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Effects of the Interventions of Controlling Myopia Onset and Progression on Choroidal Thickness and Their Mechanisms

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Abstract

Myopia is a kind of high-risk refractive problem in young children. With the rapid myopia progression, some complications may occur such as axial elongation, tigroid fundus, and macular hemorrhage. For the advancements in optical coherence tomography (OCT), more accurate image of the posterior segment can be analysed, such as choroid. Many studies compared the choroidal thickness between myopia and emmetropia by means of enhanced depth imaging optical coherence tomography (EDI-OCT), and discovered that the choroidal thickness in myopia eyes was thinner than that of emmetropia eyes. A large number of studies began to explore the effects of different interventions of controlling myopia progression on choroidal thickness. Atropine eye drops and orthokeratology contact lenses, as effective means of controlling progression of myopia, play an important role in controlling axial elongation. And outdoor activities also get attention in preventing the onset of myopia. The aim of this review was to summarize the effects of different interventions of controlling myopia onset and progression on choroidal thickness and their mechanisms.

Keywords

Choroidal Thickness, Atropine, Orthokeratology Contact Lenses, Outdoor Activity

控制近视发生发展的干预措施对脉络膜厚度的影响及机制

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摘 要

近视是青少年中高发的屈光问题，随着度数的快速增长，可能会引起眼轴变长、豹纹状眼底、黄斑部出血等问题，同时因光学相干断层扫描(OCT)的技术发展，人们可以得到关于眼后段解剖更精确的图像，如脉络膜等。许多研究利用光学相干断层扫描深度成像(coherence tomography with enhanced depth imaging, OCT-EDI)的技术比较了近视与正视眼的脉络膜厚度，发现近视眼的脉络膜厚度显著变薄。目前大量研究开始探讨控制近视发生发展的不同干预措施对脉络膜厚度的影响。阿托品、角膜塑形镜等方法在控制眼轴增长中发挥了重大的作用，是控制近视进展的有效方法，同时户外活动对预防近视的作用也受到了广泛的关注。该文将主要对这些控制近视发生发展的干预措施对脉络膜厚度的影响及其可能的机制做一综述。

关键词

脉络膜厚度，阿托品，角膜塑形镜，户外活动

1. 引言

近视眼是一种常见的屈光不正，根据近视流行病学的趋势分析，到 2050 年近视可影响全球约 50%的人口，而近视度数的增长，可导致病理性近视眼，引起眼轴变长、豹纹状眼底、黄斑部出血或形成新生血管膜等病理改变，同时相对于正视眼，近视眼脉络膜厚度还可出现变薄的表现[1] [2] [3] [4]。脉络膜厚度指的是视网膜色素上皮层与脉络膜、巩膜交界处之间的距离，组织上从外向内主要包括脉络膜上组织(构成脉络膜上腔)、大血管层(Haller’s layer)与中血管层(Sattler’s layer)、脉络膜毛细血管层、Bruch 膜[5]。在高度近视患者中，脉络膜明显变薄，其与等效球镜度及后巩膜葡萄肿高度相关[3] [6]。脉络膜厚度在控制近视发生发展的过程中发生的变化引起了人们的关注。近年来，大量研究观察了控制近视发生发展过程中脉络膜厚度的变化。因此本文将对这些防控近视的干预措施对脉络膜厚度的影响及可能的机制做一综述。

2. 阿托品与脉络膜厚度

药物控制是青少年近视中常用的控制方法，目前临床上主要应用低浓度的阿托品控制近视进展[7]，但由于其是一种非选择性毒蕈碱型受体拮抗剂，可麻痹睫状肌，引起调节功能下降、眩光及模糊等症状，这些不良反应存在浓度依赖性，临床上应用的 0.01%阿托品可保持良好的控制效果，同时减少眼部不良反应，提高依从性[8] [9]。许多研究发现使用阿托品后，脉络膜厚度出现增厚的变化。Nickla 等人的一项研究中，往鸡眼球内注射阿托品、哌伦西平、奥芬溴铵等 3 种毒蕈碱型抗体拮抗剂，不仅可阻止光学离

