·综述·

神经血管功能障碍:脑淀粉样血管病潜在治疗靶点

叶嘉禾,叶晓东,李贤贤,黄珊珊*,朱遂强*

摘要 脑淀粉样血管病(cerebral amyloid angiopathy,CAA)是一种与年龄相关的脑小血管病,主要特征为淀粉样物质在脑血管壁的沉积。近期研究认为,神经血管单元(neurovascular unit,NVU)功能障碍可能推动CAA的发生与发展。本文将主要围绕CAA中NVU的直接与间接损害及NVU功能障碍相关的临床表现、影像标志物等方面论述CAA与NVU功能障碍之间的关联,并探讨通过保护NVU的功能以减缓CAA的发生和进展的可能性。

关键词 脑淀粉样血管病;神经血管单元;淀粉样物质沉积

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Neurovascular Dysfunction: A Potential Therapeutic Target for Cerebral Amyloid Angiopathy

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Abstract Cerebral amyloid angiopathy (CAA) is a small cerebral vascular disease associated with aging, which is characterized by the excessive deposition of amyloid in cerebral vessels. Recent studies suggest that neurovascular unit (NVU) dysfunction may contribute to the development of CAA. This review will focus on the direct and indirect damage of NVU in CAA and the relationship between NVU and CAA from the aspects of clinical manifestations and imaging markers, it is hoped that by protecting the function of NVU, the occurrence and progress of CAA can be slowed down.

Keywords cerebral amyloid angiopathy; neurovascular unit; amyloid deposition

脑淀粉样血管病(cerebral amyloid angiopathy,CAA)属于常见脑小血管病的一种,主要病理特征为淀粉样蛋白β(amyloid β,Aβ)在脑血管壁的沉积[1]。CAA可见于85%~95%的阿尔兹海默病(Alzheimer's disease,AD)人群,AD的神经病理学特征包括Aβ在脑实质中以老年斑块和在血管中表现为CAA形式的聚集[2]。近年来,越来越多的研究支持神经血管功能失调是AD发病机制的关键因素,认为神经血管单元(neurovascular unit,NVU)的细胞成分在AD早期就已经受到影响[3]。虽然CAA被认为是一种不同于AD的临床现象,但它们具有广泛且共同的脑血管和神经退行性特性,表明NVU与CAA病理改变可能存在关联[4]。本文主要讨论CAA中的NVU功能障碍,包括NVU各主要细胞成分在疾病过程中的改变,以及NVU功能障碍在CAA中常见神经影像标志物和临床表现中的作用。

1 CAA概述

CAA的患病率随着年龄的增长而增加,基于人群的尸检研究表明,CAA在认知正常的老年人中发病率为20%~40%,在痴呆的老年人中为50%~60%[5]。CAA的特征是Aβ在脑膜动脉壁和大脑皮质毛细血管中进行性沉积,致使脑血管完整性丧失,继发CAA相关临床症状[5]。CAA最常见的临床表现为脑叶脑出血(intracerebral hemorrhage,ICH),CAA相关的ICH占所有ICH的20%[6],其他主要临床表现包括认知下降等[7]。确诊CAA需脑组织尸检,但近来波士顿标准认为脑叶ICH、脑叶微出血(cerebral microbleed,CMB)、皮质表面含铁血黄素沉积(cortical superficial siderosis,cSS)、多发皮质下斑点征及血管周围间隙(perivascular spaces,PVS)等影像学标志物临床上可支持CAA的诊断[8]。

CAA的发病机制至今仍未得到完整解释,最常见的病理机制是Aβ的蓄积或清除障碍,不仅Aβ过度沉积的毒性作用可诱导血脑屏障(blood-brain barrier,BBB)的分解,近年来越来越多的证据还表明BBB功能障碍可以导致大脑清除Aβ的能力降低以及促进或加速Aβ生成过程[9-11]。以此可见,Aβ沉积与BBB损伤将构成恶性循环。而BBB的完整性与功能依赖于NVU各组分之间的协调合作,由NVU精准调控[12],因此也可说Aβ沉积与NVU的损伤密切相关。

