·文献综述·

一氧化氮及一氧化氮合酶在眼部疾病中的研究进展

贺 婷[1],李文慧[1],田庆梅[1,2,3],解孝锋[1,2,3]

引用:贺婷,李文慧,田庆梅,等. 一氧化氮及一氧化氮合酶在眼部疾病中的研究进展. 国际眼科杂志, 2024, 24(12):1917-1921.

基金项目:国家自然科学基金项目(No.82305322);山东省中医药科技发展项目(No.M-2022162);山东省自然科学基金项目(No.ZR2020QH314)

作者单位:[1](250014)中国山东省济南市,山东中医药大学;[2](250002)中国山东省济南市,山东中医药大学附属眼科医院 山东省中西医结合眼病防治重点实验室 山东省眼视光与青少年视力低下防控临床医学研究中心;[3](250002)中国山东省济南市,山东省眼病防治研究院

作者简介:贺婷,女,在读硕士研究生,研究方向:屈光不正和眼底病防治。

通讯作者:田庆梅,女,博士,主治医师,中国中药协会眼保健中医药技术专业委员会青年委员,山东针灸学会中医外治专业委员会委员,研究方向:眼科疾病的中西医结合治疗. jinantqm@163.com;解孝锋,男,博士,主任医师,博士研究生导师,青年岐黄学者,研究方向:眼科疾病的中西医结合治疗. yankeboshi@126.com.

收稿日期:2024-04-12 修回日期:2024-10-31

摘要

一氧化氮(NO)是在一氧化氮合酶(NOS)催化下,由内皮细胞产生并存在于人体多器官组织中的内皮源性舒张因子,同时也是介导生物体内多种生理病理过程的关键气体信号分子。NO与NOS具有调节人体血管张力,舒张平滑肌,参与炎症反应,传递神经递质等多方面作用,已在一定范围内用于疾病的治疗。近年来眼科疾病发生多呈上升态势,不同程度降低患者生活质量,但大多数疾病治疗方式有限。研究发现,在眼球多部位组织中均可检测到NO与NOS的存在,两者参与眼表及眼底多种疾病的发生及转归过程。文章将NO、NOS与眼部疾病的相关性进行综述,分析其在疾病发生发展中的机制作用,为眼科疾病的临床治疗提供新思路。

关键词:一氧化氮;一氧化氮合酶;白内障;青光眼;葡萄膜炎;近视

DOI:10.3980/j.issn.1672-5123.2024.12.10

Research progress of nitric oxide and nitric oxide synthase in ocular diseases

He Ting[1], Li Wenhui[1], Tian Qingmei[1,2,3], Xie Xiaofeng[1,2,3]

Foundation items: National Natural Science Foundation of China (No. 82305322); Traditional Chinese Medicine Science and Technology Development Project of Shandong Province (No. M-2022162); Natural Science Foundation of Shandong Province (No. ZR2020QH314)

[1]Shandong University of Traditional Chinese Medicine, Jinan 250014, Shandong Province, China; [2]Affiliated Eye Hospital of Shandong University of Traditional Chinese Medicine; Shandong Provincial Key Laboratory of Integrated Traditional Chinese and Western Medicine for Prevention and Therapy of Ocular Diseases; Shandong Provincial Clinical Medicine Research Center of Optometry and Adolescent Low Vision Prevention and Control, Jinan 250002, Shandong Province, China; [3] Shandong Academy of Eye disease Prevention and Therapy, Jinan 250002, Shandong Province, China

Correspondence to: Tian Qingmei. Shandong University of Traditional Chinese Medicine, Jinan 250014, Shandong Province, China; Affiliated Eye Hospital of Shandong University of Traditional Chinese Medicine; Shandong Provincial Key Laboratory of Integrated Traditional Chinese and Western Medicine for Prevention and Therapy of Ocular Diseases; Shandong Provincial Clinical Medicine Research Center of Optometry and Adolescent Low Vision Prevention and Control, Jinan 250002, Shandong Province, China; Shandong Academy of Eye disease Prevention and Therapy, Jinan 250002, Shandong Province, China. jinantqm@163.com; Xie Xiaofeng. Shandong University of Traditional Chinese Medicine, Jinan 250014, Shandong Province, China; Affiliated Eye Hospital of Shandong University of Traditional Chinese Medicine; Shandong Provincial Key Laboratory of Integrated Traditional Chinese and Western Medicine for Prevention and Therapy of Ocular Diseases; Shandong Provincial Clinical Medicine Research Center of Optometry and Adolescent Low Vision Prevention and Control, Jinan 250002, Shandong Province, China; Shandong Academy of Eye disease Prevention and Therapy, Jinan 250002, Shandong Province, China. yankeboshi@126.com

