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儿童及青少年近视的药物防控及其进展

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摘　要

在全球范围内，儿童及青少年近视已经成为现代社会人们十分关注的一个公共卫生问题，目前延缓近视进展的方式多种多样如药物治疗、光学矫正及屈光手术治疗等。本文主要对近年来药物防控儿童及青少年近视的相关研究进行综述。

关键词

近视，阿托品，儿童，青少年

Research Progress on Medicine Prevention and Control of Myopia in Children and Adolescents

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Abstract

On a global scale, myopia in children and adolescents has become a public health issue of great concern in modern society. Currently, there are various ways to delay the progression of myopia, such as medication, optical correction, and surgical treatment. This article mainly reviews the relevant research on medicine prevention and control of myopia in children and adolescents in recent years.

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Keywords

Myopia, Atropine, Child, Adolescents

1. 引言

近年来，近视眼的发病率逐年上升并呈现低龄化趋势，且在学龄期儿童中，发病年龄越小，越容易发展为高度近视[1]。近视眼已经成为现代社会人们十分关注的一个公共卫生问题，若不能及时加以干预控制，随着眼轴的增长，视网膜和脉络膜发生退行性改变，有可能导致严重的眼部病理变化如视网膜脱离、黄斑出血等，甚至失明[2]。近视眼给患者带来身心危害的同时还给个人、国家带来沉重的经济负担。

2. 毒蕈碱受体阻滞剂(M 受体阻滞剂)

2.1. 阿托品

阿托品作为一种非选择性 M 受体阻滞剂，在临床中已经证实是一种能够有效延缓近视进展的药品[3]。但目前其防控近视的机制尚未定论。其中最早期的学者认为阿托品是通过使睫状肌松弛，缓解调节来实现延缓近视进展[4]。而近年来，一系列动物实验发现阿托品在通过调节机制控制近视进展中的作用十分有限[5]。而 McBrien [6]等向单眼丧失视力的小鸡的玻璃腔内分别注射阿托品与生理盐水后发现注射阿托品的小鸡轴向长度的减少主要是玻璃体腔伸长减少的结果。且在玻璃腔内注射阿托品不会减少卡巴胆碱诱导的调节或光照诱导的瞳孔收缩。所以阿托品可以通过非调节机制有效抑制小鸡的近视。BARATHI VA 等[7]向实验诱导近视的小鼠的结膜下注射 1%硫酸阿托品 4 周后通过实时荧光定量 PCR 发现，阿托品治疗后近视巩膜中 M1、M3 和 M4 的 mRNA 表达上升，但 M2 和 M5 变化不大。说明阿托品作为 M 受体阻滞剂在人体中涉及防控近视可能与拮抗睫状肌上的 M1、M3 和 M4 受体有关。此外，近视发生的机制可能与巩膜组织重塑有关，随着近视的发展，巩膜中成纤维细胞增殖减慢，ECM 蛋白和胶原酶下调，从而减少人类和灵长类动物眼睛中的 I 型胶原蛋白和糖胺聚糖(GAGs)，胶原蛋白下调导致巩膜早期组织丢失和变薄[8] [9]。而一些动物实验发现阿托品在干预小鼠[7]与小鸡[10]近视进展期间发现巩膜纤维层变厚而软骨层变薄。从而抑制眼球增长，延缓近视进展。因此，阿托品对于巩膜形态学的控制在延缓近视进展中也可能起着重要作用[7] [10]。其他机制学说还包括：阿托品可能与抑制褪黑素降解[11]有关，GABA 信号传导可能参与了阿托品的抑制近视作用[12]等。

因此，阿托品控制近视进展并不是通过单一受体或者单一通路发挥作用，而是多受体，多水平，多途径相互作用的复杂机制。其确切机制目前仍未确定，仍需要广大学者进一步探索。

在全球范围内，特别是亚洲地区，阿托品作为防控近视进展的药物在临床上已得到广泛的应用。在新加披的一项临床对照研究中(ATOM)对 6 到 10 岁的亚洲近视儿童应用 1%阿托品，结果发现 1%阿托品能够有效延缓低度及中度近视的进展，但副作用较大，包括睫状肌麻痹导致瞳孔散大及视近模糊[13]。SONG YY [14]等进行的一项临床对照研究的荟萃分析证实阿托品有效控制近视进展的浓度在 0.1%~1%，且浓度越高，控制近视进展的效果越好。Chia 等[15]的 ATOM2 试验选择了更低浓度阿托品(0.5%、0.1%、0.01%)，其近视进展分别为(−0.30 ± 0.6) D、(−0.38 ± 0.60) D、(−0.49 ± 0.63) D，对照组为(−1.20 ± 0.69) D，

