·文献综述·

褪黑素调节血管生成在眼底疾病中的研究进展

杨凌齐[1,2,3],李鉴峰[1,2],吕 洋[1]

引用:杨凌齐,李鉴峰,吕洋. 褪黑素调节血管生成在眼底疾病中的研究进展. 国际眼科杂志, 2024,24(8):1223-1228.

基金项目:国家自然科学基金资助项目(No.82000926);甘肃省卫生健康行业科研项目(No.GSWSKY2022-05);中国人民解放军联勤保障部队第九四〇医院基金资助项目(No.2021yxky033,2023YXKY033);甘肃省中医药大学导师专项(No.2023YXKY011)

作者单位:[1](730050)中国甘肃省兰州市,中国人民解放军联勤保障部队第九四〇医院眼科中心;[2](730000)中国甘肃省兰州市,甘肃省中医药大学第一临床医学院;[3](730050)中国甘肃省兰州市,中国人民解放军联勤保障部队第九四〇医院基础医学实验室 甘肃省干细胞与基因药物重点实验室
作者简介:杨凌齐,在读硕士研究生,研究方向:眼底疾病。
通讯作者:吕洋,博士,副主任医师,副教授,硕士研究生导师,研究方向:眼底疾病、眼屈光. 15117203811@163.com
收稿日期:2023-11-29 修回日期:2024-06-20

摘要

血管生成是涉及生理和病理过程的关键步骤,而促/抗血管生成因子又参与血管生成的始终,褪黑素是人脑松果体的合成产物,作用于人体各个系统。文章简述了褪黑素广泛的生物学作用及生理功能,归纳了褪黑素在不同条件下调控促/抗血管生成因子(如VEGF/MMP)在眼底疾病(如年龄相关性黄斑变性、糖尿病视网膜病变及中心性浆液性脉络膜视网膜病变等)中参与血管生成;此外,还总结了褪黑素调控多种细胞因子、炎症因子及信号通路在眼底疾病中产生抗炎症、抗氧化、免疫反应等作用,从而得出了褪黑素在眼底血管疾病中的应用及潜在治疗,以期为治疗眼底疾病提供新的思路和治疗靶点。

关键词:年龄相关性黄斑变性;糖尿病视网膜病变;中心性浆液性脉络膜视网膜病变;褪黑素;血管生成
DOI:10.3980/j.issn.1672-5123.2024.8.08

Research progress of melatonin in regulating angiogenesis in fundus diseases

Yang Lingqi[1,2,3], Li Jianfeng[1,2], Lyu Yang[1]

Foundation items: National Natural Science Foundation of China (No.82000926); Gansu Province Health Commission Fund Project (No. GSWSKY2022-05); Scientific Foundation Program of the 940th Hospital of the Joint Logistic Support Force of the Chinese People's Liberation Army (No. 2021yxky033, 2023YXKY033); Tutor Foundation Project of Gansu University of Chinese Medicine (No.2023YXKY011)

[1]Ophthalmic Center, the 940th Hospital of Joint Service Support Forces of the Chinese People's Liberation Army, Lanzhou 730050, Gansu Province, China; [2]First School of Clinical Medical, Gansu University of Chinese Medicine, Lanzhou 730000, Gansu Province, China; [3]Basic Medical Laboratory, the 940th Hospital of Joint Service Support Forces of the Chinese People's Liberation Army; Laboratory of Stem Cell and Gene Medicine of Gansu Province, Lanzhou 730050, Gansu Province, China
Correspondence to: Lyu Yang. Ophthalmic Center, the 940th Hospital of Joint Service Support Forces of the Chinese People's Liberation Army, Lanzhou 730050, Gansu Province, China. 15117203811@163.com
Received:2023-11-29 Accepted:2024-06-20

Abstract

• Angiogenesis is a key step involving physiological and pathological processes, and pro/antiangiogenic factors are involved in angiogenesis throughout. Melatonin is a product synthesized by the pineal gland of the human brain and acts in various systems of the body. This article briefly describes the wide range of biological roles and physiological functions of melatonin, and summarizes that melatonin regulates pro-/anti-angiogenic factors (*e.g.*, vascular endothelial growth factor/matrix metalloproteinase) under different conditions and is involved in angiogenesis in fundus diseases (*e.g.*, age-related macular degeneration, diabetic retinopathy, and central serous choroioretinopathy); in addition, it also summarizes that melatonin regulates various cytokines, inflammatory factors and signaling pathways to produce anti-inflammatory, antioxidant and immune responses in fundus diseases, and thus obtaining the application and potential treatment of melatonin in fundus vascular diseases, with a view to providing new ideas and therapeutic targets for the treatment of fundus diseases.

