

DOI: 10.16781/j.CN31-2187/R.20230480

• 专题报道 •

褪黑素对子宫内膜异位症病灶抑制作用的研究进展

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[摘要] 子宫内膜异位症是指子宫内膜腺体及间质在宫腔外的部位种植或生长, 其病理机制包括免疫炎症改变、氧化应激、上皮-间质转化及新生血管生成等。子宫内膜异位症好发于育龄期女性, 严重影响患者的生殖健康和生活质量, 目前主要通过手术及长期药物管理进行治疗。褪黑素是一种内源性吲哚胺类激素, 通过作用于不同的信号转导通路发挥抗氧化、抗炎、调节免疫功能和促进细胞凋亡等多种生理功能, 在癌症、心血管疾病、神经系统疾病等疾病的治疗中备受关注。近年来研究发现褪黑素可通过抑制雌激素合成、拮抗血管生成等作用抑制子宫内膜异位症的发展, 并能有效缓解盆腔疼痛。本文就褪黑素在子宫内膜异位症中作用的研究进展进行综述, 以期对子宫内膜异位症的药物治疗提供新的思路。

[关键词] 子宫内膜异位症; 褪黑素; 氧化应激; 血管生成; 雌激素

[引用本文] 寿鹤君, 段华. 褪黑素对子宫内膜异位症病灶抑制作用的研究进展[J]. 海军军医大学学报, 2024, 45(9): 1083-1088. DOI: 10.16781/j.CN31-2187/R.20230480.

Inhibitory effect of melatonin on endometriosis: research progress

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[Abstract] Endometriosis (EM) refers to the implantation or growth of endometrial glands and stroma outside the uterus. The pathological mechanism of EM includes immunoinflammatory changes, oxidative stress, epithelial-stromal transition and neovascularization. EM tends to occur in women of reproductive age and seriously affects the reproductive health and quality of life of patients. At present, it is mainly treated through surgery and long-term drug management. Melatonin is an endogenous indoleamine hormone, which has various physiological functions such as antioxidant, anti-inflammatory, immune regulation and apoptosis promotion through different signaling pathways. It has attracted much attention in the treatment of cancer, cardiovascular diseases and nervous system diseases. Recent studies have found that melatonin can also inhibit the development of EM by inhibiting estrogen synthesis and antagonizing angiogenesis, and can effectively relieve pelvic pain. This article reviews the research progress on melatonin in EM in order to provide new ideas for drug therapy of EM.

[Key words] endometriosis; melatonin; oxidative stress; angiogenesis; estrogen

[Citation] SHOU H, DUAN H. Inhibitory effect of melatonin on endometriosis: research progress[J]. Acad J Naval Med Univ, 2024, 45(9): 1083-1088. DOI: 10.16781/j.CN31-2187/R.20230480.

子宫内膜异位症 (endometriosis, EM) 是一种雌激素依赖性的良性侵袭性疾病, 主要临床表现为痛经、性交痛、慢性疼痛和不孕, 严重影响患者的身心健康。EM 在育龄期女性中的发病率约为 10%~15%, 且呈上升趋势, 目前认为 EM 的发生发展与氧化应激、免疫炎症、孕激素抵抗、上皮-间质转化 (epithelial-mesenchymal transition,

EMT)、血管新生、细胞的异常增殖和凋亡等多种因素密切相关^[1-2]。褪黑素 (melatonin) 是一种主要由松果体产生的激素, 褪黑素通过与其受体结合激活不同的信号转导通路, 发挥多种病理生理功能, 如抑制氧化应激、炎症反应等^[3]。褪黑素受体遍布全身, 在正常子宫内膜和子宫内膜异位灶均有分布, 已有研究表明褪黑素可通过抑制雌激素合

[收稿日期] 2023-08-25

[接受日期] 2024-01-17

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成、拮抗血管生成等作用抑制EM的发展,并能有效缓解盆腔疼痛^[4]。褪黑素的这些特性吸引国内外学者对其在EM治疗中的作用进行了大量基础与临床相关研究。本文对褪黑素在EM发展中的作用机制及潜在治疗作用相关研究进展进行综述。

