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P2X7R在小檗碱缓解小鼠慢性视网膜光损伤中的机制研究^{*}

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【摘要】目的 探究P2X7R在小檗碱(berberine, BBR)缓解慢性视网膜光损伤小鼠中的动态变化趋势及相关作用机制。**方法** 90只小鼠随机分为空白对照组10只, LD组40只, LD+BBR组40只, 后两组给予低能量(500 lux)蓝光照射(12 h/d)持续3个月, LD+BBR组在光照同时予200 mg/kg BBR灌胃。光照及灌胃结束后, 取小鼠眼部组织, 通过HE染色观察BBR对慢性视网膜光损伤小鼠的保护作用, TUNEL观察BBR对慢性视网膜光损伤小鼠凋亡细胞的影响, 实时荧光定量PCR检测P2X7受体在BBR缓解慢性视网膜光损伤中的表达情况。**结果** 与空白对照组比较, LD组小鼠视网膜形态异常, 部分神经节细胞核缩小, 染色变深, 排列松散; 内核层细胞排列略松散; 外核层细胞混乱排列, 视网膜外核层厚度(47.11 ± 2.01) μm ; 视网膜外核层出现大量凋亡细胞, 凋亡率为(71.16 ± 5.99)%, 差异有统计学意义($P < 0.05$)。与LD组比较, LD+BBR组小鼠视网膜形态出现轻度异常, 神经节细胞松散排序; 视网膜内、外核层细胞形态略完整、染色均匀、排列紧密; 外核层厚度为(54.07 ± 2.05) μm , 视网膜外核层有少量凋亡细胞, 凋亡率为(16.02 ± 2.68)%, 差异有统计学意义($P < 0.05$)。与空白对照组比较, LD组小鼠视网膜中P2X7R mRNA的相对表达量上调, 二者差异有统计学意义($P < 0.05$); LD+BBR组小鼠视网膜P2X7R mRNA的相对表达量下调, 差异无统计学意义, 但与LD组相比, 视网膜P2X7R mRNA的相对表达量呈现明显下降趋势, 且二者差异有统计学意义($P < 0.05$)。**结论** BBR具有缓解小鼠慢性视网膜光损伤的作用, 并抑制了P2X7R的激活进而阻止视网膜光损伤的形成。

【关键词】 P2X7受体 小檗碱 视网膜光损伤 年龄相关性黄斑变性

Berberine Alleviates Chronic Retinal Light Damage in Mice: A Study of the Role of P2X7R and the Mechanisms Involved DAI Leshu^{1,2}, YE Shanshan¹, SONG Zixuan³, SONG Jiantao^{1△}. 1. Eye Hospital, China Academy of Chinese Medical Sciences, Beijing 100040, China; 2. Institute of Basic Theory of Traditional Chinese Medicine, China Academy of Chinese Medical Sciences, Beijing 100007, China; 3. Southern Medical University, Guangzhou 510515, China

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[Abstract] Objective To investigate the trend of dynamic changes and the mechanisms of P2X7R by which berberine (BBR) alleviates chronic retinal light injury in mice. **Methods** A total of 90 mice were randomly divided into three groups, a blank control group ($n = 10$), a group exposed to low-intensity blue light (500 lux) for 12 hours per day for a duration of 3 months, which was referred to as the LD group ($n = 40$), and another group given BBR at a dose of 200 mg/kg via gastric gavage on top of the blue light exposure for the LD group, which was referred to as the LD + BBR group ($n = 40$). After the light exposure and gavage were completed, eye tissues were collected from the mice. Hematoxylin and eosin (HE) staining was performed to observe the protective effects of berberine on chronic retinal light damage in mice. TUNEL assay was performed to assess the effect of berberine on apoptotic cells in mice with chronic retinal light injury. Additionally, quantitative polymerase chain reaction (QPCR) was performed to assess the expression level of P2X7 receptors in chronic retinal light injury relieved by BBR. **Results** Compared with the blank control group, the LD group exhibited abnormal retinal morphology, with some ganglion cells displaying reduced nuclei, a deeper stain, and loose arrangement. In the LD group, the cells in the inner nuclear layer appeared to be slightly more loosely arranged, while the cells in the outer nuclear layer cells were arranged in a disorderly way. Furthermore, the thickness of the outer nuclear layer of the retina from mice in the LD group was (47.11 ± 2.01) μm , and a significant number of apoptotic cells were observed in the outer nuclear layer, resulting in an apoptosis rate of (71.16 ± 5.99)% ($P < 0.05$). In contrast, the LD + BBR group showed mild abnormal retinal morphology with loosely arranged ganglion cells. In the LD + BBR group, the cells in both inner and outer nuclear layers of retina exhibited relatively intact morphology, uniform staining pattern, and tight arrangement. Moreover, the thickness measurement for outer nuclear layer revealed a value of (54.07 ± 2.05) μm , and there were only a few apoptotic cells present, resulting in an apoptotic rate of (16.02 ± 2.68)% ($P < 0.05$). Compared