• KEYWORDS: age-related macular degeneration; diabetic retinopathy; central serous chorioretinopathy; melatonin; angiogenesis

Citation: Yang LQ, Li JF, Lyu Y. Research progress of melatonin in regulating angiogenesis in fundus diseases. Guoji Yanke Zazhi(Int Eye Sci), 2024,24(8):1223-1228.

0 引言

近年来,褪黑素受到学者们的广泛关注,其生物学作用和生理功能参与多个系统及多种疾病[1-2]。目前,大部分疾病都归因于持续的血管生成,据统计,在眼底疾病中,有40多种与新生血管形成相关,疾病随着年龄、炎症、自身免疫等各种因素持续加重,最终导致中心视力丧失[3]。本文就褪黑素靶向各种因子参与调控血管生成及其在眼底疾病中的应用进行阐述,以期为褪黑素治疗眼底疾病提供新的方法和思路。

1 褪黑素生物学作用

褪黑素(melatonin,MT)是一种吲哚类激素环类小分子,化学名称为 N-乙酰基-5 甲氧基色胺(N-acetyl-5-methoxytryptamine),主要在松果体中合成,受下丘脑视交叉上核调节。它是一种调节脊椎动物睡眠和季节性行为的神经激素[4],作用极其广泛,参与调控血脂、血糖、血管、生殖和胎儿发育、免疫系统和心血管系统等多种生理功能[4-7]。其次,褪黑素也可在眼内合成,许多眼组织中分布 MT 受体,如视网膜光感受器、睫状体、晶状体、角膜等[8-9]。已证实在哺乳动物视网膜组织中,存在 MT1 和 MT2 两种受体,且被广泛激活,利用眼部结构介导眼内昼夜节律和各种生理功能,如抗氧化、抗炎、抗凋亡及血管生成等[1-2]。

2 褪黑素在血管生成中的作用

血管生成是生理功能和病理过程中不可或缺的一部分,在其生成过程中,维持信号转导的因子主要有血管内皮生长因子(vascular endothelial growth factor,VEGF)、成纤维生长因子(fibroblast growth factors,FGFs)、血管生成素-1(angiopoietin-1,Ang-1)、基质金属蛋白酶(matrix metalloproteinase,MMP)、缺氧诱导因子(hypoxia inducible factors,HIFs)等,以上多种因子参与胚胎发育、伤口修复及缺血组织再生等各种生理功能[10-12];然而,病理状态下的血管重塑是血管生成的另一种表现。当促血管生成因子和抗血管生成因子表达不平衡时,促使内皮祖细胞(endothelial progenitor cells,EPCs)向内皮细胞迁移、分化和增殖[13],并调控多种细胞,导致血管生成失调。例如在肿瘤组织中新生毛细血管的生成有助于肿瘤细胞转移和进展[14];在眼部组织中新生血管会导致中心视力丧失[3,15]。褪黑素是一种“聪明”的分子,根据不同的条件(生理或病理),褪黑素通过不同的机制刺激或抑制新生血管形成,从而呈现多种生物效应。在眼底疾病和肿瘤病变中,褪黑素可上调抗血管生成因子/下调促血管生成因子的表达,激活/抑制其受体,从而抑制血管生成[16-17]。

