·文献综述·

多巴胺及其受体对形觉剥夺近视发展的影响

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引用:邓宇,訾迎新,秦亚丽,等. 多巴胺及其受体对形觉剥夺近视发展的影响.国际眼科杂志 2020;20(2):279-281

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收稿日期:2019-05-15 修回日期:2019-12-30

摘要
我国近视人口已近6亿,青少年近视率居世界第一,近视已成为危害我国居民视力健康的主要疾病之一。多巴胺是视网膜中主要的儿茶酚胺,众多研究发现提高多巴胺含量可有效抑制近视的发展。形觉剥夺是一种经典的近视造模方法,通过观察多巴胺及其受体对形觉剥夺近视发展的影响,可以反映其在近视发展中的作用,对指导控制近视的发生发展具有重要意义。本文就多巴胺及其受体对形觉剥夺性近视发展的影响进行综述,以期为近视的防治提供参考。
关键词:多巴胺;多巴胺受体;近视;形觉剥夺;阿扑吗啡
DOI:10.3980/j.issn.1672-5123.2020.2.19

Effect of dopamine and its receptors on the development of visual deprivation myopia

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Received:2019-05-15 Accepted:2019-12-30

Abstract
• Myopic population of China is already nearly 600 million, the rate of teenager myopic occupies the first place in the world, myopia hsa already became one of the main diseases that endangers our adolescent's health. Dopamine is the main catecholamine in retina. Many studies have found that increasing the content of dopamine can effectively inhibit the development of myopia. Form-deprivation myopia is a classical method of myopia modeling. By observing the influence of dopamine and its receptors on the development of form-deprivation myopia, its role in the development of myopia can be reflected, and it is of great significance to guide and control the occurrence and development of myopia. In this paper, the effects of dopamine and its receptors on the development of form-deprivation myopia were reviewed in order to provide reference for the prevention and treatment of myopia.
• KEYWORDS: dopamine; dopamine receptors; myopia; form-deprivation; apomorphine

Citation: Deng Y, Zi YX, Qin YL, *et al*. Effect of dopamine and its receptors on the development of visual deprivation myopia. *Guoji Yanke Zazhi*(*Int Eye Sci*) 2020;20(2):279-281

0 引言
近视的在全球范围内均属于高发疾病,预计2050年全球近视人口将占总人口的52%[1]。我国小学生近视的发病率明显高于西方国家[2]。近视的发病原因复杂,危险因素众多,找出发病原因,提出控制近视发病和发展的有效手段,在近视的研究中至关重要[3]。在视网膜内,多巴胺(DA)是由位于内核层的多巴胺能无长突细胞(amacrine cells)和内网状细胞(interplexiform cells)分泌的神经递质[4]。1989年,Stone等[5]报道了在雏鸡形觉剥夺近视(FDM)模型中视网膜DA含量降低,同年在FDM恒河猴视网膜上又有了同样的发现[6]。之后相继在树鼩、豚鼠身上也发现了同样的变化。2008年,Rose等[7]提出光刺激能够产生DA,从而减缓近视发展的假说。Cohen等[8]、Li等[9]、Smith等[10]分别在鸡、豚鼠、恒河猴实验中证明,提高光照强度可以减缓近视的发展。Wang等[11]通过观察恒河猴FDM的发展,证明自然光照可以抑制近视的形成。Cohen等[12]通过对比不同光照强度下形觉剥夺雏鸡玻璃体腔DA浓度差异,证明近视的发生与受光照调控的DA分泌有关。目前,越来越多的研究表明眼球的发育与DA息息相关[13]。

1 DA的分泌及其影响因素
DA是视网膜中发现的主要儿茶酚胺,其由多巴胺能无长突细胞和内网状细胞合成并释放[14]。DA释放受光照强度影响较大,具有昼夜节律,白天释放量高,晚上释放量低[15]。光通过控制细胞耦合调节视网膜DA的昼夜节律,在不同时间注射DA受体拮抗剂将产生不同结果[16]。研究表明,高光照水平可以延缓FDM的发展[17],这种作用是由无长突细胞活动驱动视网膜DA释放产生的[18]。光诱导DA释放的变化可能是增加户外活动时间能降低近视发病率的基础[7]。Cohen等[12]在形觉剥夺模型鸡的

实验中发现形觉剥夺鸡屈光度数的发育与光照依赖性的 DA 分泌有关。Chen 等[19]对 FDM 小鼠的研究发现,明亮光可增加一氧化氮(ON)通路中双极细胞多巴胺 D1 类受体活性,而其活性的增加降低了眼轴的生长及近视的发展,故认为明亮光抑制小鼠 FDM 发展的作用与刺激 ON 通路,增加多巴胺 D1 类受体的活性有关。而早先报道发现眼球的生长速度受 ON 通路的控制[20]。