1 褪黑素的生物学作用

褪黑素是一种内源性激素,化学式为 *N*-乙酰基-5-甲氧基色胺,在人体中可由松果体及多种松果体外器官合成。褪黑素的合成原料为色氨酸,合成过程受光照作用的调节,色氨酸经羟化作用后生成5-羟色氨酸,而后脱羧为5-羟色胺,再经5-羟色胺-*N*-乙酰基转移酶和羟吲哚-*O*-甲基转移酶的作用最终生成褪黑素^[5]。褪黑素生成后并不储存,而是会迅速释放至血液及脑脊液,并与相应的受体结合发挥作用。褪黑素还具有两亲性,可以穿过细胞、细胞器、细胞核膜,通过非受体介导作用直接与细胞内分子相互作用^[6]。

褪黑素受体主要包括位于细胞膜上的属于G蛋白偶联受体的褪黑素受体1(melatonin receptor 1, MT1)和褪黑素受体2(melatonin receptor 2, MT2),以及位于细胞质中的褪黑素受体3(melatonin receptor 3, MT3)。MT1和MT2均可在子宫内膜异位灶中表达,且其表达水平明显高于正常子宫内膜^[4]。MT1还参与子宫内膜基质细胞的增殖和凋亡,这可能与子宫内膜功能障碍及不孕症相关^[7]。MT3是一种还原酶,可以中和氧自由基,保护细胞免受氧化应激^[8]。褪黑素还可与细胞核上孤儿核激素受体家族的视黄酸Z受体/视黄酸相关孤儿核受体结合,参与免疫调节及应激反应^[9]。此外,褪黑素可与蛋白质直接相互作用,如参与调节泛素-蛋白酶体系统;褪黑素也可与钙调蛋白直接相互作用,抑制钙调蛋白依赖性蛋白激酶II的活性和自磷酸化^[10]。在EM模型中,有研究发现褪黑素可渗透异位子宫内膜细胞的线粒体膜,引起线粒体功能障碍,并通过影响氧化磷酸化系统,减少部分异位子宫内膜细胞ATP的产生,从而抑制其迁移,这提示褪黑素有潜力成为EM的新型治疗药物^[11]。

2 褪黑素抑制EM进展的作用机制

动物实验表明,在诱导大鼠形成EM后给予褪黑素20 mg·kg⁻¹·d⁻¹腹腔注射2周,异位子宫内

膜变小、组织病理学评分增加,表明褪黑素可使大鼠EM病变消退,并改善其组织病理学评分^[12]。目前,EM的发病机制尚未完全明确,除了经血逆流、子宫内膜干细胞种植、米勒管遗迹异常和体腔上皮化生这四大理论,由基因和表观遗传学改变导致的血管新生、EMT、孕激素抵抗、细胞的异常增殖和凋亡及炎症等多种因素也与EM密切相关^[2]。2.1 褪黑素降低氧化应激水平抑制EM进展 EM发病机制复杂,越来越多的证据表明氧化应激在其发病过程中具有重要作用。氧化应激是指体内氧化剂与抗氧化防御之间的不平衡,当体内活性氧(reactive oxygen species, ROS)含量过多时则会触发氧化应激反应,诱发细胞损伤^[13]。在EM中,ROS含量增加可上调转录因子NF-κB的表达,进而触发TNF、细胞间黏附分子1等细胞因子的表达,最终通过巨噬细胞诱导子宫内膜碎片黏附、增殖和新生血管形成,促进疾病进程^[14]。

褪黑素是一种自由基清除剂,多项体内研究表明,褪黑素可下调EM异位内膜病变中环氧化酶2和丙二醛等促氧化剂水平,并上调超氧化物歧化酶和过氧化氢酶等抗氧化剂水平,且该作用在给予较高剂量褪黑素时更明显^[15-17]。在切除小鼠的松果体后,抗氧化剂水平明显降低,此时补充外源性褪黑素治疗4周,也可观察到丙二醛水平降低、超氧化物歧化酶水平上升^[15]。ROS可激活基质金属蛋白酶(matrix metalloproteinase, MMP)家族,如MMP-9、MMP-2等,其参与EM中的组织重塑,使病变组织更具侵袭性^[18]。有研究表明,MMP-3参与早期EM发展,在EM大鼠模型中使用褪黑素治疗,MMP-3活性较对照组明显下降,且褪黑素组异位子宫内膜凋亡细胞数量增加,这与其抗凋亡蛋白Bcl-2表达降低、促凋亡蛋白Bax表达增强相关,表明褪黑素可通过抑制MMP-3活性、促进异位内膜细胞凋亡抑制EM进展^[19]。

