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【文献综述】

年龄相关性黄斑变性抗氧化剂治疗进展△

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Research advances in antioxidant treatment of age-related macular degeneration

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【Key words】 age-related macular degeneration; oxidative stress; antioxidant treatment

【Abstract】 Age-related macular degeneration (AMD) is a macular disease and its incidence is gradually increasing with age. It is thought that its pathogenesis is related to the age, heredity, smoking, diet, oxidative stress, immune inflammation reaction and cardiovascular disease and so on. Oxidative stress is closely related to AMD. Antioxidant therapy provides a new strategy for the prevention and treatment of AMD. Also, it provides a new way to alleviate and prevent AMD.

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【关键词】 年龄相关性黄斑变性;氧化应激;抗氧化剂治疗
【摘要】 年龄相关性黄斑变性是一种随年龄增长而发病率逐渐上升的黄斑部疾病,目前认为其发病机制与患者的年龄、遗传、吸烟、饮食、氧化应激、免疫炎症反应、心血管疾病等因素有关,其中氧化应激作用与年龄相关性黄斑变性密切相关。抗氧化剂治疗为防治年龄相关性黄斑变性提供了一种策略,为缓解和预防年龄相关性黄斑变性的研究提供了新思路。

年龄相关性黄斑变性(age-related macular degeneration, AMD)又称老年性黄斑变性,是引起全球老年人视力丧失最主要的原因之一[1]。随年龄增长,许多组织细胞的抗氧化水平降低而活性氧产生增加,逐渐累积的氧化应激损伤是AMD发病的关键因素[2]。因此,抗氧化剂的治疗或许是控制和缓解AMD发生发展的有效方法。本文就目前AMD的抗氧化剂治疗进展作一综述。

1 氧化应激的概念

自由基是指化合物分子在光热等外界条件下,共价键发生均裂而形成的具有不成对电子的原子或基团。因为存在未成对电子,自由基极其活泼,而且氧化作用非常强。常见的活性氧包括超氧阴离子($\cdot O_2^-$)、羟自由基($\cdot OH^-$)、过氧化氢($H_2O_2^-$)、一氧化氮($NO\cdot^-$)等。氧化应激是指体内氧化与抗氧化作用失衡,倾向于氧化,导致中性粒细胞炎性浸润,蛋白酶分泌增加,产生大量氧化中间产物。研究表明,人类许多的重要疾病如AMD、阿尔茨海默病、肝脏疾病等都与氧化应激的激活有着密切的关系[3-5]。

2 氧化应激与AMD

黄斑变性的产生有多种原因,如高龄退化、外伤、感染、炎症、遗传等引起视网膜色素上皮(retinal pigment epithelial, RPE)细胞对视细胞外界盆膜吞噬消化功能下降,使未被消化的盆膜残余小体潴留于基底部细胞原浆中,并向细胞外排出,形成玻璃膜疣,继而使得黄斑区结构出现衰老性改变。

尽管黄斑变性是多因素导致的眼底部疾病,但据报道,年龄是AMD最主要的危险因素,高龄AMD患者死亡率增加[6]。而细胞的氧化损伤在衰老过程中起着重要作用[7]。AMD在临床表现上有两种类型:干性AMD和湿性AMD。虽然AMD的发病机制尚不清楚,但是氧化应激和自由基损伤已被证实为AMD的致病因素之一[8]。有研究表明,许多因素如阳光照射、饮食、吸烟、维生素D缺乏等引起AMD的发生与氧化应激有着密切的关系[9-11]。

正常RPE细胞和感光细胞对氧的需求量比较大。当RPE细胞密度降低时,最终会导致RPE细胞新陈代谢、吞噬感光细胞外节等功能障碍时,活性氧(reactive oxygen species, ROS)含量增加[12]。ROS主

要存在于视网膜 RPE 细胞和感光细胞的线粒体中。在 RPE 细胞的氧化应激损伤中,存在 mtDNA 的损伤改变[13]。正常情况下,DNA 受损后其损伤和修复是同步进行的,但如果 RPE 细胞中 ROS 含量过多,超过抗氧化系统的清除能力,则会造成 DNA 氧化损伤和蛋白的表达异常。研究表明,即使是轻微的脂质过氧化作用也会引起基因表达的变化和改变组织内稳态平衡[14-15]。TOTAN 等[16]证实氧化大分子对 DNA 有损伤,进而对 AMD 有影响。因此,保护线粒体 DNA 免受氧化应激损伤是延缓 AMD 进展的一种新策略[17]。

3 抗氧化剂对 AMD 的治疗

目前已有研究表明,抗氧化剂可以中和光损伤过程中所产生的自由基,从而防止视网膜上细胞的损伤[18]。高水平摄取抗氧化剂成为早期预防和缓解 AMD 发生发展的新策略[19]。

3.1 维生素类

3.1.1 维生素 C 维生素是维持身体健康所必须的一类有机化合物,在物质代谢中起着重要的作用。维生素有很多种类,其中维生素 C 又称 L-抗环血酸,是高等灵长类动物与其他少数生物的必须营养素,广泛的食物来源是新鲜水果和蔬菜。在生物体内,维生素 C 是一种抗氧化剂,保护身体免于自由基的威胁。JACQUES 等[20]认为,维生素 C 作为供氢体,可通过调节基因 Bcl-2、p53 的表达发挥抗氧化作用及保护 RPE 细胞 DNA 免受损伤。CHRISTEN 等[21]对美国男性内科医师进行了大规模随机对照试验,发现隔日用 400 IU 的维生素 E 或每天用 500 mg 的维生素 C 对 AMD 的发生率都没有很大的益处或者坏处。由此表明,维生素 C 对 AMD 的治疗效果尚不确定。