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with that of the blank control group, the relative expression of *P2X7R* mRNA in the retinas of the LD group was upregulated, with the difference between the two groups being statistically significant ($P < 0.05$). The relative expression of *P2X7R* mRNA in the retinas of the LD + BBR group was downregulated, showing no statistical significance compared with that of the blank control group. However, compared with that of the LD group, the relative expression of *P2X7R* mRNA in the retinas of the LD + BBR group showed a significant downward trend, and the difference between the two groups was statistically significant ($P < 0.05$). **Conclusion** Berberine can alleviate chronic retinal photodamage in mice, and inhibit the activation of *P2X7R*, thereby preventing the formation of retinal photodamage.

[Key words] *P2X7* receptors Berberine Retinal photodamage Age-related macular degeneration

近年来,随着科学技术和社会经济的高速发展,光污染等问题逐渐成为危害人类视力健康的杀手,视网膜作为接收和传导光的敏感组织,在过度的光暴露下会引发其结构和功能的异常变化,严重影响人类视力健康。视网膜光损伤是导致年龄相关性黄斑变性(age-related macular degeneration, AMD)等视网膜疾病发病的重要致病因素^[1]。2020年AMD的全球患病率为1.96亿,预计到2040年将达到2.88亿。2015年,AMD是导致中度或重度视力障碍的主要原因,占全球法定失明的6%~9%^[2-4]。

但视网膜光损伤的发病机制尚未完全揭示,近年研究发现*P2X7*受体(*P2X7 receptor*, *P2X7R*)可能在光损伤的病理变化中发挥重要作用^[5-7]。本课题组前期通过小檗碱(berberine, BBR)干预急性视网膜光损伤小鼠,结果显示小檗碱具有抗氧化应激、抗炎症反应、改善视网膜功能并减少感光细胞损伤等作用^[8]。慢性光损伤更符合AMD的发病机制,为更好模拟AMD损伤时的病理状态,故本研究模型采用国内外较多使用的慢性蓝光视网膜损伤小鼠模型^[9],以*P2X7R*为切入点探究视网膜光损伤的可能内在机制以及BBR缓解小鼠视网膜光损伤的作用机制,以期对AMD治疗及其机制提供实验依据。

1 材料与方法

1.1 主要试剂与仪器

小檗碱(B802465)购于上海麦克林生化科技有限公司。HE试剂盒、抗荧光衰减封片剂购于北京博奥森生物技术有限公司, Triton-100、50xTAE溶液购于北京优尼康生物科技有限公司, SYBR® Premix Ex Taq™ II (Tli RNaseH Plus)、PrimeScript™ RT reagent Kit with gDNA Erase购于TaKaRa, DAPI染色液购于BD Pharmingrn™, 冰冻包埋剂(O.C.T)购于美国SAKURA公司, 引物合成购于GENEWIZ。EG1150模块化组织包埋中心、HI1210石蜡展片机、RM2245轮转式切片机、DM2500显微镜、CM1850冰冻切片机, 德国Leica公司; UNI382工业级照度计, UNI-T优利德公司; IX2-ZDC荧光倒置显微镜, 日本Olympus公司; PCR仪MP-32、迷你离心机Mini-10K+C,