焦性近视，还使脉络膜厚度显著增厚，相对于注射生理盐水(10 μm)，阿托品、哌伦西平、奥芬溴铵分别使脉络膜厚度增厚了 42 μm，80 μm，88 μm，与之相反，毒蕈碱型受体激动剂(如毛果芸香碱、卡巴胆碱等)则可使鸡眼的脉络膜厚度变薄[10]。Zhengwei Zhang 等人的实验中，青少年儿童使用 1%的阿托品每天滴眼 2 次，持续 1 周后，脉络膜厚度有统计学意义上的增厚，除黄斑中心凹下脉络膜厚度增加之外，周围 3 mm 以内的脉络膜厚度也有增加，其中黄斑中心凹周围颞侧及下方脉络膜厚度增加较为明显，但是眼轴长度无显著的变化[11]。另一方面，Beata P. Sander 的实验中，成年人使用了 0.01%阿托品后出现脉络膜厚度的增加，但增加的幅度只有(6 ± 2 μm) [12]，而 Zhengwei Zhang 等人的实验中，脉络膜厚度增加了(15.48 ± 16.13 μm)，这可能与两组实验的人群的年龄及使用阿托品的浓度不同有关，同时 Beata P. Sander 的实验中成年人测量脉络膜厚度的时间点是在使用阿托品后 30 min、60 min，未继续进一步观察。除阿托品外，成年人使用后马托品、环喷托酯之后，发现脉络膜有增厚[13] [14] [15]，而使用托吡卡胺后却未发现能使脉络膜增厚，不仅如此，Kara 的一项样本量为 60 例的研究中，在使用托吡卡胺及 2.5%苯肾上腺素两种实验条件下，脉络膜厚度均出现变薄(−22 ± 14 μm、−17 ± 9 μm) [16]。与使用阿托品的结果相比，使用了托吡卡胺之后脉络膜变薄的原因尚不清楚。脉络膜厚度自身有日常的节律变化，在中午变薄，晚上变厚[17]，根据脉络膜厚度日变化的节律，阿托品用药对脉络膜厚度的影响可能与不同时间点用药有关。但是，Nickla 等人的另一项动物研究结果中，阿托品抑制近视进展的作用与注药时间点无关，于中午时分在鸡眼眼内注射喹吡罗、哌仑西平却可使抑制眼球增长的效果更好[18]。

阿托品引起脉络膜厚度出现变化的可能机制

睫状肌后端附着于脉络膜当中，当调节发生时，睫状肌向前向内收缩时使脉络膜厚度出现变薄[19] [20]。阿托品使睫状肌麻痹舒张的过程或许是引起脉络膜厚度变化的原因。另外，一氧化氮(nitric oxide, NO)及多巴胺在阿托品影响脉络膜厚度的过程中可能扮演了重要角色[21]-[26]。一些动物实验发现阿托品可使视网膜 NO 及多巴胺的释放增加，其中发现多巴胺可使脉络膜厚度增加，而 NO 能让脉络膜血管扩张[21] [25] [26]。同时有实验表明，NO 抑制剂可阻止多巴胺对近视的抑制效果及对脉络膜厚度的影响[24]。脉络膜解剖上还包含着大量受自主神经支配的非血管平滑肌(non-vascular smooth muscle)，其收缩可被阿托品阻止，脉络膜厚度的变化可能与非血管平滑肌的舒张有关[27] [28]。Nickla、Schroedl 两人去除了小鸡眼睛的翼腭神经节、睫状后神经节及颈上神经节之后，发现小鸡的眼轴长度及脉络膜厚度的日常变化节律的频率增加，对于同时去除翼腭神经节、睫状后神经节的小鸡，其眼轴长度和脉络膜厚度日变化节律除频率增加之外，幅度也显著变大[29]。非血管平滑肌在阿托品与脉络膜厚度的关系中有着怎样的作用，仍需进一步观察。

