·综述·

血脑屏障与阿尔茨海默病病变的研究进展

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摘要 阿尔茨海默病（AD）是导致痴呆的重要原因，进行性认知、记忆及行动能力障碍是其临床特点。研究发现，超过40%的AD患者脑内存在血脑屏障（BBB）通透性增高现象，血管内皮细胞、周细胞损伤甚至死亡是其主要原因；同时血管内皮细胞、周细胞损伤又与痴呆的发生密切相关。本文综述总结AD与BBB的内在联系及作用机制的研究进展，以期为AD的治疗提供新的治疗方向。

关键词 阿尔茨海默病；血脑屏障；血管内皮细胞；周细胞
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血脑屏障（blood-brain barrier，BBB）是分隔大脑组织与外周环境的功能单位，由血管内皮细胞通过紧密连接蛋白（ZO-1、occludin、claudin-5等）、黏附连结蛋白相互紧密连接构成基本框架，周细胞及星形胶质细胞终足覆盖包裹内皮细胞所构成，进而限制外周大分子蛋白、细胞毒性物质、外周免疫细胞等进入神经中枢，维持中枢神经系统内环境稳定，维护脑细胞的正常功能[1]。研究证实，BBB与阿尔茨海默病（Alzheimer's disease，AD）的发生发展密切相关，同时也是防治AD的重要策略[2-5]。AD主要表现为进行性认知、记忆及行动能力障碍。神经元外淀粉样蛋白（Amyloid-β，Aβ）沉积、神经元内tau蛋白高度磷酸化形成神经纤维缠结、神经元丢失是AD的主要病理改变[6,7]。其病理机制复杂：早期主要是毒性蛋白Aβ激活炎症信号通路及Ca^{2+}信号通路诱发神经元凋亡及神经突触丢失；疾病后期Aβ诱发神经元内tau蛋白高度磷酸化，致使其与微管蛋白结合降低，损伤神经元细胞结构，最终导致患者认知、记忆等能力障碍诱发痴呆[8-10]。血管内皮细胞及周细胞损伤是BBB破裂、血管通透性增加的主要原因，血管通透性增加致使外周有害物质进入脑内激活小胶质细胞，活化的小胶质细胞释放大量促炎因子如：白细胞介素（interleukin，IL）-1β、IL-6、肿瘤坏死因子（tumor necrosis factor，TNF）-α等，进而诱发神经元凋亡[11]；同时BBB破裂又能减少Aβ的外周清除，增加外周Aβ重新进入脑，增加脑内Aβ含量，损伤神经元，诱发痴呆[12]。因此，恢复BBB结构完整，降低血管通透性，增加Aβ清除，改善脑微环境，是治疗AD的新靶点。

1 BBB破裂增加脑内Aβ蓄积

研究发现，脑内生成的Aβ通过与BBB上载脂蛋白E（apolipoprotein E，APOE）结合而被转运到脑血管内皮细胞表面，进而与脂蛋白受体相关蛋白-1（lipoprotein receptor-related protein-1，LRP-1）结合，并在ATP结合盒式转运蛋白P-g glycoprotein（P-gP）的协助下进行Aβ的外周清除，将Aβ跨BBB转运出脑[13,14]。同时，脑血管内皮细胞表达的晚期糖基化终产物（receptor for advanced gyration end products，RAGE）可与外周游离Aβ结合将其重新摄取入脑内[15]。当BBB上LRP-1含量降低，RAGE含量增高，将会导致Aβ外周清除受阻，重新入脑增多，加剧其脑内蓄积[16]。Anushruti等[17]发现慢性脑缺血时，表皮生长因子（heparin-binding EGF-like growth factor，HB-EGF）通过激活低氧诱导因子-1α（hypoxia-inducible factor-1alpha，HIF-1α）刺激基质金属蛋白酶9（matrix metalloproteinase-9，MMP-9）的表达，进而损伤脑血管内皮细胞，导致内皮细胞表面LRP-1含量降低，RAGE含量增高，Aβ重吸收增强，外周清除受阻，最终诱发神经元损伤，导致小鼠认知及记忆功能下降。

Abhay等[18]敲除AD转基因模型小鼠$APP^{wo/0}$的血小板衍生生长因子受体β（platelet-derived growth factor β，pdgfrβ）基因复制周细胞缺失AD模型，结果发现小鼠脑内$Aβ_{40}$、$Aβ_{42}$水平较单纯的$APP^{wo/0}$小鼠高，同时脑内血管淀粉样病变增多，海马及皮质淀粉样斑块数量也增加。进一步研究发现，周细胞缺失使Aβ半衰期延长，Aβ清除发生障碍；同时周细胞缺失还促进tau蛋白高度磷酸化，降低其与微管蛋白亲和力，导致神经元功能障碍。血管内皮细胞、周细胞都是BBB的细胞组成，两者的损伤缺失都将导致BBB结构破裂，导致Aβ外周清除受阻，发生脑内蓄积。同时，RAGE水平增高还将导致Aβ重新进入脑内，加重Aβ脑内蓄积。