Received:2024-04-12 Accepted:2024-10-31

Abstract

• Nitric oxide (NO) is an endothelial-derived relaxing factor produced by endothelial cells and catalyzed by nitric oxide synthase (NOS), which is present in many organs and tissues of the human body. NO is a key gaseous signaling molecule that mediates a variety of physiopathological processes in organisms. NO and NOS have many functions including the regulation of vascular tone, the relaxation of smooth muscle, activation of immune responses and modulation of neuro-transmission. They have been used in the treatment of diseases in a certain field. In recent years, the incidence of ophthalmic diseases has been on the rise, and the quality of life of patients has been reduced. However, treatment for most diseases is limited. It is find that NO and NOS can be detected in various tissue of ocular parts, and they are involved in the occurrence and transformation of

many ocular surface and fundus diseases. This article reviews the correlation between them and ocular diseases, analyzes the mechanism and principle of the occurrence and development of diseases, and provides new ideas for the clinical treatment of ophthalmic diseases in the future.

• KEYWORDS: nitric oxide; nitric oxide synthase; cataract; glaucoma; uveitis; myopia

Citation: He T, Li WH, Tian QM, et al. Research progress of nitric oxide and nitric oxide synthase in ocular diseases. Guoji Yanke Zazhi(Int Eye Sci), 2024,24(12):1917-1921.

0 引言

一氧化氮(NO)是 L-精氨酸在一氧化氮合酶(NOS)催化下由内皮细胞生成的内皮源性舒张因子[1-2]。NO 作为气体信号分子,参与调节心血管稳态[3]、肾脏疾病[4]、神经系统退行性疾病[5]及自身免疫调节[6]等过程。NOS 具有 3 种亚型,分别为内皮型 NOS(eNOS)、神经元型 NOS(nNOS)、诱导型 NOS(iNOS),各亚型间具备不同的生物学作用,现已证实在引起肥胖、胰岛素抵抗及减缓心力衰竭等方面可发挥一定功效[7-8]。随着研究不断深入,现已在房水、视网膜及脉络膜等组织中检测到 NO 及 NOS 的存在。本文将 NO 和 NOS 与眼科疾病的关联进行梳理,总结其在不同疾病中的表达情况,寻找内在规律性,为眼部疾病治疗提供更多可能性。

1 NO/NOS 与白内障

白内障是由于各种因素作用引起晶状体长期代谢紊乱,晶状体蛋白异常,最终晶状体发生混浊引起视力下降。Nagai 等[9]研究发现使用干扰素-γ 和脂多糖(LPS)孵育人晶状体上皮细胞后,iNOS 表达增多,NO 含量相应升高,且细胞中淀粉样蛋白 a-β1-42 可促进 NO 的产生,NO 过量积累会使细胞色素氧化酶活性降低且 ATP 产生减少从而促进晶状体发生混浊。白内障患者房水和泪液中的 NO、丙二醛和过氧化脂质含量与健康组相比均有升高,在糖尿病性白内障患者晶状体上皮细胞中 iNOS 表达高于正常[10-11]。研究[12]发现,连接蛋白 Cx46s-亚硝基化与晶状体混浊过程密切相关,NO 可提高 Cx46 的活性加速亚硝基化过程,最终导致白内障的发生。现已证实,NO 通过作用于晶状体代谢过程和蛋白亚硝基化影响白内障发展,但完整的信号传导过程仍需进一步研究。

