·综　　述·

白内障术后视觉重建对大脑功能和结构的影响及其潜在分子机制

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【摘要】 老龄化常伴有年龄相关性白内障的发生及大脑功能和结构的衰退。白内障术后视觉重建不仅可改善视觉功能，而且会影响大脑的功能和结构；白内障手术能增强内在光敏性视网膜神经节细胞对蓝光的有效传输，增加体内褪黑素分泌，从而调节生物节律，提高患者认知水平；褪黑素能激活其相关通路，如 Reelin、Notch 等，影响 β 淀粉样蛋白酶的聚集和沉积，减少神经细胞的凋亡，在多种神经退行性疾病中发挥重要作用。尽管临床研究证实白内障术后视觉重建能部分逆转大脑功能和结构的衰退，但其相关分子机制尚不清楚。本文将根据眼和大脑的相互关系，针对白内障术后视觉重建对大脑功能和结构的影响及潜在分子机制进行综述及讨论，为视觉重建促进大脑重塑提供新的思路和方法。

【关键词】 白内障；视觉重建；内在光敏性视网膜神经节细胞

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Advances in the effects of vision restoration on brain function and structure after cataract surgery and potential molecular mechanisms

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[**Abstract**] Aging is often accompanied by age-related cataract and concurrent degeneration in brain function and structure. Restoration of vision after cataract surgery not only improves visual function, but also affects brain function and structure. Cataract surgery can enhance the effective transmission of blue light by intrinsically photoreceptive ganglion cells, and increase the secretion of melatonin *in vivo*, thereby regulating biological rhythm and improving the cognitive level of patients. Melatonin can activate its related molecular pathways, such as Reelin, Notch signaling, etc., affecting the accumulation and deposition of β-amyloid protein, reducing neuronal apoptosis, and playing an important role in a variety of neurodegenerative diseases. Although clinical studies have confirmed that vision restoration after cataract surgery can partially reverse the decline in brain function and structure, the molecular mechanisms involved remain unclear. Based on the eye-brain relationship, this paper reviewed and discussed the effects of vision restoration after cataract surgery on brain function and structure and the potential molecular mechanism, so as to provide new ideas and methods for brain remodeling.

[**Key words**] Cataract; Vision restoration; Intrinsically photoreceptive ganglion cells

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白内障是全球首位可逆性致盲眼病，白内障摘除联合人工晶状体植入术是目前最有效的治疗方式[1]。白内障术后视觉功能的恢复，包括远视力、近视力、像差、眩光、调节能力、对比敏感度等一直都是临床医师关注的重点和难点[2-3]；近年来，白

内障术后脑功能的恢复也越来越受到大家的重视。白内障手术不仅可以提高患者的视觉功能，而且能改善大脑的功能和结构，但相关分子机制尚不清楚。本文将根据眼和大脑的相互关系，针对白内障术后视觉重建对大脑功能和结构的影响及其潜在的分子机制进行综述及讨论。

1　眼和大脑的关系及相互影响

眼和大脑密切相关，且在多种病理、生理状况下相互影响或同步变化[4-6]。从解剖上来讲，视网膜和视神经是大脑颅外段的延伸；从功能上来说，人体绝大部分的外界信息是通过视觉输入获得的，立体视觉、形式知觉等视觉功能与智力发展高度相关[7]。眼病患者不仅出现视觉功能的减退或丧失，大脑皮层（包括视觉及其他皮层）的功能亦出现明显异常。研究表明，眼病患者（主要包括青光眼、白内障、角膜疾病、视网膜疾病等）患阿尔茨海默病（Alzheimer disease，AD）的风险是正常人的 5～9.5 倍[8]；弱视患者额叶皮层、视皮层、后顶叶区及额叶皮层的功能连接均存在明显异常[9]；开角型青光眼患者颞叶、枕叶、梭回、中央前回、中央后回及小脑前叶与初级视皮层的功能连接呈显著性下降[10]。

老龄化常伴有年龄相关性白内障的发生及大脑功能、结构的减退。随着全球老龄化的到来，白内障已经成为老年人群常见的眼部疾患，很多白内障患者因未及时获得治疗而致盲[11]。晶状体的老化及混浊不仅严重损害老年患者的视觉功能，而且严重影响其身心健康及大脑功能。白内障患者因其社会活动受限，经常表现出各种负性情绪和反常行为，甚至出现抑郁症等心理疾患[12]，很多患者的认知功能和睡眠质量均出现显著下降[13-14]。Hall 等[15]通过马蒂斯器质性精神综合征筛查检查发现，白内障患者的评分明显高于未患白内障的患者，更容易出现认知功能障碍。本研究团队通过对年龄相关性白内障患者及正常人群脑部的功能性磁共振数据进行统计分析发现，年龄相关性白内障患者大脑结构和功能均显著减退，与正常人群相比，白内障患者负责认知功能的前扣带回区的灰质体积（脑结构）明显缩小，且患者顶下小叶和脑干的低频振幅值（脑功能）均显著下降[7]。

