引文格式:马誉铴,刘鹤南,底煜,陈晓隆. 直接肾素阻滞剂 Aliskiren 预防早产儿视网膜病变[J]. 眼科新进展,2015,35(4):393-396. doi:10.13389/j.cnki.rao.2015.0107

【文献综述】

直接肾素阻滞剂 Aliskiren 预防早产儿视网膜病变△

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收稿日期:2014-05-29
修回日期:2014-06-20
本文编辑:付中静
△**基金项目**:辽宁省科技厅基金资助(编号:2013225049);沈阳市科技专项基金资助(编号:F13-220-9-37)
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Received date: May 29, 2014
Accepted date: Jun 20, 2014
Foundation item: Department of Technology Foundation of Liaoning Province (No: 2013225049); Science and Technology Project Foundation of Shenyang (No: F13-220-9-37)
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Direct renin inhibitors Aliskiren preventing retinopathy of prematurity

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【Key words】 renin-angiotensin system; retinopathy; premature infant; Aliskiren; vascular endothelial growth factor

【Abstract】 Renin, a upstream growth factor of renin angiotensin system (RAS), has the effects of specific-speed-limiting on the RAS chain. In many ischemic retinopathy cases such as retinopathy of prematurity (ROP), as the RAS increases, the RAS of retina is activated, which might stimulate the rise of vascular endothelial growth factor (VEGF), result in vascular pathological changes, led to the leakage of blood vessels and the proliferation of vascular endothelial cell and neovascularization. Being adopted as a new way of blocking the RAS, Aliskiren plays a distinctive role in the process of preventing and abating pathological angiogenesis. The application of Aliskiren is becoming a promising approach for the prevention and treatment of ROP.

【关键词】 肾素-血管紧张素系统;视网膜病;早产儿;Aliskiren;血管内皮生长因子

【摘要】 肾素作为肾素-血管紧张素系统(renin-angiotensin system,RAS)中上游生长因子,对 RAS 链起着特异性限速的作用。在早产儿视网膜病变等缺血性视网膜病变中,RAS 上调,视网膜 RAS 被激活,刺激血管内皮生长因子等上调,导致血管渗漏、血管内皮细胞增生和新生血管形成等血管病理性改变。直接肾素抑制剂 Aliskiren 作为阻断 RAS 的新途径,在防止和减弱病理性血管生成的过程中发挥了明显作用。Aliskiren 的应用有望成为早产儿视网膜病变的预防及治疗途径。

早产儿视网膜病变(retinopathy of prematurity,ROP)是早产儿严重的视网膜病变,是导致患者失明的重要原因,其发病率与患儿的胎龄、体质量及吸氧有关,ROP 病理学表现以新生血管和纤维组织化瘢痕形成等为主要特征,上述病理改变与肾素-血管紧张素系统(renin-angiotensin system,RAS)以及血管内皮生长因子(vascular endothelial growth factor,VEGF)有密切关系。已有研究表明,阻断 RAS 有预防 ROP 的作用,肾素抑制剂 Aliskiren 作为阻断 RAS 的上游抑制剂,有望为我们认识和防治 ROP 提供新的思路。本文就近年来有关 RAS 和 VEGF 在 ROP 中的作用机制,以及 Aliskiren 对 RAS 的阻断作用进行综述。

1 ROP

ROP 是早产儿的未成熟视网膜在各种因素互相作用、影响下发生的一种视网膜新生血管(retinal neovascularization,RNV)形成和纤维异常增生的视网膜增生性病变,可导致视力下降、视野缺损甚至失明[1]。随着围产医学的进步,以及新生儿监护病房(NICU)的发展,早产低出生体质量儿生存率不断提高,而 ROP 的发生率也呈逐年增多之势。预防和治疗 ROP 已成为提高早产低出生体质量儿生活质量、减少社会压力及经济负担的重要课题。

孕龄小、出生体质量低和高浓度吸氧为已知的 ROP 发病因素,其病理特征为:正常视网膜血管发育的停滞和微血管的退化;局部缺血和视网膜缺氧导致血管异常增殖;血管异常增殖导致纤维瘢痕形成和视网膜剥离[2]。目前治疗 ROP 较为有效的方法以冷凝[3]、氩离子激光治疗[4]、二极管激光治疗[5]、巩膜扣带术[6]、玻璃体切割术[7]、玻璃体内注射 Bevacizumab 药物治疗[8]等为主。近年来不断对 ROP 发病机制进行深入的研究,发现 RAS 在 ROP 的发生、发展及转归中起着相当重要的作用[9]。近年来在早期预防及治疗 ROP、抑制 RNV 形成的研究中,RAS 系统阻滞剂受到广泛关注。