3 褪黑素促/抗血管生成

3.1 褪黑素调控 VEGF 参与血管生成 VEGF 是褪黑素研究最广泛的下游靶点,在哺乳动物体内,细胞膜存在褪黑素两种受体,即 MT1 受体、MT2 受体,它们属于 G 蛋白偶联受体超家族,褪黑素通过受体依赖性或非受体依赖性途径调节 VEGF 及其受体的表达,使其在不同条件下对血管生成产生不同的影响,但具体机制仍然在探索中[18]。在缺血缺氧条件下,血管内皮生长因子受体-2(VEGFR-2)在 VEGF 的刺激下可上调活性氧(reactive oxygen species,ROS)的表达,而在 ROS 过表达的前提下又可以提高 HIF-1α的稳定性,褪黑素可通过下调 HIF-1α/ROS/VEGF 抑制血管生成[19]。视网膜色素上皮(RPE)细胞表达的 VEGF 在视网膜病理生理中起双重作用,既可以保护视神经元细胞及脉络膜,维持视网膜健康,又可使视网膜脉络膜新生血管生成,加重视力损伤;而褪黑素可降低视网膜 VEGF 水平,防止眼部血管生成[20]。在人脐静脉内皮细胞(HUVEC)中,褪黑素在不降低 VEGFR-2 表达的前提下,以剂量依赖性的方式明显抑制 VEGFR-2 磷酸化;相反,在乳腺癌组织中,褪黑素可降低 VEGFR-2 的表达[21-22],抑制血管生成。同样,褪黑素通过降低 VEGF、基质金属蛋白酶 2(matrix metalloproteinases,MMP2)、MMP9 改善高血糖和 IL-1β 引起的眼部视网膜病变;同时,褪黑素还可以激活磷酸肌醇 3 激酶(PI3K)及核因子 E2 相关因子(Nrf2)相关信号通路,从而抑制糖尿病视网膜病变[23]。关于褪黑素调控 VEGF 对血管生成的影响见表 1。

3.2 褪黑素调控 MMP 参与血管生成 MMPs 通过作用于Ⅰ型和Ⅳ型胶原、层黏连蛋白、VE-钙黏蛋白在促进血管内皮细胞迁移及管腔形成中具有不可争议的地位。MMPs 的功能不仅仅是暴露特定的结合位点与细胞整合素结合促进血管生成(如细胞整合素 α5β1 通过结合 MMP2、MMP9 暴露位点,上调 MMP2、MMP9 的表达从而促进血管生成[24]),且能上调 IGF 结合蛋白、血管基底膜中的蛋白多糖、转化生长因子 B(TGF-B)结合蛋白等细胞因子的表达,共同促进血管生成。其中 MMP9 在血管生成中具有独特的作用,它能激活 IL-8,产生强大的促炎和促血管生成功能[25]。褪黑素通过抑制特定的 MMP 功能,从而起到血管生成抑制剂的作用。研究发现,在肾癌组织中加入小剂量的褪黑素能抑制肿瘤组织血管生成,进一步抑制瘤组织转移,这是因为褪黑素不仅抑制 NF-κB p65、NF-κB p52 与 MMP9 启动子的结合,还能抑制 Akt/MAPKs 信号下调 MMP9 的表达[26]。Yeh 等[27]发现褪黑素通过抑制 ERK1/2 信号下调 MMP-9 特异性共激活因子(cAMP 反应元件结合蛋白、EP300)的表达以及降低组蛋白乙酰化,逆转了佛波醇 12-十四酸酯 13-乙酸酯(12-O-tetradecanoylphorbol-13-acetate)的促血管生成和迁移作用。由此可见,褪黑素通过多种通路调控 MMP 影响血管生成。关于褪黑素调控 MMP 对血管生成的影响见表 1。

4 褪黑素在眼部疾病中的作用

4.1 褪黑素与年龄相关性黄斑变性 年龄相关性黄斑变性(age-related macular degeneration,ARMD)是一种与年龄相关的眼部疾病,可导致视力障碍、黄斑水肿、视网膜色素改变和视网膜血管新生[48]。预期寿命增加和人口老龄化导致 ARMD 的全球患病率稳步上升[49]。形成这种趋势的原因有两点:(1)与 RPE 细胞功能障碍有关;(2)目前对于 ARMD 的治疗仍然在探索中。光感受器外节(POS)持续更新对于光感受器存活及功能正常发挥不可或缺;而 RPE 在每日清除和吞噬已经耗尽的 POS 片段中发挥了关键作用[50]。然而,在年龄、氧化、炎症等各种因素的作用下,RPE 细胞变性死亡,导致 POS 代谢碎片及脂褐素大量累积,从而使 RPE 吞噬清除机制降低引起光感受器功能退化。此外,大量的脂褐素又会降低 RPE 内源性抗氧化防御、吞噬及溶酶体酶功能[51],从而诱发 ARMD。ARMD 患者 RPE 细胞损伤后,光感受器功能退化及数量减少,分泌褪黑素水平不断降低,其受体活性也随之减弱;MT1 和 MT2 受体位于这些光感受器中,褪黑素水平可直接影响视杆细胞和视锥细胞的功能[52-54]。重要的是褪黑素对 RPE 细胞具有抗氧化、抗凋亡及调节自噬作用。研究表明,褪黑素通过降低 Bax/Bcl-2 比值及下调细胞凋亡相关蛋白细胞色素 c 和半胱天冬酶 7 的表达,上调自噬相关蛋白 LC3-Ⅱ和 Beclin-1 的表达,从而能显著抑制过氧化氢(H_2O_2)诱导的 RPE 细胞损伤,增加了线粒体膜电位、自噬效应的同时降低了 RPE 细胞凋亡率[55]。在新生血管性 ARMD(nARMD)中,褪黑素不仅通过抑制 VEGFR2/c-Src/FAK 信号通路,且抑制 NF-κB 和 AP-1 的激活,从而抑制 VEGF 诱导的 EPCs 增殖、迁移和血管生成[16]。激光诱导的小鼠 nARMD 模型中,经过褪黑素处理过的视网膜