3.1.2 维生素 E 维生素 E 由几种抗氧化剂组成,是所有具有 α-生育酚活性的生育酚和生育三烯酚及其衍生物的总称,又名生育酚,是一种脂溶性维生素,在蔬菜、豆类中含量丰富。CHEW 等[22]认为,长期服用维生素 C、维生素 E、β 胡萝卜素和锌,有助于减缓年龄相关性黄斑疾病的进展。但 EVANS 等[23]认为补充维生素 E 对 AMD 的发生没有影响。CHRISTEN 等[24]在大规模的健康女性群体中进行随机对照试验,发现长期隔日服用 600 U 的维生素 E 对 AMD 发生的风险没有大的益处或坏处。所以维生素 E 是否有利于改善 AMD 还需进一步研究探讨,抗氧化剂的联合应用或许有助于减缓 AMD 的发生和发展。

3.2 矿物质

3.2.1 锌 锌是一种化学元素,也是人体必需的微量元素之一,是超氧化物歧化酶和过氧化物酶抗氧化作用的辅因子。人体内的锌可以促进人体生长发育、增强免疫力、维持正常食欲等,并对维生素 A 的代谢和正常视觉有影响,锌元素主要存在于海产品和动物内脏中。研究表明,每日摄取 50 mg 的硫酸锌可以抑制 AMD 患者补体的分解代谢并加强补体的激活,从而延缓 AMD 的发生和发展[25],这也解释了锌可以延缓 AMD 发生发展的原因。VISHWANATHAN 等[26]通过统计分析表明,锌治疗可以有效阻止 AMD 的进程。

有实验证明:大剂量联合口服锌和抗氧化剂可以有效地预防中晚期 AMD 的发展[22,27],所以在治疗 AMD 时可考虑联合锌和抗氧化剂治疗。综上所述,锌对 AMD 的发生和发展可能有着积极的治疗作用。

3.2.2 铜 铜是一种微量元素,具有传递电子的功能,因此,在氧化还原和自由基的清除中扮演着重要角色。最新研究表明,铜水平的降低可能在 AMD 的发病机制中起重要作用[28]。ERIE 等[29]发现,AMD 患者 RPE 和脉络膜上的铜水平比正常人减少了 23%。由此说明,铜水平的高低可能与 AMD 的发生有一定关系。

3.3 类胡萝卜素类

3.3.1 叶黄素和玉米黄质 叶黄素是类胡萝卜素家族的一员,又名"植物黄体素"。在人体内,叶黄素和玉米黄质都是抗氧化剂,是光感受器的自由基清除剂。广泛存在于菠菜、猕猴桃、玉米等天然植物中,在自然界中与玉米黄质共同存在。玉米黄质又叫玉米黄素,属于类胡萝卜素,人体和动物无法自身合成玉米黄质,必须通过食物或补充剂获得。玉米黄质食物来源主要是黄玉米、橙汁、蜜瓜等。叶黄素和玉米黄质是组成视网膜黄斑的颜色的主要成分,正是由于黄斑色素含有叶黄素和玉米黄素,才能保护感光细胞层过滤蓝光以使视网膜免受光损害[30-31]。李慧丽等[32]用多焦视网膜电图(muctifocal electroretinography,mfERG)评价叶黄素和玉米黄质治疗 AMD 的视网膜功能变化情况,结果显示 mfERG 叶黄素和玉米黄质治疗能有效提高 AMD 患者 mfERG 的 b 波振幅密度,改善患眼视网膜光感受器功能。CHEW 等[33]在试验中发现,对于 AMD 患者,补充叶黄素和玉米黄质比补充 β-胡萝卜素更适合。因此,叶黄素和玉米黄质对 AMD 的治疗有可期待的前景,具体可行性仍需进一步探索。

3.3.2 β-胡萝卜素 β-胡萝卜素也是属于类胡萝卜素类,是胡萝卜素的一种异构体,广泛存在于动物与植物的叶、花、根中。由于 β-胡萝卜素具有抗氧化功能,因此被广泛应用[34]。GOPINATH 等[35]发现,AMD 患者比正常人摄入的 β-胡萝卜素更少,这可以从侧面反映 β-胡萝卜素的摄入与 AMD 的发生有一定的关系。然而,早期有研究表明,β-胡萝卜素和维生素 A 可能增加患肺癌和心脏疾病的风险[36]。最近几项研究表明,高膳食 β-胡萝卜素和维生素 A 对癌症的发病率没有影响甚至可以降低患肺癌的危险[37-38]。因此,摄取 β-胡萝卜素来预防 AMD 的发

生发展具有一定的潜力,但其严重的副作用不容小觑,还需要进一步研究。

4 展望

研究天然药物抗 AMD 的有效药理活性和作用机制,将更好地了解它们的疗效和未来作为新型药物的潜力。维生素 C、维生素 E、矿物质、叶黄素/玉米黄质及 β-胡萝卜素具有抗 AMD 潜力,但仍需要临床试验的结果证实,以及存在生物利用度和最佳剂量等问题仍需进一步研究。

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