2 RAS 系统及其主要成员

关于 RAS 的研究已有近百年的历史,近些年来

不断有新的生物活性血管紧张素肽和受体以及其相互作用机制被发现,RAS 也更为复杂。肾素原(Prorenin)是肾素的前体,比肾素多 43 个氨基酸,呈低活性,在内肽酶作用下,通过非蛋白水解和蛋白水解机制,肾素原被降解为肾素。2002 年,Nguyen 等[10]首次报道从人的肾小球系膜细胞中发现并克隆了肾素原受体(prorenin receptor,RnR),从而证实了人体中肾素原受体的存在。RnR 的序列分析表明它拥有多重身份:H^+ 载体、ATP 酶、内质网Ⅰ型跨膜接头前体和溶酶体辅助蛋白 2。因此,RnR 在细胞的生化反应过程中发挥出重要作用[11]。肾素原与 RnR 结合非蛋白水解后可产生酶活性,使血管紧张素原(Angiotensinogen,AGT)向血管紧张素Ⅰ(AngⅠ)的转化率提高 4 倍,并激活 MAPK 信号转导通路(ERK1/2)。AGT 的 N 端释放的 AngⅠ再经过血管紧张素转化酶(Angiotensin converting enzyme,ACE)作用生成血管紧张素Ⅱ(AngⅡ)[12],而后在血浆和组织中经血管紧张素酶 A 的作用成为 AngⅢ。其中 AngⅡ活性最大,其生理作用是由 AngⅡ 1 型受体(AT1R)和 AngⅡ 2 型受体(AT2R)介导的。AngⅡ直接或通过上调 VEGF、转化生长因子 p(TGF-p)、胰岛素样生长因子和血小板衍生生长因子(platelet derived growth factor,PDGF)等作用于血管平滑肌细胞,诱导细胞生长、增生以及细胞外基质蛋白质类沉积来发挥促新生血管生成的作用[13-14]。

3 VEGF

VEGF 是主要的眼内新生血管形成因子[15],它参与血-视网膜屏障的破坏,于 ROP 疾病的早期出现,并持续存在于整个疾病过程中[16]。增生性糖尿病视网膜病变(proliferative diabetic retinopathy,PDR)、视网膜静脉阻塞、早产儿视网膜病变等疾病的共同特征是新生血管形成。RAS 系统中主要效应介质 AngⅡ可能与特异性生长因子(特别是 VEGF)相互作用导致 RNV 形成,影响视网膜的发育和功能[9],可促进内皮细胞分裂、增殖、迁移,在调节血管新生中发挥重要作用。VEGF 基因家族包括 VEGF-A、VEGF-B、VEGF-C、VEGF-D 和 PDGF[17],其中 VEGF-A(通常称为 VEGF)与肿瘤的血管新生关系密切,VEGF 在人体的脑、肾、肝、脾、肺、眼等许多组织器官中广泛分布,其基因位于 6 号染色体短臂的 p12 ~ p21,转录的 mRNA 以多种剪切方式形成 5 种异构体:VEGF121、VEGF145、VEGF165、VEGF189、VEGF206,每种异构体可结合成有活性的二聚体,共同构成 VEGF 家族的 6 个亚型[18]。VEGF 有 4 种受体:VEGFR1、VEGFR2、VEGFR3、NRP-1。VEGF-A、VEGF-C、VEGF-D 与 VEGFR1/KDR 结合同血管新生关系密切[19]。VEGFR2 在参与血管生成的内皮细胞中高表达,VEGF 的信号主要通过它转导。VEGF 与 VEGFR2 结合后,VEGFR2 发生二聚化和磷酸化,激活下游信号通路,刺激内皮细胞增殖,同时诱导内皮细胞迁移,促使血管生成[20]。

4 直接肾素抑制剂 - 阿利吉仑

阿利吉仑(Aliskiren)为第 2 代直接肾素抑制剂,分子式为 $C_{30}H_{53}N_3O_6$,相对分子质量为 609.8,是小分子口服直接肾素抑制剂,是一个亲水性分子,水溶性好[21],生物利用度较高,在动物实验中有较好的药动学特征。Aliskiren 作为治疗原发性高血压药物,经 FDA 批准于 2007 年在美国上市。该药物作用机制有所创新,它直接作用于 RAS 的限速步骤,是阻断 RAS 的新途径,人们希望通过此靶点从源头阻断 RAS 以获得更佳疗效。