褪黑素还可通过抑制氧化应激、炎症反应减轻EM患者痛经症状,改善生育结局。EM相关疼痛包含痛经、慢性盆腔痛、性交痛、周期性和非周期性下腹痛,疼痛程度轻重不一,较重者甚至会出现中枢致敏的伤害性反应,严重影响患者的生活质量^[20]。EM疼痛的发病机制复杂,与前列腺素过度产生、炎症介质释放、外周及中枢神经敏感密切相关^[21],其中脑源性神经营养因子(brain-derived

neurotrophic factor, BDNF) 在伤害性神经疼痛中起重要作用^[22]。研究表明,褪黑素可降低EM中BDNF的水平,且其可通过调节线粒体凋亡途径有效保护神经,从而改善慢性盆腔痛及痛经症状^[23-24]。除严重的痛经外,约35%~50%的EM患者合并不孕症,因此,如何促进生育也是EM治疗中亟待解决的问题^[25]。研究表明,卵母细胞发育能力显著依赖其与相邻颗粒细胞的通讯水平,该过程由颗粒细胞延伸出的跨带突起结构(transzonal projection, TZP)介导,而褪黑素补充治疗可能通过降低ROS水平抑制卵母细胞的损伤和凋亡,防止TZP回缩,修复卵母细胞和颗粒细胞之间的通讯失调^[26]。此外,褪黑素还可保护滋养层细胞免受炎症和自噬的侵袭,在妊娠早期重塑子宫螺旋动脉,降低先兆子痫及胎儿生长受限的发生率,改善妊娠结局^[27]。

2.2 褪黑素改善EM病灶孕激素抵抗、抑制雌激素合成 EM发病与孕激素抵抗、雌激素依赖密切相关。EM病灶局部呈高雌激素水平,可促进异位内膜细胞的增殖及炎症反应,这可能与芳香化酶、17 β -羟基甾体脱氢酶1(17 β -hydroxysteroid dehydrogenase 1, HSD17 β 1)等雌激素合成酶水平升高有关,因此,阻断雌激素合成是EM的治疗核心^[28]。孕激素可下调雌激素受体水平,并通过降低芳香化酶、HSD17 β 1水平抑制局部雌二醇的产生,但EM中孕激素受体(progesterone receptor, PR)转录、翻译和功能异常,这使孕激素对雌激素的对抗作用减弱,无法抑制异位内膜的发展^[29]。

临床研究表明,每日服用褪黑素连续4个月可有效降低促黄体生成素、雌二醇水平,夜间给予褪黑素可使体内卵泡刺激素水平下降,从而降低雌激素水平^[30]。在对乳腺癌的研究中,褪黑素与MT1结合后可通过抑制细胞生长功能来降低环腺苷酸水平,并通过降低芳香化酶的活性抑制雌激素的生成^[31]。褪黑素还可通过MAPK途径抑制排卵前卵泡中雌二醇的合成^[3]。此外,在对人颗粒细胞的体外研究中,褪黑素通过增强孕激素受体的表达、激活PI3K/Akt信号通路,上调孕激素合成关键酶类固醇激素合成急性调节蛋白(steroidogenic acute regulatory protein, StAR)的表达,促进黄体酮的合成^[32]。以上研究均表明褪黑素可抑制雌激素的产生并刺激孕激素的生成,这为其改善孕激素抵