杭州米欧仪器有限公司; 荧光定量PCR仪 ABI7500, Applied Biosystem公司。

1.2 实验动物及造模

SPF级雄性C57BL/6J小鼠90只, 约8~10周龄, 体质量(20±2)g, 购自北京维通利华实验动物技术有限公司, 生产许可证号SCXK(京)2016-0006, 遵循实验动物伦理委员会要求(批准号: YKEC-KT-2024-038-P002)。每笼5只饲养在中国中医科学院眼科医院动物房(清洁级), 自由进食和饮水, 温度21~23℃, 相对湿度40%~70%, 光照条件按照12h昼夜节律, 适应性饲养1周后进行实验。对LD组与LD+BBR组进行慢性光损伤造模, 每天6:00-18:00将小鼠置于LED蓝光下照射12h, 采用低能量(500 lux)蓝光照射, 其余夜晚时间处于暗环境中, 此模式下照射3个月。

1.3 动物分组及给药

C57BL/6J小鼠90只, 随机取10只为空白对照组, 剩余80只随机分两组, 即模型组(LD组)与灌胃组(LD+BBR组)。

给药剂量: 配制浓度200 mg/kg的灌胃溶液, 制作方式称取300 mg小檗碱和15 mL PBS缓冲液, 混合后放置在涡旋仪上震荡直至药物溶解。小鼠灌胃体积=(200 mg/kg)/(300 mg/15 mL)×小鼠体质量(kg)。每周监测小鼠体质量, 根据体质量变化调整给药剂量。

给药方法: 光照开始时同时灌胃, 每周连续灌胃4d, 停药3d。直至光照结束。LD+BBR组予配置好的小檗碱溶液灌胃, LD组予等量的PBS缓释液灌胃。

1.4 小鼠视网膜组织病理学HE染色

光照3个月结束后(光照结束后第0周), 取空白对照组、LD组、LD+BBR组各6只右眼, 进行视网膜组织取材, 放入体积分数为4%多聚甲醛固定, 梯度乙醇脱水处理, 随后组织包埋, 沿视神经长轴方向以4 μm连续切片, 而后用常规HE染色, 封片后光学显微镜观察记录视网膜各层变化。

1.5 小鼠视网膜细胞凋亡检测

TUNEL法观察细胞凋亡情况, 光照3个月结束后(光照结束后第0周)取正常对照组、LD组、LD+BBR组各5只

左眼,进行组织取材、固定、包埋,冰冻切片机切片,沿视神经长轴方向行8 μm切片,每一张片上收集2~3个样本,常规TUNEL法染色,用荧光倒置显微镜观察染好的组织,分别用绿光和紫外光进行激发,随机选空白对照组、LD组和LD+BBR组各3张切片,拍摄时以视神经为中心,左右两侧各选取2个视野进行拍片,分别计数每一个视野内外核层细胞总数和外核层凋亡细胞数,将所得数据进行凋亡率计算,外核层凋亡率(%)=外核层凋亡细胞数/外核层细胞总数×100%。

1.6 实时荧光定量PCR

于光照结束后的第1周、第2周、第3周,取正常对照组、LD组、LD+BBR组各3只小鼠。使用TRIzol法提取小鼠视网膜组织总RNA,进行浓度和纯度测定,使用分光光度计测量RNA浓度和260/280、260/320吸光度比值,使用Agilent 2100 bioanalyzer检测RNA完整性,对样品进行质控。将RNA转录为cDNA,反应体系为SybrGreen qPCR Master Mix 10 μL, ROX 0.4 μL, dH2O 4.6 μL, cDNA 4 μL, 上下游引物各0.5 μL。反应条件为95 ℃预变性30 s; 95 ℃ 5 s, 60 ℃ 34 s, 循环40次扩增。以Actin为内参,采用 $2^{-\Delta\Delta Ct}$ 相对定量计算公式进行计算和分析mRNA相对表达量,引物序列详见表1。

