Melatonin for Endometriosis

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Melatonin may offer an excellent opportunity to restore normal physiological function of the affected tissues. By alleviating oxidative damage in the placenta, melatonin favors nutrient transfer and improves vascular dynamics at the uterine–placental interface.

Melatonin Endometriosis placenta

1. Introduction

Endometriosis (EMS) is a chronic inflammatory and estrogen-dependent disorder in which the ectopic endometrium grows outside the uterine locations such as in the ovary or other pelvic tissue and in peritoneal surface; in most cases, this seems to arise by retrograde menstruation [1]. Beyond the classical pelvic pain, EMS is associated with poor quality of life, reduced work productivity, and with a number of clinical repercussions such as affective disorders, metabolic dysfunctions, anxiety, inflammation, cardiovascular diseases, and increased cancer risks [2]. The origin of EMS appears to be related to genetic and environmental factors, but its causality requires additional evidence. There are still considerations that an endocrine-disrupting chemical, refluxed tissue, presence of Mullerian rests, bone marrow-derived stem cells, and hematogenous and lymphatic dissemination may be involved in the development of EMS [3]. Numerous molecular defects are described in eutopic endometrium of women with EMS, such as oncogenic pathways, high production of estrogen and its receptor ERβ, high levels of cytokines, prostaglandins, and metalloproteinases (MMPs) [4]. Some agents (e.g., gonadotropin-releasing hormone antagonist, cyclooxygenase inhibitors) associated with suppression of ovulatory menses and estrogen production, and surgical removals of lesions are used to control the pelvic pain [4]; however, the pathology of this complex disease remains an unsolved issue.

2. The Benefits of Melatonin in the Treatment of Endometriosis

Circadian disruption is associated with lower levels of melatonin and a higher risk of EMS [5]; the melatonergic pathway is thought to be suppressed in EMS. Conversely, endometrial biopsies of women with endometriomas (n = 20) or peritoneal lesions (n = 11) showed variations in the expression of melatonin receptors (MR1A and MR1B) according to the site of the ectopic tissue [6]. Pinealectomy, in a rat model of EMS, caused an augment in spherical explant volume accompanied by higher lipoperoxidation and lower antioxidant activities (e.g., SOD and CAT); melatonin efficiently reversed these EMS-related parameters [7]. Melatonin has been proven to have greater effectiveness than letrozole, an aromatase inhibitor, during the treatment of EMS [8]; these effects are mostly

attributed to a reduction in endometriotic foci and histopatologic scores associated with increased levels of SOD and CAT. **Figure 1** depicts the molecular mechanisms by which melatonin hampers EMS progression.