2 NVU概述

NVU是大脑独有的具有复杂功能的多细胞解剖结构,是BBB的基本元素。NVU的细胞基础包括血管细胞(脑微血管内皮细胞)、与脑微血管内皮细胞密切接触的壁细胞(周细胞和平滑肌细胞)、神

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经胶质细胞(小胶质细胞、星形胶质细胞以及少突胶质细胞)、血管周围巨噬细胞和神经元,每个组成部分彼此紧密相连,建立结构和功能单元,调节中枢神经系统血流和能量代谢,并形成BBB,其中,BBB特点是高度选择性的内皮-周细胞-星形胶质细胞分层,以此将外周血与脑实质分离[13,14]。NVU各组分中,内皮细胞和周细胞参与基底膜的形成,不仅如此,位于内皮细胞上的特定转运蛋白可以调节分子进出大脑。周细胞还与免疫细胞相互作用迅速传递来自外围的炎症信号[12,15]。星形胶质细胞数量在神经胶质细胞中占比最多[16],其重要特征之一是在血管周围的末端足与血管壁联系密切,几乎完全覆盖了整个脑血管系统,而且星形胶质细胞具有呈递抗原和产生细胞因子的能力,在调节大脑免疫反应方面起关键作用[17,18]。小胶质细胞是主要的脑免疫效应细胞,在脑损伤和疾病期间可被激活转变为活化表型,参与组织修复等[19],少突胶质细胞可形成髓鞘以包裹神经元的轴突促进动作电位的快速传播以及维持适当的中枢神经系统功能。血管周围巨噬细胞可以通过产生炎症介质和执行吞噬作用来调节血管通透性和免疫功能[20]。

NVU是负责确保大脑内适当血液供应的一个重要因素,体现了神经活动与脑血流之间的密切的时间和空间关联,可以动态控制局部血流以响应神经活动引起的代谢需求增加[21]。因此,NVU中任一成分的损害都可能造成NVU功能障碍,从而引起神经系统疾病。

3 神经血管单元在CAA病理成分上的改变

CAA中NVU的功能障碍主要分为两方面:Aβ血管沉积造成的损害;间接效应引发损害。

3.1 Aβ血管沉积造成NVU直接损害

BBB是介导脑实质中Aβ清除的主要通路之一,而脑毛细血管内皮细胞是BBB介导的Aβ清除的关键成分[22]。过量的Aβ会对内皮细胞造成损害,Aβ通过诱导内皮细胞中烟酰胺腺嘌呤二核苷酸磷酸氧化酶(nicotinamide adenine dinucleotide phosphate oxidase,NOX)的活化来促进活性氧的产生,活性氧与内皮细胞产生的血管松弛剂一氧化氮反应可以形成过氧亚硝酸盐,氧化亚硝酸化应激触发内皮细胞中的DNA损伤并发挥血管损害作用[23]。

星形胶质细胞是NVU功能和整体中枢神经系统的核心。CAA中Aβ生成和清除之间的不平衡导致脑Aβ沉积水平升高,随之导致星形胶质细胞活化、炎症成分释放、补体系统活化、氧化应激、BBB通透性改变和神经毒性[24],星形胶质细胞可以通过多种机制介导Aβ的清除,然而,当积累的Aβ斑块达到一定程度时,也可能导致斑块周围的星形胶质细胞死亡,而受Aβ影响的星形胶质细胞可能成为炎症细胞而丧失神经支持作用[25]。小胶质细胞是单核-吞噬细胞,疾病早期小胶质细胞可通过清除Aβ来延缓临床症状发生,随着疾病进展,Aβ沉积会过度刺激小胶质细胞致使神经毒性作用[26]。同样地,Aβ诱导的氧化应激也可导致少突胶质细胞的死亡和功能障碍[27]。