表 1 引物序列
Table 1 Primer sequences

Gene	Primer sequences (5' to 3')	Product length/bp
P2X7R	F: TGTCCCTATCTCTCCACGACTCAC	119
	R: ATTTCCACACTGGCACCAACTCGG	
Actin	F: TGGGAATGGGTCAGAAGGA	289
	R: ATTGAGAAAGGCGCTGGC	

1.7 统计学方法

使用Graphpad Prism 10进行统计分析。符合正态分布的计量资料以 $\bar{x} \pm s$ 表示,通过方差齐性检验组间比较采用单因素方差分析,方差不齐时采用两独立样本非参数检验Mann-Whitney U检验,组间两两比较采用

Bonferroni法。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 视网膜病理组织HE染色结果

由图1可见,空白对照组视网膜外核层厚度为(62.72±2.86) μm,形态未见异常,无明显病理变化,各层结构规整。神经节细胞核规整排列;内、外核层细胞核形态完整、染色均匀、排列紧密;光感受器细胞内外节边界清晰、排列规则。

光照及PBS缓释液灌胃3个月后,LD组视网膜外核层厚度为(47.11±2.01) μm,比空白对照组薄($P < 0.01$)。视网膜形态异常,各层结构发生变化,部分神经节细胞核松散排列,染色变深;内核层细胞核略有松散排列;外核层排列混乱无序,可见部分细胞核出现了核的聚集、浓缩且染色变深的现象;感光细胞内节和外节紊乱排列,视杆外节同样可见紊乱排列,部分膜盘间隙出现断裂。

光照及小檗碱灌胃3个月后,LD+BBR组视网膜外核层厚度为(54.07±2.05) μm,较空白对照组更薄($P < 0.05$),较LD组略厚($P < 0.01$)。视网膜形态略有异常,神经节细胞排列稍稀疏;内核层、外核层细胞核形态略完整、染色均匀、排列紧密;光感受器细胞内外节排列略有混乱。

2.2 TUNEL检测视网膜外核层细胞凋亡

荧光显微镜下染色后的凋亡细胞呈紫红色,呈现“环形”和“新月形”等典型阳性凋亡细胞。见图2。空白对照组小鼠视网膜组织中未见明显阳性凋亡细胞。经过3个月低能光照后,LD组小鼠视网膜组织中出现大量TUNEL阳性细胞,且细胞核皱缩,染色质凝结成密集的团块,大部分聚集在核膜下,阳性凋亡细胞多于空白对照组($P < 0.01$),凋亡率为(71.16±5.99)%。在BBR干预条件下,LD+BBR组凋亡率为(16.02±2.68)%,凋亡细胞较LD组变少($P < 0.01$),但仍多于空白对照组($P < 0.05$)。

2.3 PCR检测小鼠视网膜P2X7R mRNA的动态表达

各组小鼠视网膜P2X7R mRNA的相对表达量见表2。

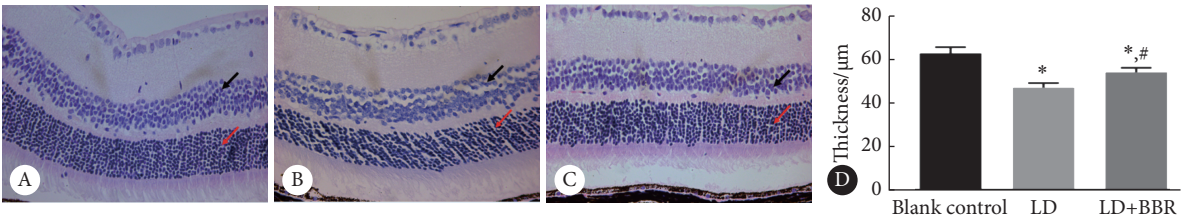


图 1 小鼠视网膜全层切片HE染色(×400)和视网膜外核层厚度

Fig 1 Whole-layer slices of mouse retina were stained by HE (original magnification×400) and thickness of outer nuclear layer of mouse retina

A, Blank control group; B, LD group; C, LD + BBR group. The red arrows indicate the outer nuclear layer of the retina, and the black arrows indicate the inner layer of the retina. D, Thickness of outer nuclear layer of mouse retina ($n = 6$). * $P < 0.05$, vs. blank control group; # $P < 0.05$, vs. LD group.

