These anti-cancer effects of melatonin are due to its multimodal mechanism of action in the cells. Melatonin possess exceptional direct and indirect antioxidant activity which in turn limits oxidative DNA damage. This way it reduces carcinogenesis and antagonizes the pro-angiogenic effects of nitric oxide (NO). Interestingly, the antioxidant effect of melatonin seems to be selective i.e. melatonin may paradoxically demonstrate pro-oxidant activity in cancer cells depending on their state of NF-κB activation [36,37] leading to their apoptosis [38]. Additionally, melatonin can block growth factor signaling in cancer cells and arrest cell cycle causing decreased proliferation. It also reduces metastases via modulation of intercellular interactions and disrupts cytoskeletal structures leading to cell death. Moreover, the enhancement of the immune system by melatonin augments its anti-cancer effects [39].

Methodology.

Databases including PubMed, Scopus, Reaxys and Web of Science were searched using the keywords “gastric cancer” and “melatonin” to find studies published by May 2017 according to PRISMA guidelines. Full length articles related to animal and human studies were retrieved. A total number of 113 records were obtained, and after screening the articles based on the inclusion/exclusion criteria, 10 studies were found relevant that constituted the main structure of the present review. The extracted data from 10 articles were included and summarized in Table 1.

Melatonin as a multifunctional molecule.

Melatonin functions through a diverse network of biochemical and signaling pathways. These signaling pathways are triggered both by receptor-mediated actions and direct interactions with various molecules ranging from free radicals to proteins. Receptors of melatonin include trans-membrane and nuclear binding proteins. Membrane receptors include MT1 and MT2, both belonging to G-protein coupled receptors (GPCR) coupled with G_i proteins which reduce cAMP and subsequently PKA and CREB activity. Activation of MT1 receptors signals G_i proteins and increase cytoplasmic calcium by G_{q11} activation. MT2 receptors activation reduces cGMP formation and activates PKC. Both MT receptors are connected to PLC-dependent pathways. Activation of PKC and PLC triggers MAPK/MEK/ERK pathway and additionally, PI_3K/AKT signaling can be also involved. In the nucleus, melatonin binds to RZR/ROR orphan receptors subtypes α, β, and γ. RORα binding can upregulate HIF-1α expression which is invloved in the response to hypoxia and oxidative stress [40]. A number of cytoplasmic proteins have been found to interact with melatonin. Notably, enzyme quinone oxidoreductase 2, initially considered as “MT3” receptor, mediates some of the antioxidant effects of melatonin [41]. Other proteins such as calmodulin, calreticulin, and tubulin could also interact with melatonin. These receptor-mediated activities could be implicated in the antineoplastic effects of melatonin in various cancers [41]. Recently, a study on 30 patients suffering from gastric adenocarcinoma revealed higher expression of MT2 receptor in the patients compared to the healthy subjects. This finding may suggest a compensatory upregulation of MT2 receptor aiming at potentiationg the benefits of melatonin [42].

The antioxidant actions of melatonin are carried out by several mechanisms. Melatonin decreases the oxidative stress in the cell by (a) direct radical scavenging activity (b), upregulating antioxidant and inhibiting pro-oxidant enzymes, (c) protection of mitochondria and decreasing free radical formation, and (d) chelation of Fe^{2+}/Fe^{3+} ions participating in radical formation by Fenton reaction (43, 44).

The principal understanding about melatonin alongside the observations suggesting its beneficial effects in cancer therapy have prompted researchers to evaluate the outcomes of treatment with melatonin in GC. In this paper, we aimed to review the studies conducted on the effects of melatonin on GC with a special focus on the molecular mechanisms involved. It is hoped that the gathered information could aid in increasing the knowledge regarding gastric tumors and melatonin's modes of action in the treatment of GC and to encourage the scientific community to devise further studies with the intention of finding safer and more efficacious cancer therapeutics as well as to better identify melatonin's anti-cancer mechanisms.

Melatonin and gastric carcinogenesis.

Carcinogenesis denotes the process by which various carcinogenic stimuli transform normal cells into cancerous cells leading to tumor formation. The primary determinant of carcinogenesis is the DNA damage and mutations which bring about the activation of oncogenes and/or deactivation of tumor suppressor genes ultimately giving rise to exaggerated cell proliferation. Gastric cells can be exposed to a variety of carcinogens such as nitroso compounds, reactive oxygen and nitrogen species and other mutagenic compounds [45]. *Helicobacter pylori* is one of the leading causes of gastric carcinogenesis induces its carcinogenic effects via increased ROS and RNS formation, local inflammation and ulceration, and other pathogenic factors [46]. Relation of the aforementioned factors to gastric carcinogenesis have been confirmed by a copious number of studies, which have also shown that consumption of antioxidant-rich foods and eradication of *H. pylori* infections compensate these injurious factors [47]. Melatonin has already been confirmed to attenuate gastric ulcers in various conditions [48] and to promote gastric ulcer healing in patients suffering from *H. pylori* infections [49]. These protective effects engage numerous mechanisms such as increasing blood flow, scavenging free radicals, inhibiting matrix metalloproteinases (MMP)-3 and −9 and reducing inflammation [50–52]. Furthermore, *H. pylori* infections have been shown to increase the susceptibility of gastric cells to carcinogens such as nitrosamines and heterocyclic amines. When compared to normal cells (cells without *H. pylori*), a higher DNA damage was observed in *H. Pylori* infected cells, which was attenuated by melatonin and other antioxidants [53,54]. Similarly, amoxicillin was observed to induce DNA damage via oxidative stress, which is augmented in *H. pylori* infected cells. The extent of this damage was also decreased by melatonin possibly via its antioxidant action [55].

Melatonin and gastric tumor growth.

Rampant proliferation of tumor cells is a characteristics feature of all cancers. The primary goal of cancer therapy is to reduce the unstrained growth and dissemination of tumors. In previous studies on GC cells, melatonin has proven to be effective in arresting tumor cell growth.

A study on a number of human tumors including GC, melatonin displayed cytotoxic activity on DNA synthesis and gastric cancers were