周细胞对建立和维持BBB的结构和功能完整性的重要作用在许多实验和临床研究中得到证实,在控制内皮细胞层的完整性、血管细胞的再生和微循环的调节中均有突出贡献[28]。功能正常的周细胞对维持脑组织的充足的血液供应并提供Aβ的清除率至关重要[29],但是在衰老过程中会出现周细胞丢失、有效内皮细胞-周细胞相互作用数量减少以及周细胞形态和生理的损害[30]。周细胞积极参与Aβ通过BBB的转运,但Aβ沉积和CAA进展引起的线粒体功能障碍会导致周细胞的变性[31]。

3.2 NVU在CAA中其他间接损害模式

CAA中常见出血性脑损伤如ICH,ICH属于破坏性脑卒中,脑出血后可通过小胶质细胞活化,自由基、促炎细胞因子及基质金属蛋白酶(matrix metalloproteinase,MMP)的产生,神经元的凋亡等多种途径来促使NVU损伤[32],或为ICH患者中多发CMB及cSS的可能原因。除出血性脑损伤外,缺血性脑损伤亦可见于CAA中,如腔隙性梗死、脑白质病变等将会使脑血流量降低,继发组织缺氧、脑灌注不足等引发炎症反应、少突胶质细胞功能障碍、降低毛细血管周细胞覆盖率等途径继发NVU功能障碍[33,34]。

4 NVU功能障碍对CAA临床症状及影像学标志物的影响

不仅CAA可以引起NVU功能障碍,NVU障碍亦可继发CAA相关临床症状,同时在影像学征象上表现为特征性变化,还会在病理上促进Aβ在血管的沉积。

4.1 NVU功能障碍对CAA临床症状的影响

反复发生的自发性脑叶ICH是CAA的特征性表现[35]。研究发现,在CAA-ICH患者脑组织切片中,急性出血区域中的MMP表达增加,其他无急性出血的血管周围也存在富含MMP的反应性星形胶质细胞[36]。MMP是一类能够降解细胞外基质成分的酶,星形胶质细胞会在Aβ沉积的病理状态下增加MMP的生成,从而导致血管壁的断裂和血管破损出血[37]。此外,人载脂蛋白E(apolipoprotein E,APOE)ε4等位基因是大家熟知的CAA-ICH的危险因素,不少研究表明,APOEε4携带者中存在NVU功能障碍[38-41],这可能是APOE ε4通过激活周细胞中的CypA-NF-κB-MMP9通路来介导的[42]。

关于认知障碍,Aβ沉积可导致氧化应激,最终导致神经炎症,慢性炎症可能通过持续性的小胶质细胞活化导致神经元损伤、改变神经元形态尤其是通过大脑易感区域树突棘的重组等机制来导致认知障碍[43]。NVU在脑血流调节以及最终维持大脑的正常灌注中起重要作用[44],而脑灌注不足的小鼠可以表现出空间工作任务和参考记忆任务上的缺陷[45]。此外,甚至还有研究发现,无论Aβ相关生物标志物的变化如何,患有早期认知功能障碍的老年个体都会发生周细胞损伤,这表明周细胞功能障碍可能是独立于Aβ的人类认知功能障碍的早期生物标志物[46]。

4.2 NVU功能障碍对CAA影像学标志物影响

CAA常见的神经影像学标志物包括出血性标志物:脑叶ICH,脑叶CMB,cSS和缺血性标志物:脑白质高信号(white matter hyperintensities,WMH)和PVS等[47]。NVU功能障碍或NVU细胞成分的改变在CAA相关神经影像标志物形成过程中均有体现。

在出血性影像标志物中,CMB在磁敏感加权成像(suscepti-

bility weighted imaging，SWI）上表现为直径＜10 mm的圆形或卵圆形的低信号病变[48]。病理学研究表示，CMB最有可能由脑小血管（如毛细血管）的红细胞渗漏引起，是血管脆性增加的标志[49]。研究表明，Aβ负荷与脑叶CMB的发生率增加有关[50]，Aβ沉积可以导致小血管破裂，从而导致血细胞的外渗，进而导致CMB形成[51]。此外，还有研究发现，合并CMB的AD患者脑脊液中MMPs较无CMB的AD患者中多，这也表明CMB患者中NVU功能受损将更严重[52]。cSS在SWI上表现为在脑回皮质表面曲线状的局灶或弥散性信号缺失区域，在病理学上表示蛛网膜下腔和皮质表面含铁血黄素沉积[53]。有研究报道在有cSS的大脑中反应性星形胶质细胞的数量显著增加，CAA相关cSS中的铁沉积与以星形胶质细胞活化为主的局部神经炎症有关[54]。类似地，Aβ沉积可以通过损伤周细胞以此增加血管的通透性等方式显著增加ICH的风险[55]。