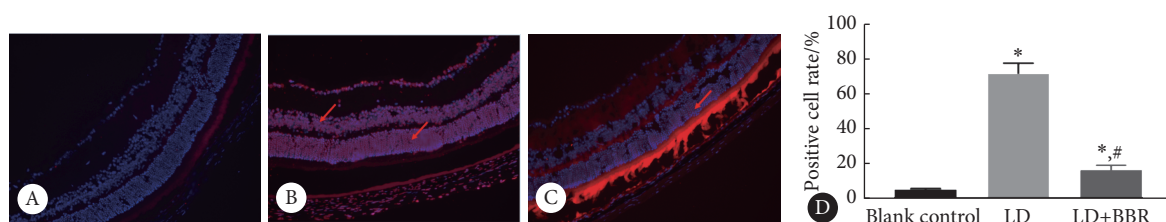


图 2 TUNEL检测各组小鼠视网膜细胞凋亡情况 (×200)

Fig 2 TUNEL assay to assess apoptosis of retinal cells in each group of mice (original magnification × 200)

A, Blank control group; B, LD group; C, LD + BBR group. The red arrows indicate positive apoptotic cells. D, Apoptosis cells in the ONL layer of the retina of mice in different groups ($n = 5$). * $P < 0.05$, vs. blank control group; # $P < 0.01$, vs. LD group.

表 2 光照结束后第1、2、3周各组视网膜P2X7R mRNA的相对表达量 ($\bar{x} \pm s$, $n=3$)

Table 2 The relative expression of P2X7R mRNA in the retina of mice from different groups at 1, 2, and 3 weeks after the end of irradiation ($\bar{x} \pm s$, $n = 3$)

Group	Time	Relative expression
Blank control	/	$1.00 \pm 0.44^{\#}$
LD	1 week	$1.94 \pm 1.04^*$
	2 weeks	$1.61 \pm 0.79^*$
	3 weeks	$1.47 \pm 1.04^*$
LD + BBR	1 week	$0.67 \pm 0.16^{\#}$
	2 weeks	$0.86 \pm 0.21^{\#}$
	3 weeks	$0.76 \pm 0.13^{\#}$

The abbreviations are explained in the note to Fig 2. * $P < 0.05$, vs. blank control group; # $P < 0.05$, vs. LD group.

与空白对照组比较,光照结束后的第1周、第2周、第3周,LD组小鼠视网膜P2X7R mRNA表达上调,虽然P2X7R mRNA的表达在3周内呈现下降趋势,但仍高于空白对照组,差异有统计学意义($P < 0.05$);光照结束后3周内,LD+BBR组小鼠视网膜P2X7R mRNA表达呈上升趋势,组内各时间点差异无统计学意义,与LD组比较,LD+BBR组各时间点P2X7R mRNA表达均下调,差异有统计学意义($P < 0.05$)。

3 讨论

视网膜光损伤的病理变化主要围绕细胞凋亡、氧化应激、炎症反应等^[6-7]。光损伤会引发视网膜变性以及感光细胞凋亡,最终出现视力丧失。P2X7R属于嘌呤受体的亚型,嘌呤受体在许多慢性炎症性疾病中起重要作用^[9-10],正常生理条件下,P2X7R保持较低活性水平,随年龄增长视网膜色素上皮(retinal pigment epithelial, RPE)中的P2X7R上调,或在氧化应激和炎症刺激下,RPE细胞或视网膜细胞会释放大量的三磷酸腺苷(adenosine triphosphate, ATP),而ATP是内源性P2X7R激动剂,P2X7R