3. 光学矫正方法与脉络膜厚度

近视眼由于其眼轴延长，周边视网膜的屈光状态相对形成远视性离焦，与正视眼形成的周边近视性离焦不同[30]。在一些动物实验中，非黄斑中心凹的周边视网膜远视性离焦条件可使幼猴发生近视[31]。而近视性离焦可抑制眼轴的增长，使脉络膜增厚，远视性离焦则出现相反的结果[32] [33] [34]。临床上许多光学干预方法可使周边视网膜形成近视性离焦，例如角膜塑形镜(orthokeratology，简称 OK 镜)、双焦点角膜接触镜及多焦点光学镜片等，这些光学干预方法在临床上表现出了延缓近视进展的作用[8] [35]。其中，OK 镜是一种反几何设计的硬性透气性角膜接触镜，持续配戴可以改变角膜曲率，使近视患者配戴 OK 镜后周边远视性离焦变成相对近视性离焦[36]，OK 镜的近视控制效力中等(0.25~0.50 D/年)，对近视眼眼轴增长的减缓量约为 0.15 mm/年[8] [35]。近年一些研究发现青少年近视人群佩戴 OK 镜后，与控制组配戴单焦点框架镜相比，脉络膜的厚度较配戴 OK 镜前有小幅度地增加，具有统计学意义，黄斑周围

颞侧脉络膜厚度增厚最显著，鼻侧脉络膜厚度增厚最少[37] [38] [39] [40] [41]。Li Z 等人的研究中，青少年近视人群配戴 OK 镜 1 个月、6 个月、9 个月后黄斑中心凹下脉络膜厚度相对于未配戴前分别增厚了 16 ± 11 μm、21 ± 13 μm、19 ± 14 μm，都具有统计学意义(3 组数据均 $P < 0.05$)，但 3 组数据之间无统计学意义，说明脉络膜厚度在一定范围内增厚之后，不会因配戴时间增加而继续增厚[39] [40]。Gardner 等人的一项样本数为 9 例的研究发现，配戴 OK 镜 9 个月的过程中脉络膜厚度未出现明显变化，这可能与该研究样本数太少有关[42]。停戴 OK 镜后，脉络膜厚度会恢复至原先水平，但是在 Lau 等人的研究中，停戴后脉络膜的厚度恢复基线水平后持续减少，并伴随着眼轴的增长，这样的结果是否会加重近视的进展，值得以后进一步的观察[38]。除 OK 镜外，BreherK 等人的研究探讨了渐进性多焦点接触镜与脉络膜厚度的关系，发现配戴渐进镜后，脉络膜厚度虽有小幅度的增加，但跟配戴前相比无统计学意义，仍需要更多的证据来确定渐进性多焦点接触镜干预是否会影响脉络膜厚度[43]。目前大多数研究只探讨了角膜塑形镜对脉络膜厚度的影响，对于其它光学干预方式的研究尚少。在脉络膜厚度的日常节律变化方面，有动物研究发现近视性离焦可使脉络膜厚度日常的变化高峰提前，并使变化幅度下降，而远视性离焦使眼轴长度及脉络膜厚度变化幅度增加，对两者最高峰的出现时间无影响[33] [34]。光学干预方法是否会影响脉络膜厚度的节律，目前仍不清楚。

光学离焦引起脉络膜厚度出现变化的可能机制

Li Z 等人的实验表明脉络膜大血管直径的变化是脉络膜厚度变化的重要因素[40]，NO 可能是影响血管直径变化的原因，有实验发现使用一氧化氮合酶(nitric oxide synthase, NOS)阻滞剂后可抑制近视性离焦诱导的脉络膜增厚[44]。脉络膜血管周围同时还分布着大量的非血管性平滑肌[27]，脉络膜血管直径或许受到了非血管性平滑肌收缩及舒张的影响[45]。另一方面，在动物实验(豚鼠、小鸡)中发现，近视性离焦的条件下出现视黄酸(retinoic acid)水平的升高及粘多糖(proteoglycan)合成增多，远视性离焦则出现相反的结果，视黄酸与粘多糖的合成增多也许影响了脉络膜厚度的变化[46] [47]。