2 NO/NOS 与青光眼

青光眼是由眼压升高引起的慢性进行性疾病,因可对视神经造成不可逆性损伤,已成为全球最常见的致盲原因[13]。有研究表明,眼压每升高 1 mmHg,视网膜神经纤维层每年将变薄 0.143 μm[14],眼压对于青光眼病程进展具有决定性作用。有研究发现,小梁网中瞬时受体电位香草蛋白 4(TRPV4)-eNOS 信号通路受损是导致眼压升高并引发青光眼的重要机制;TRPV4 是存在于小梁网上的阳离子通道,为 Ca^{2+} 进入胞内的途径之一,敲除小鼠 TRPV4 基因后,NOS 表达下降,NO 释放减少,小梁网功能发生障碍,最终小鼠眼压升高并引起原发性开角型青光眼,此表明 NOS 与 NO 可能通过改善小梁网的功能进而降低眼压[15]。Madekurozwa 等[16]发现当小鼠眼压升高时,眼脉冲可能通过刺激施累姆氏管(Schlemm 氏管)细胞产生 NO 并作用于流出通道,使流出量增加 16%进而维持眼压稳态。另有学者发现眼压升高时 Schlemm 氏管内皮细胞促使 NO 产生增加,小梁网平滑肌松弛,减小房水外流阻力,从而降低眼内压,提示生理状态下眼压的高低与 NO 的含量间存在某种作用方式从而使眼压处于相对稳定的状态[17]。

此外,NO 作为第一信使,可作用于下游靶点鸟苷酸环化酶(GC),进而产生高浓度 cGMP,最终调控蛋白激酶的产生及 Ca^{2+} 通道开放,NO-GC-cGMP 通路可起到调节眼内压和控制眼血流量及保护视神经的作用[18]。

Bastia 等[19]证实在兔、狗及非灵长类动物模型中,NCX667 作为 NO 的新型供体可使人工构建的小梁网/Schlemm 氏管的房水流出增加。Hu 等[20]发现将二氧化硅纳米颗粒携带的 NO 供体运送至动物眼模型中的小梁网及 Schlemm 氏管,用于产生并维持高浓度的外源性 NO 含量,可以达到降低眼压并治疗原发性开角型青光眼的目的,表明 NO 可以从根本上控制眼压,在青光眼的治疗上具有一定应用价值。另有实验表明体外合成含硫杂合 NO 供体-抗氧化剂小分子 SA-9、活性氧化代谢产物 SA-10 及 NO 供体利帕舒地尔衍生物,均可显著降低小鼠眼内压,且具有保护视功能的作用,外源性 NO 为治疗提供更多可能性[21-22]。综上,NO 有助于维持眼压和房水的稳态,作为生物活性分子,NO 的临床应用可能会降低单纯使用外源性降眼压药物发生不良反应的风险。

3 NO/NOS 与葡萄膜炎

葡萄膜炎作为自身免疫性疾病,治疗和预后欠佳。Liversidge 等[23]发现在自身免疫葡萄膜炎实验鼠体内,NO 可通过促进过氧亚硝酸盐生成进而引起视网膜外层单核细胞浸润,使视网膜发生炎症反应并造成感光细胞的凋亡,这可能是某些葡萄膜炎会引起视网膜病变的原因之一。另有研究表明,在内毒素诱导的小鼠葡萄膜炎模型中,造模 48 h 后视网膜微循环中白细胞升高达到峰值,而使用 iNOS 抑制剂后,24 h 白细胞较正常减少 74%,48 h 后较正常减少 98.2%,这提示 iNOS 介导了微循环中内皮细胞对白细胞的迁移作用,致使白细胞发生聚集进而引起葡萄膜发生炎症反应[24]。

白塞病作为葡萄膜炎的常见类型,其中 50%患者均出现眼部症状,有研究者发现,白塞病患者体内 NO 和 IL-1β过度表达,随之发生炎症反应,免疫稳态继而被打破[25]。除 NO 外,白塞病患者体内谷胱甘肽过氧化物酶及超氧化物歧化酶水平均降低,总抗氧化指标呈下降趋势,表明在白塞病活动期患者体内抗氧化系统处于失衡状态[26-27]。Djaballah-Ider 等[28]发现白塞病患者活动期血清中 NO 及亚硝酸盐的水平高于非活动期,且皮肤黏膜及血管受累的患者体内 NO 含量高于一般患者。综上,免疫系统的失衡与抗氧化能力的下降是白塞病发生的相关病理机制之一,通过改善 NO 等相关因子以减缓炎症反应是治疗白塞病的关键。另有研究[29]表明,蜂胶醇提取物(EEP)可下调 NOS 和核因子 NF-κB 的水平,继而减轻炎症反应引起的血管损伤作用。因葡萄膜炎病程较长且易反复,炎症反应程度对预后有重要影响,NO 和 NOS 可作为干预炎症反应发展的重要因子,其水平变化也可作为评