结果表明三种浓度阿托品在控制近视进展方面具有相当的疗效，但 0.01%阿托品不良反应最小。且在后续第二阶段的停药回弹试验中[16]，0.5%和 0.1%浓度的阿托品表现出更大程度的近视回弹，而 0.01%浓度的阿托品导致的近视回弹程度最少。ATOM2 第三阶段实验[17]则证实了在停止使用阿托品后出现近视进展(至少一只眼屈光度增长 > 0.50 D)的儿童中，重新使用 0.01%浓度的阿托品仍然能够有效控制近视的进展。Yam 等[18]在中国香港进行了一项为期两年的随机临床试验(低浓度阿托品治疗近视进展(LAMP)研究)，第一阶段在 4~12 岁儿童中使用 0.01%、0.025%以及 0.05%浓度的阿托品滴眼液 12 个月，结果显示，三种浓度阿托品均可有效控制近视进展，且呈浓度依赖性，其中以 0.05%浓度阿托品控制近视进展最有效，对受试者日常生活也无明显不良影响。第二阶段[19]将第一阶段安慰剂组儿童从第二年随访开始时转为接受 0.05%阿托品。结果显示在 2 年内，观察到的 0.05%浓度的阿托品的疗效是 0.01%浓度阿托品的两倍，并且仍然是所研究的阿托品浓度中减缓近视进展的最佳浓度。Hieda 等[20]在日本地区进行的一项研究显示 0.01%阿托品的依从性好，对预防儿童近视进展有效且安全。因此，对于阿托品控制近视进展的使用计量、最佳浓度尚未统一结论，仍需要进一步的研究。

2.2. 哌仑西平

哌仑西平是一种相对选择性毒蕈碱受体拮抗剂，且仅作用于眼内 M1 及 M4 受体，故受 M3 受体控制的瞳孔扩大及睫状肌麻痹的副作用并不明显[21]，TAN 等[21]和 Siatkowski 等[22]分别进行了为期 1 年和 2 年的临床研究，结果显示 2%哌仑西平凝胶在治疗期内减缓近视的进展是有效，主要的副作用包括轻度到中度睫状肌麻痹、畏光、弥散、结膜过敏和调节功能障碍。并且 Arumugam 等[23]在哺乳动物(树鼩)实验中发现了较明显的胃肠道反应。目前，哌仑西平在临床实验中并未发现明显的不良反应。但还需长期的，大样本量的研究来证明哌仑西平的有效性及安全性。

3. 腺苷受体拮抗剂

7-甲基黄嘌呤(7-MX)作为非选择性的腺苷受体(ADAR)拮抗剂，是咖啡因和可可碱的代谢产物，有研究发现 ADAR 能够增加巩膜后部胶原蛋白浓度和胶原纤维直径[24]，即能够以增加了巩膜后部强度并有望降低眼轴增速。Trier 等[25]进行的一项临床研究结果显示 7-MX 能够有效减缓近视的进展，未发现明显的不良反应，并且口服的给药方式依从性更好。而在 Trier 等最新研究中表明口服 7-MX 与近视进展减少和轴向伸长减少有关。且未发现不良反应，但需要随机对照试验来确定这种关联是否具有因果关系[26]。7-MX 虽然在全球范围内，已有国家进行了临床实验，在控制近视方面未来有着很大潜力。但目前并没有相关药物正式上市用于临床治疗。

4. 降眼压药

很早以前就有学者提出眼压的增加与屈光不正、IOP 增加与眼轴长度呈正相关[27]。蔡晓静等也发现葛根素能够延缓近视的进展。因此推测葛根素可能是通过降低眼内压从而抑制眼球扩张延缓近视进展的[28]。而马来酸噻吗洛尔在人体[29]和小鸡[30]实验中都表明未发现有明显延缓近视的作用。Liu 等在对于豚鼠的研究中发现，单独使用 0.1%溴莫尼定和单独使用 0.2%溴莫尼定以及与 2%哌仑西平联合治疗可有效抑制近视[31]。且 Yang 等研究给药途径中发现玻璃体内注射溴莫尼定对于 FD 豚鼠减缓近视进展的最有效[32]。此外，也有部分研究[33] [34]显示拉坦前列素对于豚鼠近视的进展有明显作用。高峻[35]进行了一项卡替洛尔联合阿托品控制近视的临床研究，结果表明两药联合使用能够明显改善青少年近视情况。目前，降眼压药控制近视进展的机制尚不明确，需要进一步研究，但豚鼠实验的结果让延缓近视进展的方式多了一种可能。

5. 多巴胺类药物

早期研究就表明，视网膜中 DA 的含量与近视的发展有关。Stone 等[36]发现 FDM 小鸡视网膜多巴胺的减少仅在光适应期间很明显，并且伴随着多巴胺生物合成速率的降低。Weiss 等[37]也提出 DA 的含量呈现处昼夜规律，昼多夜少，小鸡 FDM 会引起白天的 DA 减少。一些针对哺乳动物的研究[38] [39] [40]也表明了 DA 的含量与近视的发展有着一定的关系。Thomson 等[41] [42]研究表示向 FDM 小鸡的玻璃腔内注射左旋多巴能够有效抑制小鸡近视进展，并且联合卡比多巴使用能够增加左旋多巴的利用率从而增强其延缓近视的效果。阿扑吗啡(apomorphine)作为非选择性多巴胺受体激动剂在动物实验中也表明对近视的进展有控制效果[43] [44] [45]。此外，包括 2-氨基-6,7-二羟基-1,2,3,4-四氢萘氢(2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene, ADTN) [43]、D1 激动剂(SKF38393) [46]以及喹吡罗[47] [48] [49]等在动物实验中都表现出了控制近视进展的潜力。但其确切的机制尚需进一步的研究。