的激活会打开一个可渗透小阳离子(Na^+ , Ca^{2+} , K^+)的膜通道,若ATP大量累积,膜通道会从小阳离子通道变为更宽的孔,从而允许高达900 Da的分子通过,进而促使RPE细胞凋亡^[11]。P2X7R的激活可导致不同细胞死亡,例如RPE细胞的凋亡和感光细胞坏死^[12],免疫细胞的凋亡和坏死^[11],取决于P2X7R激动剂的剂量和持续时间以及细胞类型。在视网膜出血的小鼠模型中,选择性的P2X7R拮抗剂(brilliant blue G, BBG)可阻止感光细胞凋亡^[13],这表明内源性激动剂ATP激活P2X7R后可能介导了视网膜下出血的感光细胞凋亡。通过使用P2X7R敲除小鼠模型也证明了P2X7R依赖的感光细胞凋亡^[14]。P2X7R是氧化应激的关键因素^[15]。本研究通过慢性光刺激造成小鼠视网膜损伤模型,并经过小檗碱干预,P2X7R作用结果与上述实验相似。从HE、TUNEL检测观察光照后LD组小鼠视网膜出现病理变化,观察到神经节细胞核排列松散,染色加深;内核层细胞核略有松散排列;外核层细胞核混乱排序,出现大量凋亡细胞等,经BBR干预后视网膜凋亡细胞明显减轻。且发现P2X7R参与了视网膜光损伤所引发的相关病理反应,显示小檗碱可抑制P2X7R的激活进而阻止视网膜光损伤的形成。

小檗碱是从中药黄连提取的一种生物碱,《神农本草经》中载“黄连味苦、寒,主治热、目痛、眦伤、泣出、腹痛、明目作用等”。选取黄连的理论基础来源于对“光毒”理论的认识及临证经验^[16-17],认为AMD的发病机制,不仅局限于肝肾亏虚,创新性提出“光毒”是AMD形成的重要致病因素,黄连具有清热解毒明目的作用,中医理论通过现代科学研究得以验证,黄连的中药成分小檗碱抗氧化应激、抗炎作用,从而起到缓解视网膜光损伤的作用。小檗碱在心血管、神经、脂代谢、糖代谢、抗炎、抗肿瘤和胃肠道等多领域应用安全好^[18-19],可连续安全口服。

本研究结果显示持续蓝光照射可建立稳定的小鼠慢性视网膜光损伤模型,小檗碱通过抑制P2X7R的激活而缓解小鼠慢性视网膜光损伤。在造模结束后3周的动态变化监测中,以空白对照组为标准比较两组变化趋势。

LD组小鼠经光照后视网膜表达出大量的P2X7R mRNA,这与HE病理检测和TUNEL细胞凋亡检测结果一致,表明小鼠视网膜出现光损伤特征,而P2X7R mRNA的表达在3周内呈现下降趋势,但仍高于空白对照组,这也表明慢性光损伤的形成即使在停止光照后仍存在视网膜光损伤的特征,推断光照所带来的损伤在短期内是不可逆的。LD+BBR组小鼠视网膜P2X7R mRNA的表达量出现明显下调的趋势,且3周内与空白对照组接近,提示在小檗碱干预下P2X7R的激活受到明显的抑制,表明P2X7R具有抑制视网膜光损伤形成的作用,而在此3周内已停止小檗碱的干预,这亦表明小檗碱作用有一定持续性。LD+BBR组P2X7R mRNA的表达量随着时间延长呈现出上升趋势,小檗碱的有效治疗效应能持续多久,对于AMD这种慢性病给药方法,包括给药途径、给药频度;以及P2X7R拮抗剂、激动剂在视网膜光损伤类疾病中的真实作用等仍需进一步探究,有望为临床治疗慢性视网膜光损伤类疾病提供理论支撑。

* * *

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