表 1 关于褪黑素通过调控 VEGF/MMP 对血管生成的研究

实验模型	褪黑素剂量	靶基因	实验结果	参考文献
道尔顿淋巴瘤细胞系及动物模型	1 mmol/L 或 5 mmol/L	VEGF,FGF	内皮细胞增殖、迁移能力下降,肿瘤体积减小	[28]
HepG2 细胞系	1 mmol/L	VEGF,HIF-1α	降低癌细胞的生存能力	[29]
大鼠下颌唾液腺(walker 256 癌肉瘤)	10 mg/kg	VEGF	VEGF 表达降低	[30]
RPE	$10^{-5}/10^{-7}/10^{-9}/10^{-11}$ mol/L	VEGF,HIF-1α	血管生成能力降低	[31]
HUVECs	1 mmol/L	VEGF,VEGFR-2	具有抗 VEGF 特性,逆转 VEGF 细胞效应	[21]
犬乳腺肿瘤 CF-41 和 CMTU229 细胞系	1 mmol/L	VEGF,IGF-1,IGF-2,TNF-RII	降低肿瘤细胞活力抑制血管生成	[32]
大鼠子宫内膜异位症模型	10 mg/kg	VEGF,MMP9,MDA,TIMP-2	调控 VEGF 及其下游信号导致子宫内膜异位症消退	[33]
雌性 Wistar 大鼠垂体前叶	1 mg/d	VEGF,MMP-9	下调 VEGF/MMP9 并抑制分泌颗粒释放	[34]
高血糖及 IL-1ß 诱导的人视网膜内皮细胞(REC)和 RPE	100 μmol/L	VEGF,ICAM-1,MMP-2,MMP-9	下调 VEGF,ICAM-1,MMP-2,MMP-9 抑制炎症及血管生成	[35]
口腔鳞状细胞癌	1 mmol/L	MMP-9	抑制肿瘤血管生成	[36]
胃腺癌 AGS 细胞系	不同浓度	MMP-9	抑制 MMP-9 活性是治疗以细胞外基质转换失调为特征疾病的靶点	[37]
乳腺癌 MCF-7 和 MDA-MB-231 细胞系	1 mmol/L	VEGF-A,VGEF-C,VEGFR2,MMP-9	抗血管生成且癌细胞的活力降低	[38]
胃癌(小鼠)	100 mg/kg,150 mg/kg	RZR/RORγ,HIF-1α,VEGF	褪黑素通过降低褪黑素核受体 RZR/RORγ、HIF-1α 和 VEGF 的表达而抑制肿瘤血管生成	[39]
卵巢癌(大鼠)	2 mg/kg	VEGF,VEGFR2,HIF-1α	给褪黑激素后,癌组织中的 VEGF、VEGFR2 和 HIF-1α 显著降低	[40]
胃内皮细胞	10 μmol/L	VEGF,MT1,MT2	外源性褪黑素上调线粒体膜 MT1 和 MT2 的表达,增加了体外血管生成	[41]
缺氧条件下的 HUVECs	10 μmol/L,1 mmol/L	HIF-1α/ROS/VEGF	褪黑素通过下调 HIF-1α/ROS/VEGF 抑制 HUVECs 的活力和血管生成	[19]
绵羊垂体内皮细胞	内源性褪黑激素	VEGF-A	褪黑激素诱导 VEGF-A 不同亚型表达,导致新生血管的改变	[42]
Balb/c 小鼠	60 mg/kg,25 mg/kg	MMP-3,ROS,Caspase-3	褪黑素通过下调 MAPK-ERK 通路并激活 MMP-3 结合位点达到保护胃黏膜的作用	[43]
雌性 Wistar 大鼠卵巢细胞	50 mg/kg	VEGF,VEGFR-1,VEGFR-2	外源性褪黑素治疗显著上调卵巢中 VEGF、VEGFR-1 的表达且降低退化的卵泡数量	[44]
人卵泡液颗粒细胞	内源性褪黑激素	VEGF,MT2,iNOS	褪黑素可上调颗粒细胞中 VEGF、MT2 的表达,下调 iNOS 的表达,可作为卵巢过度刺激综合征的预测指标	[45]
胶质母细胞瘤细胞系(U251 和 U87)	1 nmol/L,1 mmol/L	VEGF,MMP-2,HIF-1α	褪黑素抑制下游靶点 VEGF,MMP-2,HIF-1α 抑制肿瘤细胞转移	[46]
消炎痛引起的胃溃疡	20 μg/mm^2 40 μg/mm^2	VEGF,MMP-2,MMP-14,TIMP-2	上调 VEGF 导致血管生成和溃疡修复	[47]