2 BBB破裂诱发神经元死亡

脑组织通过BBB将脑细胞与外周分离开，一旦BBB结构破裂，屏障功能受损，必将导致外周毒性蛋白进入脑内，进而诱发神经元损伤。研究发现[19]，各种血管危险因素，如吸烟、高血压、糖尿病及各种脑血管病变均可导致周细胞、血管内皮细胞损伤、丢失，BBB通透性增高，外周纤溶酶、凝血酶、纤维

蛋白等进入脑实质，损伤神经元；此外，血浆白蛋白进入脑实质将导致血浆胶体渗透压改变，诱发颅内水肿，进而压迫神经血管，导致神经元低灌注发生，引发神经元的损伤。周细胞内表达平滑肌肌动蛋白-α（smooth muscle a-actin，α-SMA），还参与脑血流量的调节[20]。研究证实，周细胞缺失将导致脑血流量的减少，直接导致神经元能量代谢障碍、代谢废物不能及时清除，诱发神经元的死亡[21,22]。

3 Aβ导致BBB破裂的内在机制

对APP/PS1双转基因AD模型小鼠及SAMP8快速衰老AD模型小鼠的研究均发现，小鼠脑内血管内皮细胞损伤，BBB通透性明显增高[23,24]，细胞实验发现血管内皮损伤与Aβ密切相关。Yoonjin等[25]利用微流体技术3D离体培养ReN Cells（一种能够表达APP/PSEN1基因，进而合成Aβ的脑血管内皮细胞）发现Aβ水平增高，导致血管内皮细胞活性降低，细胞膜上紧密连接蛋白claudin-1及claudin-5蛋白水平降低，进一步检测发现MMP-2及活性氧水平增高，MMP-2能够降解紧密连接蛋白，活性氧能诱发内皮细胞氧化损伤，导致BBB通透性增高；而减少Aβ生成后，BBB通透性降低。Elvis等[26]离体培养小鼠血管内皮细胞rBMVEC复制BBB模型，观察Aβ类似物质$Aβ_{25-35}$对BBB的影响，结果表明，细胞内活性氧水平增高，细胞活性降低，BBB通透性增高。可见，在AD病变过程中，Aβ能够诱发血管内皮细胞损伤，导致BBB破裂。

Matthew等[27]对携带载脂蛋白E4（apolipoprotein E-4，APOE4）的AD患者尸检发现，患者脑内周细胞数量明显较不携带APOE4的AD患者减少；对APOE4转基因小鼠研究发现，小鼠脑内LRP-1水平降低，导致LRP-1依赖的促炎信号通路亲环素A（cyclophilin A，CypA）/MMP-9被激活，进而诱发周细胞损伤。此外，Nina等[28]对AD患者尸检发现，患者脑内周细胞数量减少与$Aβ_{40}$水平密切相关；研究证实纤维状$Aβ_{40}$处理周细胞后，细胞内半胱氨酸天冬氨酸蛋白酶caspase3/7活性增强，周细胞凋亡增加。在AD发展中，Aβ能诱发血管内皮细胞、周细胞损伤导致BBB破裂，同时AD高致病基因APOE4亦能通过LRP-1/CypA/MMP-9信号通路诱发周细胞损伤。

4 血管内皮细胞、周细胞移植，修复BBB结构及功能可改善AD痴呆症状

Zhang等[29]将血管内皮祖细胞植入APP/PS1转基因AD模型小鼠海马内，结果显示海马区毛细血管数量增多，紧密连接蛋白ZO-1、occludin、claudin-5表达增高，BBB通透性降低；同时淀粉样斑块数量减少，Aβ诱导的凋亡因子Bax、caspase-3活性降低，抗凋亡因子bcl-2表达增加，神经元凋亡减少；小鼠空间学习和记忆能力得到显著改善。提示改善脑微血管内皮细胞损伤可以有效治疗AD。

同样的治疗效果在周细胞移植治疗AD中得到了验证。Masaya等[30]将C3H/10T1/2小鼠间充质干细胞诱导分化为周细胞并注射入APP/PS1小鼠右半脑内，探究周细胞对AD的治疗作用。3周后检测发现，右脑较左脑血液循环明显改善，同时脑内$Aβ_{40}$、$Aβ_{42}$水平明显降低，海马区淀粉样斑块数量也显著降低，其内在机制是周细胞通过其表面的LRP-1增加了对Aβ的摄取，并通过其内在的Aβ降解酶降解Aβ，减少脑内Aβ沉积。这提示，脑微血管内皮细胞与周细胞修复能够有效恢复BBB细胞及分子结构；恢复BBB屏障与转运功能改善认知及记忆损伤，是治疗AD的有效策略。

5 问题与展望

BBB是脑实质与外周联系的桥梁，血管内皮细胞、周细胞是BBB重要的细胞组成，一旦二者发生损伤，将导致BBB功能障碍，进而诱发多种神经疾病，如AD。同时，AD也能导致血管内皮细胞、周细胞损伤，导致BBB功能障碍，加剧AD的病理改变。因此，修复BBB结构，恢复其功能具有延缓AD进展的作用。但如何促进内皮细胞、周细胞修复损伤BBB，降低AD对BBB的损伤还需更深入的研究。

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