4. 户外活动与脉络膜厚度

户外活动时间增加对预防近视发生的作用大于对近视进展的作用，其可使近视的发生率降低，与室内活动相比，多种不同环境因素可能是户外活动控制近视发生发展的原因[8] [48] [49]。光照被认为是户外活动预防近视的重要因素，光照条件又可分为光照强度、频率、不同波长等不同因素[49]。一些实验在小鸡、猕猴的近视眼动物模型中发现光照因素对脉络膜厚度的变化有着重要的影响[50] [51] [52]。Nickla 等人使用 12 Hz 闪光刺激不仅抑制了小鸡近视眼的进展，还使脉络膜增厚[51]。而 Weizhong Lan 等人比较了不同光照度，发现强光照(15,000 lux)要比普通光照(500 lux)使小鸡脉络膜增厚更加显著[50]。除了光照强度对脉络膜厚度有影响，有实验发现相同光照度下，相比白光，长波长的红光引起的脉络膜增厚更加显著[52]。另一方面，Read、Pieterse 等人一项样本数为 22 例的研究中，每日早上 7 点对研究对象使用照度 506 lux 的蓝绿色光光疗 30 min，持续一周后发现黄斑中心凹下脉络膜厚度有统计学意义上的增加(平均增加+5.4 ± 10.3 μm) [53]。而 Jaemoon Ahn 等人让 27 名成年男性在晚上 20:00 到凌晨 12 点时段，先暴露在 150 lux 的光照下 2 晚，接着 5 晚暴露在 1000 lux 光照下，测量脉络膜厚度后发现相比前者的脉络膜厚度(268.00 ± 57.10 μm)，1000 lux 光照条件下黄斑中心凹下脉络膜厚度显著减少(245.37 ± 52.84 μm)，($p < 0.001$) [54]。上述两项研究出现了相反的结果，这可能与脉络膜厚度本身的日常节律变化有关。Nickla、Totonelly 等人使小鸡每天夜间暴露在 700 lux 的光照下 2 小时，持续 7 天后发现，在 18 点至凌晨 12 点间，相比夜间未暴露在光照下，实验组脉络膜厚度出现变薄，小鸡脉络膜厚度日常节律变化受到了光照条件的影响[55]。

光照条件引起脉络膜厚度出现变化的可能机制

光照条件下，脉络膜厚度增厚的机制可能与脉络膜血管血流量有关。Karl Heinz 等人的研究对比了光照及黑暗两种条件，发现从有光照条件切换到黑暗条件脉络膜血流量出现可逆性的下降，Antonio 等人的实验也证实了相比光照条件下，黑暗条件下脉络膜血流量出现下降[56] [57]。而 Sekaran 等人的实验表明光刺激可引起多巴胺及 NO 的释放增加，多巴胺受体阻滞剂却可抑制光刺激引起 NO 释放的影响[58]。光照条件下脉络膜血流量的变化可能与多巴胺及一氧化氮有关。另一方面，有研究发现黑素蛋白(melanopsin)可以影响脉络膜厚度在光照条件与黑暗条件下的变化。在 Bruce A 等人的研究中，光照情况下小鼠脉络膜厚度出现增厚，而敲除了与黑素蛋白相关基因的小鼠在光照情况下脉络膜厚度却无增厚[59]。

户外活动与近视的关系可能还受更少的近距离工作、更高水平的维生素 D、更多的体育运动等因素影响[49]，但目前尚无研究对比这些因素对脉络膜厚度的作用。

5. 其它

有研究发现近视患者行屈光矫正手术之后，脉络膜厚度较术前增厚，眼内植入人工晶体矫正也出现了脉络膜增厚的变化[60] [61]。其它如软性隐形眼镜、减少近距离工作等防控近视的方法是否对脉络膜厚度也有影响，尚缺乏相关的研究。

6. 小结与展望

综上所述，控制近视发生发展的不同干预方式可影响脉络膜的厚度，目前较多证据证明了阿托品、角膜塑形镜、光照条件都可影响脉络膜厚度的变化，但三者对脉络膜厚度的影响机制是否一样，目前尚不清楚，之后研究对比这 3 种不同情况对脉络膜厚度的作用将是一个重要方向。阿托品及光照的条件下，眼底组织都有多巴胺及 NO 的释放增多，多巴胺、NO 在两者的脉络膜厚度变化中作用机制仍不清楚，同时脉络膜厚度本身的生物节律变化也应当受到重视。少数研究还发现了角膜屈光手术及眼内植入人工晶体可使脉络膜厚度增厚[60] [61]，目前仍不清楚这种脉络膜厚度变化的过程在近视矫正过程扮演了怎样的角色。

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