注:TNF-RⅡ为肿瘤坏死因子 2 型,IGF-1 为胰岛素样生长因子 1,TIMP-2 为基质金属蛋白酶抑制因子 2,ICAM-1 为细胞间黏附分子 1,RZR/RORγ 为褪黑素核受体维甲酸 Z 受体/维甲酸相关孤核受体,Caspase-3 为天冬氨酸特异性半胱氨酸蛋白酶 3,iNOS 为诱导型一氧化氮合酶。

小胶质细胞高表达 M1 型标记物,如 iNOS、趋化因子-3(CCL-3)、CCL-5 和 TNF-α,低表达 M2 型标记物,如精氨酸酶 1(Arg-1)、缺氧诱导分化因子(hypoxia induced differentiation factor)、IL-10、YM-1 和 CD206,表明褪黑素通过抑制 nARMD 中 RhoA/ROCK 信号通路,将巨噬细胞/小胶质细胞从促血管生成的 M2 表型极化为抗血管生成的 M1 表型,从而减小 nARMD 病变区域,抑制血管渗漏,达到抑制血管增殖的能力[56]。以上研究表明褪黑素有望成为治疗 ARMD 的一种新选择。

4.2 褪黑素与糖尿病视网膜病变 糖尿病视网膜病变(diabetic retinopathy,DR)是全球范围内最常见的致盲原因之一。分为非增殖性糖尿病视网膜病变(NPDR)和增

殖性糖尿病视网膜病变(PDR)。氧化应激、炎症、内质网应激和自噬等诸多因素参与 DR 疾病发展,特别是抗氧化酶,如超氧化物歧化酶(SOD)、谷胱甘肽还原酶(GR)、谷胱甘肽过氧化物酶(glutathione peroxidase,GPx)和过氧化氢酶(CAT)在 DR 中活性明显降低[57-58]。体内长期高血糖可导致呼吸链功能障碍,复合物Ⅰ和Ⅲ丢失电子,导致 ROS 水平升高,线粒体 ATP 的产生也受到影响,从而诱导细胞色素 C 等促凋亡因子的释放[57]。褪黑素可上调糖尿病大鼠视网膜中的谷胱甘肽,并维持过氧化氢酶的活性,不仅能促进抗氧化酶的产生,还能抑制促氧化酶[髓过氧化物酶(MP)、嗜酸性粒细胞过氧化物酶(EPO)、一氧化氮合酶(NOS)和环氧合酶-2 等]的活性、清除自由基、减少氧化应激损伤[59]。褪黑素还可以减少线粒体呼吸链中的电子遗漏,并防止促凋亡因子从线粒体中释放出来。基于这些作用,褪黑素可以降低 DR 中的 Müller 细胞和星形胶质细胞突起肿胀,以及 NO 合成和血管渗漏[8,60]。此外,研究表明,口服褪黑素补充剂能明显降低硫代巴比妥酸反应物质(TBARS)和高级氧化蛋白产物(AOPP)的浓度,在 DR 中可以预防视网膜变性[61]。DR 引起的视网膜毛细血管缺血、闭塞,褪黑素通过抑制 NF-κB 信号活化从而减轻视网膜炎症和微血管障碍[62]。褪黑素在不同条件下调控自噬产生不同的结果,如在生理环境下诱导自噬,提高细胞存活率,在慢性氧化应激的条件下,褪黑素抑制自噬,降低细胞死亡率[63]。DR 晚期伴随着大量新生血管生成,各种因素如炎症和氧化应激可刺激 RPE 细胞释放大量的 VEGF,且巨噬细胞分泌 TNF-α 等促炎细胞因子也可诱导 RPE 细胞分泌 VEGF,视网膜中高浓度 VEGF 诱发的新生血管可导致血-视网膜屏障(BRB)破坏,引起血管渗漏并促进视网膜新生血管的生成。在这种情况下,褪黑素通过抑制 iNOS 减少 NO 产生,降低过氧亚硝酸盐引起的脂质过氧化及视网膜中 VEGF、NO 水平,在抑制视网膜新生血管的生成中发挥了重要作用[64]。