2　白内障术后视觉重建促进大脑功能和结构的恢复

白内障术后视觉重建可促进大脑功能恢复。Kheirkhah 等[13]研究发现，白内障术后 3 个月，患者的老年抑郁量表评分显著降低，简易智力状态检查量表评分（Mini-Mental State Examination，MMSE）显著提高；Ishii 等[16]通过国家眼科研究所视功能问卷和 MMSE 评估发现，白内障术后患者视觉功能和认知状况均显著提高，且两者之间呈明显正相关。

白内障术后视觉重建亦会促进大脑结构的改善。Lou 等[17]研究发现，单眼白内障患者术后视皮层灰质体积明显增大。本课题组前期的临床研究发现，白内障术后 6 个月，白内障患者的大脑结构显著改善，患者视觉相关区域（距状沟）、认知区域（扣带回前部）、情感区（额叶）、躯体感觉区（中央后回）、躯体运动区（中央前回）等脑区的灰质体积均明显增大[7]。

然而，白内障术后视觉重建对大脑功能和结构影响的分子机制尚不清楚。近年来，伽马振荡和内在光敏性视网膜神经节细胞（intrinsically photoreceptive ganglion cells，ipRGCs）对大脑功能和结构的影响越来越受到研究者的重视和关注。Iaccarino 等[18]研究发现，采用 40 Hz 的闪烁光进行视觉刺激能激发视皮层区的伽马振荡，降低脑脊液中 β 淀粉样蛋白酶（β-amyloid protein，Aβ）的表达水平，改善大脑的功能和结构，延缓或治疗 AD。ipRGCs 作为视网膜上的光感受器细胞，对蓝光（波长＜500 μm 的可见光）敏感，通过视网膜下丘脑纤维束将光照信息传递至下丘脑视交叉上核（suprachiasmatic nucleus，SCN）[19-20]，通过多突触传导途径调控神经内分泌功能（包括刺激松果体分泌褪黑素），从而调节生物节律，改善睡眠质量，提高认知水平[21-23]。

老年患者白内障的形成及加重或将影响其体内褪黑素的分泌，而白内障术后大脑功能和结构的恢复可能与体内褪黑素分泌的增加密切相关。研究表明，眼部屈光间质混浊对短波长光线的阻挡作用更为明显。当白内障形成或加重时，会导致晶状体对短波长光线（如蓝光）的透光程度显著下降，严重影响 ipRGCs 对蓝光的有效吸收，从而导致褪黑素分泌的异常，引发睡眠障碍、情绪异常、认知减退等相关问题[14,24]。众多老年患者可能因视力欠佳，更倾向于室内活动，更加降低了蓝光对 ipRGCs 的有效刺激，导致其体内褪黑素分泌的减少。研究发现，当增加光线照射，尤其是蓝光光源，可显著增加脑内 5-羟色胺的水平，恢复夜间褪黑素的分泌水平，减轻失眠和抑郁，改善情绪和认知功能[25-26]。因此，当用透明的人工晶状体置换混浊的晶状体时，白内障手术将显著提高患者眼部对蓝光的透光率，调节其体内褪黑素的分泌。Shenshen 等[27]的研究充分证实了这一点，该研究发现白内障术后患者体内褪黑素分泌明显增加，睡眠和认知功能显著改善。此外，蓝光对视网膜和脉络膜亦具有一定的毒性作用，蓝光照射产生的自由基会加速视网膜色素上皮细胞的损伤及凋亡，引发或加重黄斑病变，提高脉络膜黑色素瘤的发病风险[28-30]。蓝光在调节人体正常的生理功能中发挥重要的作用，其缺乏可能导致其他的不良影响，蓝光应用仍是当前研究争论的焦点。

3　白内障术后视觉重建影响大脑功能和结构的潜在分子机制

与同为退行性疾病的 AD 相似，白内障的发生及术后眼、脑功能改变可能与 Aβ 相关。作为 2 种年龄相关性疾病的典型代表，彼此之间关系密切。从起源上来讲，晶状体和脑组织均起源于外胚层；从分子机制上讲，Aβ 在白内障和 AD 的发病过程中起着至关重要的作用。Aβ 是 β-淀粉样前体蛋白的一种降解产物，是 AD 老年斑的主要成分（主要包括 Aβ1-40 和 Aβ1-42 2 种亚型）[31]。脑内 Aβ 的聚集和沉积会促进轴突损伤、突触丢失、炎症级联反应以及神经元纤维缠结，从而导致神经元凋亡，引发 AD 的形成[32-33]。晶状体细胞内 Aβ 能促进 αB 晶状体蛋白聚集，形成沉淀并影响光折射率，加速白内障的形成[34]。近年来，有研究进一步证实了 AD 与白内障的相关性。Goldstein 等[35]研究发现，在 AD 患者的晶状体和脑组织中均能