抗、抑制异位子宫内膜生长提供了理论依据。

2.3 褪黑素抑制异位子宫内膜细胞EMT EMT指上皮细胞转化为间充质细胞的过程,其可增加细胞迁移和侵袭的能力,对EM的形成和发展至关重要。在EM发生和发展机制的相关研究中发现, lncRNA MALAT1在异位子宫内膜组织中表达水平明显升高,其可通过NF- κ B、ERK/MAPK等多种途径促进EMT发生、发展^[33-34]; miRNA-200可通过抑制上皮型钙黏蛋白(E-cadherin)的降低抑制EMT的发展^[35];其他信号通路,如NF- κ B、Wnt、Notch等,也可通过降低E-cadherin和波形蛋白的表达水平促进EMT^[3]。有研究发现,雌二醇可通过上调MALAT1水平及下调miRNA-200水平促进EMT的发生^[36]。另一项研究在分别使用17 β -雌二醇和褪黑素处理上皮细胞后检测相关介质的表达,结果表明,褪黑素组Notch1蛋白表达水平显著降低,而Notch1抑制性调节剂Numb和E-cadherin表达水平显著升高。这表明褪黑素通过调节Numb/Notch1/Snail/E-cadherin等多种信号通路抑制EM患者内膜上皮细胞运动和EMT^[37]。

2.4 褪黑素拮抗异位子宫内膜的血管生成 血管生成是EM发展过程中的关键步骤,新生血管能为异位病变组织提供营养和氧气,从而促进疾病发展^[38]。EM患者腹腔冲洗液中血管内皮生长因子(vascular endothelial growth factor, VEGF)含量明显高于健康人群,活化的巨噬细胞是VEGF的主要来源^[39]。在EM动物模型中,抑制VEGF可抑制血管生成及异位内膜的生长^[40]。Yilmaz等^[15]将异位子宫内膜组织经腹腔植入20只大鼠后,将其随机分为两组,分别在腹腔内注射褪黑素及生理盐水,结果发现褪黑素组VEGF显著降低。一项体外实验发现,慢性缺氧环境可促进人脐静脉内皮细胞释放高浓度ROS及VEGF,而褪黑素以剂量依赖的方式通过下调缺氧诱导因子水平、清除自由基、降低VEGF水平限制血管内皮细胞的活力,抑制血管生成^[41]。

3 褪黑素对EM的潜在治疗作用

EM是一种需要长期管理的慢性疾病,现有的一线治疗药物主要包含孕激素类、复方口服避孕药、促性腺激素释放激素激动剂等,其主要通过抑制下丘脑-垂体-卵巢性腺轴来降低雌激素水平

或通过引起假性蜕膜化阻断月经,从而抑制EM发展或进展^[42]。褪黑素作为一种有效的自由基清除剂、EMT抑制剂及血管生成抑制剂,已被证实存在癌症、阿尔茨海默病、2型糖尿病、多发性硬化、炎症性肠病、骨质疏松症等多种疾病的治疗中发挥作用^[43-46]。

在褪黑素治疗EM相关的研究中,Güney等^[47]首次在EM大鼠模型中发现,腹腔注射褪黑素可引起EM异位内膜的消退和萎缩。一项Ⅱ期随机双盲临床对照研究纳入了40例重度痛经的EM患者,将其随机分为褪黑素组与安慰剂组,结果表明,每日口服褪黑素10 mg持续8周后,褪黑素组痛经评分降低38.01%,止痛药使用率降低80%,这为将褪黑素作为EM潜在治疗药物提供了有力支持^[24]。

目前研究表明,褪黑素在高剂量使用时也是相对安全的,一项纳入了79项临床研究的meta分析表明,在每天补充高剂量褪黑素 ≥ 10 mg时,2 114名受试者中有913名出现了不良反应,最常见的为乏力、头痛、发热和腹泻,但相较于安慰剂组严重不良事件并未增加^[48]。褪黑素有望成为EM治疗中一种安全且不良反应较小的药物,但目前仍缺乏足够的证据。

4 小 结

EM在育龄期女性中的患病率仍有升高趋势,寻求满意的药物治疗方案对于有效缓解患者症状、改善生育结局、提升生活质量至关重要。褪黑素是人体内天然存在的抗氧化活性物质,具有多种生理功能。随着体内、体外研究的广泛展开,人们发现褪黑素在EM的发生、发展中具有抗氧化、调节性激素、抑制异位子宫内膜细胞黏附与抑制血管增生等作用,这为褪黑素作为治疗EM的潜在药物提供了理论依据。然而,褪黑素在遏制EM发生、发展中的作用机制仍需进一步阐明,还需要开展多中心、大样本的临床研究进一步明确褪黑素对EM的治疗效果,从而将褪黑素更好地应用于EM的预防、治疗与长期管理策略中。

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[本文编辑] 孙 岩