4.3 褪黑素与中心性浆液性脉络膜视网膜病变 中心性浆液性脉络膜视网膜病变(central serous chorioretinopathy,CSC)是一种视网膜疾病,因脉络膜血管渗漏导致视网膜下积液和神经感觉视网膜浆液脱离。CSC 患者的临床表现为中央暗区,视物变小、视力下降、暗瘤、微视、变形视、色差视、对比敏感度下降,影响患者的视觉质量[65]。临床中存在一些急性病例,可以自发消退,几乎没有后遗症,但慢性或复发性 CSC 伴有视网膜下积液的患者因光感受器损伤或 RPE 萎缩,导致永久性视力障碍[66]。大量研究表明,褪黑素对内皮功能障碍、血管炎症和 BRB 的破坏具有多重保护作用,通过抑制多种炎症因子及 p38/TXNIP/NF-κB通路,减少细胞旁渗漏和增强紧密连接来维持 BRB 的完整性[67]。在一项前瞻性研究中,13 例 CSC 患者口服褪黑素(9 mg/d)1 mo 后黄斑中央厚度明显降低,视网膜下积液明显减少且视力得到改善,同时,未观察到明显的副作用[68]。但由于研究数量较少,作用机制仍无法解释。在醛固酮诱导的大鼠模型中,通过注射褪黑素降低钙活化钾通道(KCa2.3)的表达,抑制了醛固酮诱导的脉络膜增厚和血管舒张,并减轻脉络膜血管的畸形;褪黑素还降低了该模型中紧密连接蛋白(ZO-1,Occludin,Claudin-1)的水平,而维持了 BRB 的完整性[69]。玻璃体内注射醛固酮后可激活 IL-17A/NF-κB 信号通路[47,70],而在用褪黑素预先处理的大鼠模型中,发现褪黑素可抑制醛固酮诱导的巨噬细胞/小胶质细胞浸润,使得炎症因子(IL-6、IL-1β 和 COX-2)、趋化因子(CCL-3 和 CXCL1)和基质金属蛋白酶(MP-2 和 MMP-9)的水平明显降低;同时又可抑制 IL-17A/NF-κB 信号通路,进一步降低上述炎症因子、趋化因子及 MMPs[71]。Luzindole 作为非选择性 MT1 和 MT2 拮抗剂,4-P-PDOT 作为选择性 MT2 拮抗剂,可以中和褪黑素诱导的脉络膜增厚和脉络膜血管舒张的抑制作用,表明褪黑素可能通过与其受体结合发挥作用[71]。上述表明,褪黑素的应用有助于 CSC 的预防和治疗。

5 总结与展望

RPE 细胞损伤、新生血管形成是大部分眼底疾病共有的病理特点,抗 VEGF 治疗是抑制新生血管形成的主要手段,但复发率高,部分患者存在无应答现象。因此探索眼底疾病的其他治疗方法尤为重要,目前研究表明,褪黑素通过靶向各种因子调控血管生成,以及通过发挥抗炎、抗氧化、抗免疫反应等作用保护眼部组织。本文汇总了褪黑素靶向 VEGF/MMP 调控血管生成的研究,并阐述了褪黑素作用于 RPE 细胞抑制视网膜/脉络膜新生血管。基于此,褪黑素可考虑与抗 VEGF 药物、抗炎剂联用,也可考虑作为玻璃体视网膜手术、全视网膜光凝的术后给药,或许能促进预后、减少复发。

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