2 视网膜 DA 含量对 FDM 的影响

2.1 视网膜 DA 含量增加对 FDM 的影响 Jiang 等[21]研究发现,葡萄糖酪氨酸酶依赖性多巴胺能系统参与豚鼠 FDM 的发展,增强葡萄糖酪氨酸酶活性可能会增强多巴胺能系统活性,减缓近视的发展。Luo 等[22]发现 FDM 小鼠 DA 水平呈下降趋势。左旋多巴(L-DOPA)是 DA 前体,增加 L-DOPA 的含量可以促进 DA 的合成。Mao 等[23]对 FDM 豚鼠腹腔注射 L-DOPA,结果发现腹腔注射 L-DOPA可抑制 FDM 的发展。在对白化豚鼠球周注射 L-DOPA的实验中也得到同样的结果[24]。阿扑吗啡(APO)是一种多巴胺受体激动剂,其与视网膜内 D2 受体的亲和度是 D1 受体的 22 倍[25]。Dong 等[26]对豚鼠结膜下注射 APO 发现其能抑制 FDM 的进展,另有研究在鸡[27]、猴[28]等动物模型上也有类似的发现。Yan 等[13]对小鼠腹腔注射 APO,同样观察到 APO 对 FDM 具有抑制作用,该研究还发现持续泵入 DA 对 FDM 无抑制效果。Huang 等[29]对 D1、D2 类受体基因敲除小鼠玻璃体腔注射 APO,结果发现 D1 类受体参与了 APO 对 FDM 的抑制过程,而 D2 类受体无特殊作用。此外,非选择性多巴胺受体激动剂 2-氨基-6,7-二羟基-1,2,3,4-四氢化萘(2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene,ADTN)也被证实对 FDM 有抑制作用[30]。Mao 等[31]发现玻璃体腔注射胞磷胆碱可抑制豚鼠 FDM 的发展,并增加其视网膜的 DA 水平。

2.2 视网膜 DA 含量减少对 FDM 的影响 6-羟基多巴胺(6-OHDA)是一种非选择性多巴胺能神经元抑制剂,关于 6-OHDA 的研究较为复杂。研究发现,6-OHDA 可以抑制 FDM 的形成[32],这与 DA 可以抑制 FDM 发展的假说相矛盾[33]。推测可能与 6-OHDA 非选择性抑制儿茶酚胺能神经元有关[34],也有学者认为 DA 的作用与视网膜 DA 浓度无关,而与 DA 分泌昼夜节律的振幅有关[35]。Wu 等[36]对 FDM 和正常视觉鼠玻璃体腔注射 6-OHDA,两组动物均观测到了眼轴变短、角膜屈光度变大的现象。

3 DA 受体对 FDM 的影响

3.1 D2 受体对 FDM 的影响 目前研究发现,视网膜内存在两种 DA 受体,其中 D1 类受体包括 D1、D5 受体,D2 类受体包括 D2、D3、D4 受体[37]。D1 受体可以刺激细胞内环磷酸腺苷(cAMP)的分泌,而 D2 受体可以抑制其合成[38]。大量实验证据表明,DA 激动剂对 FDM 的抑制作用可以通过刺激 D2 受体介导[39]。Ward 等[40]在树鼩 FDM 实验中发现,激动多巴胺 D2 受体通路可抑制 FDM 的发展,而 D1 受体通路对 FDM 的发展无明显改变。Stone 等[41]关于 D2 受体拮抗的研究也得到了相似的结论。喹吡罗是一种特异性的 D2 受体激动剂。Nickla 等[42]研究发现喹吡罗可抑制 FDM 的发展,而 D1 受体激动剂 SKF-38393 无明显作用。McCarthy 等[43]对 FDM 模型鸡分别在光条件和暗条件下去遮盖 3h,光组玻璃体内注射 D1、D2 类受体拮抗剂,暗组玻璃体内注射 D1、D2 受体激动剂,实验结果表明 FDM 模型鸡短时间内给予去剥夺,对 FDM 发展的抑制作用是通过增加 D2 受体活性实现的,但单独抑制 D2 受体活性对正常情况下动物眼部的发育无明显影响[44]。也有研究认为,D2 受体激动剂在低剂量时可抑制 FDM,在高剂量时可增强 FDM 的发展[32]。然而,也有研究结果与上述结论不符,Zhang 等[37]对 FDM 花豚鼠的实验结果则表明 D2 受体活化具有增强 FDM 的作用;Huang 等[44]通过对比 D2 受体基因敲除小鼠和正常小鼠玻璃体腔注射 D2 受体拮抗剂舒必利(sulpiride)后 FDM 程度的变化,证明 D2 受体激活产生的 DA 是促进小鼠 FDM 形成的主要原因。

3.2 D1 受体对 FDM 的影响 Zhang 等[37]研究发现 D1 受体活化可抑制 FDM 的发展。Huang 等[44]对 D1 受体、D2 受体基因敲除小鼠腹腔注射 APO,结果发现 D2 受体基因敲除小鼠和正常组鼠腹腔注射 APO 可明显减轻 FDM 的形成,认为多巴胺受体激动剂 APO 是通过 D1 受体活化对 FDM 产生抑制作用。

4 总结

众多研究表明,增加视网膜 DA 含量可有效抑制 FDM 的发展,但其具体作用的方式、作用受体、影响因素仍需要进一步研究。多巴胺 D2 类受体激活可以抑制 FDM 的发展,D1 类受体的作用尚不明确,但有关 D1、D2 类受体的作用仍存在争议,部分研究结果仍有分歧,产生这种分歧的原因可能与多巴胺受体激动剂/抑制剂复杂的药理作用有关,且尚缺乏不同物种 D1、D2 类受体在视网膜中分布特性的相关研究[45]。另有研究发现 D1、D2 类受体在视网膜上活动的平衡可能是影响眼部发育及 FDM 发展的重要因素[46]。因此,有关 DA 及其受体在近视发展中的作用仍需要进一步深入研究。

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