6. 胆碱能通路类药物

胞磷胆碱(Citicoline)是合成 Ach 途径中胞苷 5-二磷胆碱(cytidine 5-diphosphocholine)的外源性药物形式，常被用作治疗神经系统疾病、弱势及青光眼[50]。在其治疗弱势和青光眼后，视觉功能改善的一部分原因可能就与胞磷胆碱能够刺激 DA 通路，提高视网膜上 DA 水平有关。Rejdak 等[51]向兔子腹腔内注射胞磷胆碱(50 mg/kg，每日两次)，共七天。发现 DA 水平明显升高。MAO 等[52]在 FDM 豚鼠腹腔中注射胞磷胆碱后发现能有效延缓 FDM 豚鼠的近视进展。为近视防控增加一项新的可能，但目前胞磷胆碱控制近视进展的机制尚不清楚，且尚无临床实验研究证明其有效性。

7. 核黄素及紫外线(UVA 波段)联合治疗

核黄素及 UVA 联合治疗主要被用于圆锥角膜[53]，其通过使巩膜胶原交联以提升巩膜强度，延缓近视进展。在动物实验中，对于因巩膜胶原减少的近视有着不错的效果[54] [55]。然后长时间接受 UVA 入侵性照射可能引起光损伤，因此，服用核黄素以及增加户外运动以延长太阳光暴露时间，对近视进展可能也有延缓作用。但目前尚无相关临床研究来评估巩膜交联后的强度能否延缓近视进展。

8. 其他类药物

药物防控近视是当下热点，目前还有许多药物在实验阶段。有研究表明慢性炎症可能与近视存在某种关联，一项对幼年慢性关节炎(JCA)患者 26 年的随访显示，这些患者中近视屈光不正的比例高于对照组，并解释了可能与结缔组织强度变弱有关[56]。一些炎症介质包括白细胞介素-6 (IL-6)、肿瘤坏死因子-α (TNF-α)、C-Fos、核因子 κB (NF-κB)在近视仓鼠中的水平上升，经过免疫抑制剂的治疗后，仓鼠近视发展速度减缓，而使用炎症刺激剂后仓鼠近视出现了明显的进展[57]。这表明，慢性炎症与近视进展有着较强的相关性。前文提到了阿托品防控近视与褪黑素降解有关[11]，Wang 等[58]将豚鼠随机分为白光(对照组)、绿光组(530 nm)和蓝光组(480 nm)组。每天测量两次松果体褪黑激素水平。发现绿光下长大的豚鼠松果体褪黑素水平明显较高，而在蓝光下长大的豚鼠褪黑素水平下降，而在绿光下长大的豚鼠出现了更多的屈光不正，推测可能是因褪黑素过多，眼睛生长过快导致。而另一项关于雏鸡的实验则表明褪黑素能够显著影响前房和玻璃体腔深度以及脉络膜的厚度并参与了眼部生长昼夜节律的调节[59]。但其确切机制尚不明确，且尚无相关临床实验，仍需进一步的研究。

此外，包括酮咯酸氨丁三醇、一氧化氮、碘化二乙氧膦酰硫胆碱(echothiophate iodide)以及生长因子等大量药物尚处在实验初级阶段，需要更多的，大样本的动物以及临床实验加以证明和评估其防控近视的潜力。

9. 总结

综上，随着儿童及青少年近视人口的快速增加，高度近视带来的威胁也会越来越多，近视防控已然成为人们所关注的重点，也是当下的热门研究主题。目前，低浓度的阿托品是现阶段研究防控近视最有效且安全的药物手段，且联合光学治疗能提高效果及患者依从性，但针对个体化的给药剂量、用药时间尚无统一定论。其余药物尚处在动物实验阶段，或者有少量的临床研究。且大量动物实验的给药方式为玻璃腔注射，若作为常规临床实验方式，患者依从性差，效果不理想。如今近视的发生机制还不明确，全球范围内，对于近视的防控还存在地域及种族差异，因此需根据不同个体，制定个性化的，联合多种治疗方式(光学治疗，手术治疗等)的治疗方案。还要充分考虑环境因素，如增加户外互动时间或减少近距离视物时间。以此在确定安全性的情况下尽可能延缓儿童及青少年的近视进展。在今后的研究中，应着力于明确近视机制，探索更多可能的药物，注重各治疗方式的联合使用及其长期使用的安全性及有效性的评估，为临床上防控儿童及青少年近视提供更多安全有效的方案。

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