在缺血性影像标志物中，WMH的病理机制包括髓鞘苍白或肿胀、少突胶质细胞丢失导致组织稀疏和轴突-少突胶质细胞粘附松动等[56]。有研究发现，WMH中小胶质细胞活化、星形胶质细胞增生和血管周围神经炎症增加[57]。NVU受损和血流灌注不足程度在WMH附近更明显[58]。PVS是从蛛网膜下腔穿过脑实质时围绕小血管壁的生理空间[59]，被认为是清除例如Aβ的代谢废物的重要通道[60]。研究表明，白质PVS与血管组织中较低的溶血磷脂酸受体1（lysophosphatidic acid receptor 1，LPAR1）表达有关，其中LPAR1主要在少突胶质细胞中表达，参与出生后髓鞘形成和跨大脑区域的功能连接[61]。

4.3 NVU功能障碍对CAA血管中Aβ沉积的影响

神经血管耦合（neurovascular coupling，NVC）由NVU调节，NVU功能障碍导致的NVC受损致使大脑氧合减少，使Aβ生成增加[62]。内皮细胞中的晚期糖基化终产物受体（receptor for advanced glycation end products，RAGE）和低密度脂蛋白受体相关蛋白1（low density lipoprotein receptor-associated protein 1，LRP1）通过发挥Aβ的内吞作用以此来调节大脑中的Aβ稳态，内皮细胞受损则会使Aβ清除率降低导致Aβ沉积[11]。周细胞可将Aβ转运至BBB后进入血液，有研究发现有周细胞缺陷的小鼠大脑中有更多的Aβ沉积[63]。星形胶质细胞在脑淋巴系统中形成特殊的血管周围通道以清除包括Aβ在内的神经毒性废物，星形胶质细胞功能障碍会降低Aβ通过淋巴系统的引流，从而加剧Aβ细胞外和血管的聚集[64]。小胶质细胞通过吞噬作用清除Aβ，活化的小胶质细胞不仅会使Aβ的清除减少，还会释放细胞毒性因子导致神经元[65]。

5 CAA潜在的治疗靶点

迄今仍没有针对CAA的特异性治疗，但由于NVU在CAA过程中的重要性，恢复NVU的功能完整性可能预防或阻止CAA的进展。

既往临床药物研究表明，非竞争性谷氨酸受体拮抗剂吡仑帕奈可以通过增加线粒体脱乙酰酶Sirt3的表达来保护NVU系统[66]；MMP抑制剂IPR-179可以减少NVU的破坏[67]等。在日常生活中，长期高血压被证明会导致血管重塑、脑血管阻力增加、脑灌注不足和NVU受损[68]，高饱和脂肪饮食会影响星形胶质细胞、血管周巨噬细胞和基底膜蛋白标志物的表达[69]。因此维持正常的血压及血脂水平是有必要的。另有证据表明，中等强度的连续训练和心肺健康的相应改善可以通过减少Aβ蛋白沉积、改善NVU结构完整性等机制增加脑灌注和血管反应性[70,71]，由此可知，进行适当中等强度的训练也对NVU功能有益。新的可保护NVU功能完整性有望延缓CAA疾病的药物有待进一步研究。

综上所述，本文分析了NVU在CAA的损伤机制，NVU损伤后继发CAA临床症状、影像学及病理层面改变，最后提出保护NVU正常功能或可延缓CAA的发生和发展过程，以求减轻CAA患者临床症状，提高其生活质量。目前对于在CAA中NVU损伤的相关发现表明这可能是CAA治疗的潜在靶点，为未来开发更有效的治疗策略提供了新思路，有望能给予CAA患者更多的治疗选择。

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