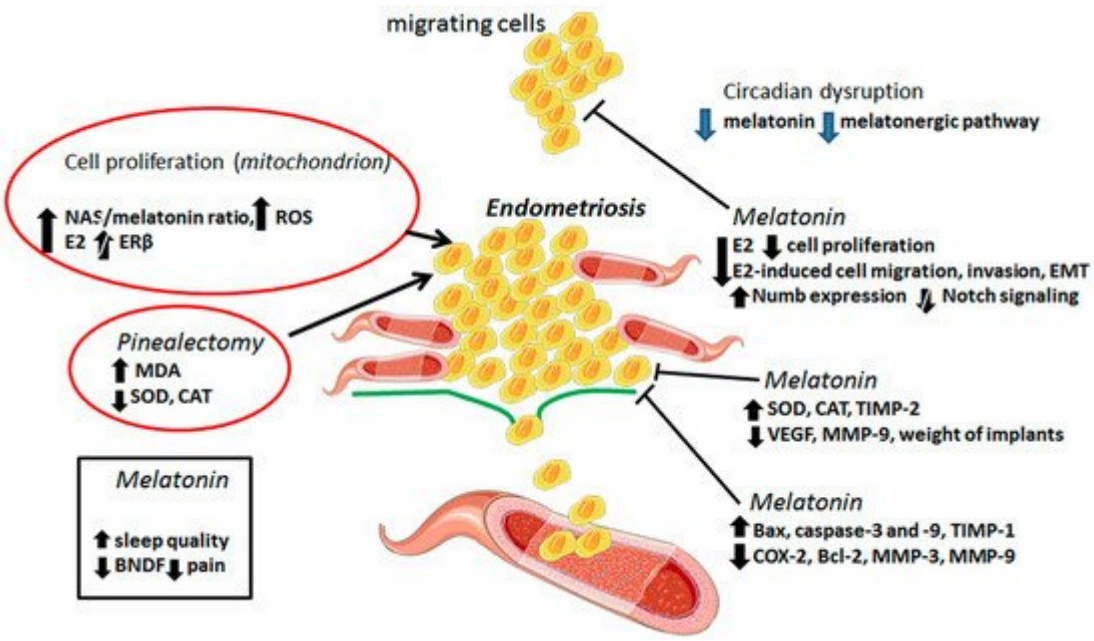

Figure 1. This figure illustrates possible mechanisms by which melatonin influences endometriosis (EMS). It is well-accepted that elevations in mitochondrial NAS/melatonin ratio, E2 levels, and ROS formation are associated with EMS development; other conditions like pinealectomy and circadian clock disruption are also reported to suppress melatonin which may possibly enhance the risk of EMS. Through a number of mechanisms, melatonin is documented to control growth and invasion of endometriotic cells; these include regulation in matrix remodeling, suppression of the epithelial to mesenchymal transition (EMT), induction of apoptosis, reduction of angiogenesis, and enhancement in antioxidant activity. Furthermore, melatonin promotes a reduction in the size of implants while improving sleep quality and alleviating pain or discomfort in EMS patients. NAS: N-acetylserotonin, ROS: reactive oxygen species, E2: 17β-estradiol, ERβ: estrogen receptor subunit β, MDA: malondialdehyde, SOD: superoxide dismutase, CAT: catalase, VEGF: vascular endothelial growth factor, TIMP: metallopeptidase inhibitor, MMP: matrix metalloproteinase, Bax: BCL2 associated X, apoptosis regulator, Bcl-2: B-cell lymphoma protein 2, antiapoptotic protein, COX-2: cyclooxygenase.

To investigate melatonin's action on endometriotic cells collected from women with EMS, a model of severe combined immunodeficient (SCID) mice were administered subcutaneously with endometriotic cells. After EMS induction, SCID animals received 20 mg/kg/day of melatonin for four weeks; implantation rates were increased after melatonin administration and the levels of malondialdehyde (MDA) were significantly reduced in the presence of E2 without changing SOD levels [9]. The same group showed that melatonin, especially at higher doses, is effective in promoting the regression of endometriotic lesions in oophorectomized rats [10]. Rats that were experimentally induced for EMS and received daily doses of melatonin had a prominent reduction of endometrial explants in addition to a decrease in COX-2 and MDA levels and enhanced activities of SOD and CAT [11]. Furthermore, when melatonin (10 mg/kg/day) was intraperitoneally injected into endometriotic cell-implanted rats, the weight of implants and related histologic scores were profoundly reduced. In addition, activities of SOD and

TIMP-2 were higher after melatonin treatment in contrast to reductions in VEGF and MMP-9 levels in implanted tissues [12].

EMS is difficult to analyze during its early phase in humans. The activity of MMPs in the pathogenesis of EMS is believed to be one of the central players in the formation of endometriotic lesions [13]. To verify the involvement of melatonin in the early development of EMS, ovariectomized mice were induced with endometriotic samples of patients and implanted with E2 pellets [14]. After developing EMS, the animals were given melatonin at doses of 48 mg/kg/day for 10–20 days; notably, melatonin promoted apoptosis in endometriotic region via Bax and caspase-9 activation along with reduction in Bcl-2 expression. Melatonin also suppressed early induction of MMP-3 through regulation of c-Fos and TIMP-3 and attenuated EMS through caspase-3-mediated signaling. In an earlier study, Paul et al. [15] had reported that melatonin prevented lipid peroxidation and protein oxidation while downregulating MMP-9 activity and expression in peritoneal EMS in mice; the reduced activity of MMP-9 was negatively correlated with TIMP-1 expression, thereby indicating MMP-9/TIMP-1 ratio as a novel marker for EMS progression.

Ectopic endometriotic tissue often presents with higher mitochondria-related ERβ, which is linked to increased bioenergetics associated with ROS production and enhanced SOD2 levels [16][17]. Increased production of N-acetylserotonin (NAS), at the expense of melatonin, seems to drive cell proliferation in EMS; the NAS/melatonin ratio may further result in elevation of estrogen and mitochondria ERβ. Data arrays of the pathoetiology of EMS have determined an increase in the mitochondria N-acetylserotonin (NAS)/melatonin ratio and a decrease in the levels of vitamin A and its retinoic acid derivatives as a possible molecular link to EMS development in women [18].

In a more recent investigation of endometriotic epithelial cells, Qi et al. [19] reported that the expression of Notch1, Slug, Snail, and N-cadherin is increased whereas expression of E-cadherin and Numb is reduced in the eutopic endometrium of patients; melatonin, at doses of 1 mM, significantly inhibited E2-induced cell proliferation and attenuated migration and invasion via upregulation of Numb and low activity of Notch in these patient-derived cultured cells. The efficacy of melatonin in EMS has also been documented in a phase II double-blind clinical study; in addition to improving the sleep quality, melatonin regulated the secretion of brain-derived neurotrophic factor (BDNF) while reducing daily pain, dysuria, and dysmenorrhea by 40% [20].

It has been consistently demonstrated that endometrial immune cells play a role in the pathophysiology of EMS and in related morbidities of pelvic pain and infertility; notably, pro-inflammatory M1 macrophages are higher than the anti-inflammatory M2 phenotype, and NK cells showed abnormal function in the endometrial tissue [21]. Since the escape of endometrial tissue involves proliferation, migration, adhesion, as well as angiogenesis, melatonin is suggested to have a contributory role in the control of ectopic immune cells. Yang et al. [22] summarized the pleiotropic role of melatonin in a wide variety of gynecological disorders affecting women at reproductive age. New clinical trials mapping the melatonin levels in patients with early symptoms of EMS are urgently needed.

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