研究表明,在长期应用经典的 RAS 阻断剂 - AngⅡ受体拮抗剂(AngⅡ receptor blocker,ARB)和血管紧张素转换酶抑制剂(angiotensin converting enzyme inhibitors,ACEI)时,会发生一种“AngⅡ逃逸”的现象,这是由于 ARB 和 ACEI 类药物长期阻断 AngⅠ向 AngⅡ转变,导致 AngⅠ的堆积激活了旁路途径,因此除了通过 ACE 作用生成 AngⅡ外,还通过旁路途径使 AngⅠ重新转化成 AngⅡ,从而使得血循环、组织中的 AngⅡ浓度逐渐回升到治疗前的水平,使得经典的 RAS 阻断剂治疗效果减弱[22]。临床研究表明[23-28],阿利吉仑的不良反应发生率与 ARB、ACEI 或安慰剂相当。因为直接肾素抑制剂可减少 AngⅠ向 AngⅡ的转化,从源头上使 AngⅡ的生成减少,不会出现 AngⅡ堆积的现象,且不会升高缓激肽的水平,而 ACEI 类药物产生不良反应的重要原因被认为是缓激肽水平升高。并且随着阿利吉仑剂量的增加,不良反应发生率不会随之增加。

5 RAS 与 ROP 的关系

RAS 包含一系列激素,这些激素调节血压、水电解质平衡、血管生长,改善组织灌注[29-30]。RAS 在全身多种疾病中发挥着十分重要的作用,包括心血管疾病、神经系统疾病、肾脏疾病、肿瘤以及缺血缺氧性视网膜病变[31]。Smith 等[32]研究发现,RAS 基因可以通过培养的人 Müller 细胞来表达,结果证实,RAS 可在眼局部被激活,Müller 细胞在此局部激活过程中发挥作用,由此推测眼部存在独立完整的 RAS 系统,它不依赖于全身的 RAS 而存在,即它包含了 RAS 的各个成分 - AngG、AngⅠ、AngⅡ、肾素及 ACE。这一体系中,各种成分受其基因调控。Wagner 等[33]发现肾素 mRNA 只存在于视网膜色素上皮层、脉络膜和视网膜,而不存在于前部葡萄膜和巩膜,用反转录多聚酶链反应技术检测发现在肾素 mRNA 阳性表达的组织中,AGT 和 ACE 两种基因的表达也呈阳性,通过这两种基因调控血浆中其产物的浓度再影响血管系统的改变,进一步从基因水平证实眼部组织有独立合成 RAS 的能力。局部 RAS

的发现,使传统的经典观点发生了根本性的变化。由于RAS瀑布下游各成分的作用和调控越来越复杂,而处于RAS瀑布上游的肾素则是该系统的第一个限速酶,所以肾素可能是一个更好地研究治疗一些疾病的靶点。

6 Aliskiren与Ras及ROP的关系

Wilkinson-Berka等[34]在氧诱导视网膜病变(oxygen-induced retinopathy,OIR)的大鼠模型的实验研究中发现直接肾素抑制剂Aliskiren减少了视网膜新生血管、降低了视网膜VEGF和ICAM-1的表达水平,充分说明Aliskiren能够减弱视网膜病理性血管的增殖。还有研究表明,Aliskiren不仅能使视网膜正常表达VEGF,并且能够控制细胞间Adhesion molecule-1的正常表达[35]。在OIR模型的实验中发现视网膜的缺血缺氧病变不仅涉及到视网膜的微脉管系统,还导致神经元和神经胶质的损害[36]。在ACEI和ARB抑制OIR模型的研究中,ACEI和ARB并没有改善OIR模型中神经元和神经胶质的损伤[37],视网膜电流图并无改变[38-40],并且没有防止神经元和神经胶质细胞的变性等[41-42]。而研究中发现肾素存在于视网膜Müller细胞和神经节细胞中[43-44],这一现象给了我们启示,Aliskiren可能会影响这些细胞群,从而防止神经元和神经胶质细胞的损伤。目前看来,在动物模型中Aliskiren对动脉粥样硬化[45]、糖尿病肾病[46-47]、心脏疾病[48-49]和糖尿病视网膜病变的治疗作用已经得到证实。我们将Aliskiren应用在ROP实验模型上,从RAS瀑布上游阻断其对视网膜的伤害,更有希望成为一种预防及治疗ROP的新方法。

7 小结

RAS与VEGF相互作用导致许多器官纤维血管化病变。Renin、AngG、ACE、Ang Ⅱ及其受体存在于构成视网膜的细胞群即Müller细胞和血管中。肾素作为RAS的限速位点成为一个关键性因子。在ROP这种以新生血管形成和纤维化为特征的疾病中,RAS的作用及其与生长因子和血管活性途径的研究近年来受到关注,而Aliskiren应用在ROP模型上的研究相对较少,Aliskiren抑制RNV的实验和临床研究有可能促进药物预防及治疗ROP的发展,有望成为ROP的药物治疗途径。

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