估葡萄膜炎严重程度的指标之一。

4 NO/NOS 与糖尿病相关眼底病变

糖尿病视网膜病变(DR)已成为威胁视力、造成失明的主要视网膜疾病之一[30]。一项临床研究发现,2 型糖尿病患者血清中 NOS 水平高于健康对照组[31]。Hein 等[32]分离 1 型糖尿病猪的视网膜小动脉进行离体血管舒张试验,发现在糖尿病早期,NOS 可介导血管紧张素转换酶发生作用,从而引起血管扩张并损害血管内皮细胞,使用 NOS 抑制剂 NG 硝基-L 精氨酸甲酯后可减轻血管扩张和细胞损伤程度,提示 NOS 对视网膜的损害可能是通过影响眼底微循环所实现的。Liu 等[33]也发现在大鼠糖尿病视网膜微血管内皮细胞中 NOS 表达显著增多,且阻断 NOS2/JAK/STAT 信号通路表达可以减轻血管内皮的炎症反应,说明 NOS2/JAK/STAT 信号通路可作为治疗 DR 视网膜微血管损伤的重要靶点。Carpi-Santos 等[34]在体外高糖环境下培养鸡视网膜,发现在短时间(30 min)高糖环境中培养后,NO 含量在视网膜外核层和内核层分别增加 36%和 40%,正常葡萄糖条件培养下 NO 含量则无明显变化,高浓度的 NO 则可继发引起视网膜血管发生不可逆损伤。Robinson 等[35]研究发现,DR 小鼠体内过氧化氢酶和 eNOS 水平较非糖尿病组分别降低 0.54 倍和 0.47 倍,而超氧化物和氧化 DNA 损伤标记物的水平明显增加,氧化应激作用增强及抗氧化能力下降是 DR 发生的重要原因,这表明 eNOS 参与 DR 进程中的氧化与抗氧化失衡过程。

糖尿病患者眼底还易并发糖尿病视神经病变(DON)。研究发现,DON 与 DR 患者体内糖化血红蛋白、高密度脂蛋白、NO 和内皮素等水平均发生不同程度改变,共同参与 DON 的病理变化[36-37]。宗志峰等[37]检测 60 例 DON 患者体内 NO 水平,发现与对照组相比,NO 含量降低,表明 NO 与 DON 发生密切相关,但具体内在机制仍有待研究。上述研究表明,NO 及 NOS 含量的变化对眼底微循环造成不利影响,通过调节两者的含量进而改善眼底微循环血供状态,是未来减缓糖尿病眼底病变进展的重要方向。

5 NO/NOS 与年龄相关性黄斑变性

年龄相关性黄斑变性(ARMD)的主要病理特点为黄斑组织结构退行性病变及视网膜色素上皮细胞(RPE 细胞)异常。Zhu 等[38]使用全反式视黄酸(atRAL)作用于人视网膜色素上皮细胞(APRE-19 细胞)后发现其 iNOS、NO 表达增强,继而单核细胞发生聚集黏附,APRE-19 细胞内发生氧化应激反应和亚硝基化反应,引起细胞功能障碍进而凋亡,上述过程表明 atRAL 的细胞毒性作用影响 ARMD 的病理过程;在使用核因子 κB(NF-κB)抑制剂 SN50 后,RPE 细胞内 NO 的产生减少,并进一步抑制上述反应,阻断 NF-κB-iNOS-NO 信号通路后 RPE 细胞凋亡数量增多,表明 NO 及 iNOS 增加可加快 ARMD 进展[38]。体外培养野生型小鼠 RPE 细胞时发现炎症引起 RPE 细胞产生更多的 iNOS,且 iNOS 协同 VEGF 对 ARMD 脉络膜新生血管生成具有促进作用[39]。在血管生成过程中 Cavin/eNOS/NO 通路发挥重要作用,Cavin 在小鼠视网膜新生血管中高表达,从而维持 eNOS 的活性与稳定性,使 NO 水平保持较高水平[40]。另有研究使用 2 种新型一氧化氮释放分子姜黄素(VP10/12)和咖啡酸苯乙酯(VP10/39)处理人 RPE 细胞,发现 VP10/39 可以显著诱导人 RPE 细胞产生血红素加氧酶-1,具有较强的抗氧化和保护作用,表明 NO 可以保护 RPE 细胞免受氧化应激损伤[41]。上述结果间存在一定差异,但在 ARMD 发生过程中,NOS 与 NO 所在信号通路及含量的变化对 RPE 细胞的活性确有影响,具体的内在联系仍需进一步研究证实。