检测到 Aβ，而且通过电子致密物沉淀定位检查发现，AD 患者的晶状体核上部纤维细胞胞质内 Aβ 免疫反应性明显增强。

褪黑素的生成受白内障手术前后光信号成分与强度刺激影响，可能通过影响 Aβ 的聚集和沉积，在眼、脑作用通路中发挥作用。目前，褪黑素对神经退行性疾病的治疗作用及其相关机制已被广泛研究。AD 患者脑脊液和血清中褪黑素水平大幅降低[36]，补充褪黑素能减轻 AD 动物模型和患者 Aβ 的异常累积、神经元变性、神经炎症反应及记忆损伤。因此，褪黑素及其受体激动剂被认为可能是治疗 AD 的潜在药物[37]。褪黑素治疗 AD 的作用机制主要包括：(1)增强胆碱能系统的功能；(2)激活抗氧化酶，减少自由基产生；(3)减少 Aβ 产生，对抗 Aβ 的神经毒性；(4)抑制 tau 蛋白过度磷酸化，阻止神经细胞退行性改变；(5)抑制细胞内钙超载和神经细胞的凋亡[38-40]。因此，白内障术后患者体内褪黑素的增加可能会抑制或减缓大脑神经细胞的退行性改变。

Reelin 和 Notch 信号通路可能在白内障术后眼、脑功能协作中发挥作用。Reelin 和 Notch 通路是目前研究褪黑素对 AD 大鼠脑神经细胞保护机制的热点。研究显示，AD 患者神经系统功能紊乱可能与 Reelin 信号通路异常密切相关[41-42]。在转基因 AD 小鼠模型中，Reelin 蛋白表达的降低会促进 tau 蛋白过度磷酸化，增加 Aβ 生成[43]。而褪黑素能激活 Reelin 相关通路，增强突触可塑性、抑制 tau 蛋白过度磷酸化，减少 Aβ 产生[44-45]，预防认知功能减退，减少相关的神经病理学改变。研究发现，Notch 信号通路在调节神经、突触可塑性、神经元网络以及人脑的记忆和学习功能中发挥关键作用[46-49]。褪黑素能增强神经核糖核酸结合蛋白 Musashil 的功能，通过抑制 Numb (Notch 1 抑制剂)的翻译过程，激活 Notch1 信号，完成神经细胞的保护作用[50]。此外，褪黑素还可通过干扰淀粉样蛋白前体(amyloid precursor protein，APP)的完全成熟，抑制正常可溶性 APP 的分泌，有效减少 Aβ 的生成和沉积[51]。因此，我们推测，白内障术后视觉重建通过增强 ipRGCs 对蓝光的有效输入，调节体内褪黑素的生成，从而可能激活相关分子通路(图 1)，减少神经细胞凋亡，重塑大脑的功能和结构。

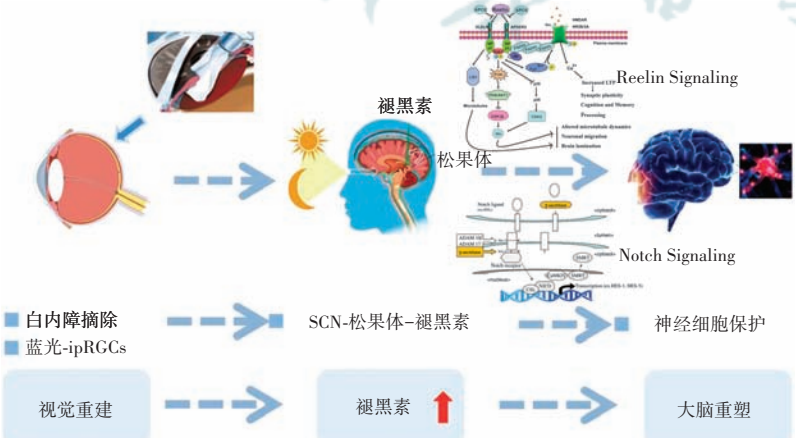

图 1　白内障术后视觉重建促进大脑功能和结构改变的潜在分子机制　白内障术后视觉重建可能通过增加 ipRGCs 对蓝光的有效传输，刺激 SCN，调节松果体分泌褪黑素，激活 Reelin[52] 或 Notch 信号通路[53]，减少细胞凋亡，促进神经细胞的保护，实现大脑重塑　ipRGCs：内在光敏性视网膜神经节细胞；SCN：下丘脑视交叉上核

综上，白内障摘除联合人工晶状体的植入不仅可改善患者的视觉功能，而且可影响患者大脑的功能和结构。尽管有研究发现，白内障术后视觉重建能部分逆转大脑结构和功能的衰退，但相关分子机制尚未被证实。期待在不久的将来，我们能揭示白内障术后视觉重建对大脑功能和结构影响的分子机制，为大脑重塑寻求新的思路和方法。

利益冲突　所有作者均声明不存在利益冲突

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