6 NO/NOS 与近视

眼轴过度伸长和巩膜重塑被认为是近视发生的直接原因,近年来发现眼内炎症和氧化应激作用也介导近视发生发展过程,NO 作为主要信号分子之一参与氧化应激反应[42-43]。有研究发现 NO 可上调脉络膜中 IL-6 基因表达从而使鸡眼轴增长速度减缓,在玻璃体腔注射非特异性 NOS 抑制剂 L-NAMA 后 NO 及 IL-6 表达相应减少,证明两者共同参与鸡在近视过程中脉络膜的改变和眼轴的增长过程[44]。较薄的脉络膜厚度会增大近视发生的可能性,这与 NO 系统失衡所引起脉络膜血流动力学改变有关[45]。在形觉剥夺性近视豚鼠体内发现,NOS 含量高于对照组,在解除剥夺条件后,豚鼠体内 NOS 含量继续升高,且 NOS 含量越高,脉络膜血管直径越大,提示 NOS 可能通过改善脉络膜血流间接影响近视发展[46]。

另有研究发现,在近视发生过程中,豚鼠视网膜及脉络膜中 NOS 表达增加,脉络膜厚度、脉络膜毛细血管密度及脉络膜层血管密度均降低[47]。Li 等[48]在给豚鼠注射 NOS 抑制剂 L-NMMA 后发现,与透镜近视组豚鼠相比,注射 NOS 抑制剂组豚鼠眼球屈光度和脉络膜厚度显著增加,脉络膜纤维化程度改善,眼轴长度变短。一项研究表明,透镜诱导近视小鼠视网膜内 nNOS 及下游 NO 介导的蛋白 s-亚硝基化表达水平降低,且用特异性蛋白组学方法检测到 19 个 s-亚硝基化位点发生分化,可见 NO 蛋白 s-亚硝基化修饰在调控近视发展过程中可能发挥一定作用[49]。NO 水平变化与脉络膜厚度和血流之间的具体关系,不同研究之间存在一定差异性,仍需要进一步实验验证两者内在的关联。

7 NO/NOS 与其他眼科相关疾病

向征等[50]使用外源性 NO 供体 $NaNO_2$治疗角膜碱烧伤模型大鼠,发现与对照组相比,使用 $NaNO_2$后大鼠角膜上皮愈合率升高,角膜混浊度减轻,提示 NO 可参与损伤修复过程。有研究发现使用脂多糖诱导角结膜发生炎症后,结膜上皮细胞产生 NO 含量下降,角膜上皮细胞产生较多的 NO,NO 总量与正常情况下相比无明显改变,这表明细胞之间可能存在某种拮抗关系维持 NO 的恒定[51]。在早产儿视网膜病变(ROP)研究中,给患儿补充 BH_4,因其作为 NOS 的辅助因子可增强酶的活性,提高了 NOS 的生物利用度,减轻高氧对视网膜血管的损伤作用,可见 BH_4是 NOS 维持活性功能的重要分子,可作为研究 NOS 在氧化还原反应中作用功能的机制分子之一[52]。此外,在视网膜色素变性(RP)的小鼠视网膜中,当视网膜感光细胞显著凋亡时,相比于无明显感光细胞凋亡的视网膜,iNOS 明显降低,可能与细胞凋亡后免疫反应终止有关[53]。

8 总结和展望

NO/NOS 在眼部各组织中具有不同程度地表达,两者不仅参与炎症反应及氧化反应等,在控制眼压、形成新生

血管、调节微循环等方面也具有重要作用。NO 可使眼压和房水循环维持稳态,作为新型治疗方式现已在青光眼的治疗上取得开创性进展,有望从根本上防止青光眼的发生。在 DR 与 ARMD 疾病发展中,因 NO 和 NOS 可干预眼底血管损伤和再生过程,通过改善眼底微循环状态可预防眼底病变的进一步发展。近视发展是不可逆过程,已发现 NO 和 NOS 作为信号分子参与此过程,若有实证表明 NO 可调节脉络膜血流动力学,从根本上延缓近视发展,便可为近视的可防可控提供理论基础。但在葡萄膜炎,ARMD 及近视相关研究中,NO 及 NOS 的变化水平在不同结果中存在一定差异,可能由于疾病发展阶段不同和严重程度差异所导致,今后研究可以以此作为切入点进一步探究其内在关联,为眼科疾病治疗提供更多可能性。

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