

血小板源性生长因子与血脑屏障的研究进展

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摘 要

血脑屏障(blood brain barrier, BBB)是存在于外周血液和脑组织之间的结构, 保护大脑免受内源性 & 外源性毒素和病原体的侵害, 从而维持脑内环境稳定。在中枢神经系统疾病中, 血脑屏障的破坏将进一步加剧疾病的进展。研究表明血小板源性生长因子(platelet-derived growth factor, PDGF)在血脑屏障的形成及功能维持中发挥重要作用, 本文总结了PDGF及其受体在生理及病理情况下对血脑屏障的影响, 初步探讨PDGF在中枢神经系统疾病中的治疗可能性, 并对当前靶向PDGF及其受体的治疗手段进行简要综述。

关键词

血小板源性生长因子, 血脑屏障, 脑卒中, 神经退行性疾病

Research Progress on Platelet-Derived Growth Factor and Blood-Brain Barrier

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Abstract

The blood brain barrier (BBB) is a structure that exists between peripheral blood and brain tissue,

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protecting the brain from endogenous and exogenous toxins and pathogens, thereby maintaining the stability of the brain internal environment. In central nervous system diseases, the disruption of BBB further exacerbates disease progression. Compelling data indicates that platelet-derived growth factor (PDGF) plays an important role in the maintenance and formation of BBB. This article summarizes the effects of PDGFs and their receptors on the integrity of BBB under physiological and pathological conditions. Finally, we briefly summarize the potential therapeutic strategy of PDGFs in central nervous system diseases, and review the current therapeutic methods targeting PDGFR.

Keywords

Platelet-Derived Growth Factor, Blood Brain Barrier, Stroke, Neurodegenerative Diseases

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1. 引言

血脑屏障(BBB)是一个将中枢神经系统与外周血液循环分开的结构,帮助建立和维持中枢神经系统的微环境[1]。它严格控制物质的通过,为神经元输送生长发育所需营养因子,并且保护大脑免受内源性 & 外源性毒素和病原体的侵害,从而维持大脑内环境稳定[2]。正常 BBB 功能的维持主要依靠脑内独特的微血管内皮细胞结构[3],同时由周细胞(pericyte, PC)、星形胶质细胞、神经元及细胞外基质共同组成[4][5],共同维护中枢神经系统稳态。

许多神经营养因子在 BBB 的形成及功能维持中发挥着重要作用,包括血小板源性生长因子(PDGF)、基质金属蛋白酶 9 (matrix metalloproteinase 9, MMP 9)、转化生长因子(transforming growth factor- β , TGF- β)等[6]。研究表明,PDGF 在中枢神经系统中大量表达,并且在生理及病理情况下对 BBB 的发育及功能调节起作用。中枢神经系统出现病理改变时, BBB 的完整性即受到破坏, PDGF 在此过程中发挥正性或负性的作用。其所介导的 BBB 变化的机制主要分为两个方面:(1) PDGF/PDGFR 信号通路上调或受抑制;(2) PDGF 家族成员的表达变化。现有的研究主要聚焦于脑梗死、脑出血以及帕金森等神经系统变性疾病,同时 PDGF 及其受体拮抗剂已广泛应用于神经系统疾病、癌症等相关调节,本文总结了 PDGF 及其受体对 BBB 的调节机制,简要介绍了 PDGF 作用于 BBB 对神经退行性疾病的影响,探讨 PDGF 在中枢神经系统疾病中治疗上的可行性,为将来开发神经系统疾病治疗新模式提供研究方向。

2. 血小板源性生长因子家族

PDGF 家族于 1974 年首次被发现,广泛表达于多种组织中,主要由内皮细胞、巨噬细胞、血小板分泌,为贮存于血小板中的促成纤维细胞生长因子,具有刺激特定细胞趋化和生长的生物活性[7][8]。PDGF 家族由四条不同肽链组合而成,通过同源或异源二聚化构成以二硫键连接的二聚体,目前已知如下五种类型:PDGF-AA、PDGF-AB、PDGF-BB、PDGF-CC 和 PDGF-DD,包括两种酪氨酸激酶受体 PDGFR- α 和 PDGFR- β 。PDGF-AA、-BB、-AB 和-CC 结合并激活 PDGFR- α 同二聚体,PDGF-BB 和-DD 结合并激活 PDGFR- β 同二聚体[9]。所有成员都携带有半胱氨酸残基组的生长因子核心结构域,为受体的结合和活化提供必须结构[10]。PDGF 及其受体信号通路通过激活下游传导通路,诱导细胞增殖、迁移和分化,调节平滑肌细胞、内皮细胞等多种细胞功能[11]。

PDGFR- α 与 PDGF-AA 和 PDGF-CC 结合发挥其活性作用,PDGFR- α 主要在间充质细胞中表达,另

外还在肺、皮肤以及少突胶质祖细胞中表达, 通过使用基因缺陷小鼠可观察到血管周围 PDGFR- α 的表达降低。活化的 PDGFR- α 通过激活下游信号通路发挥作用, 包括 Ras、p38 促分裂原活化蛋白激酶(Mitogen-Activated Protein Kinase, MAPK)和磷酸肌醇 3-激酶(Phosphatidylinositol 3 kinase, PI3K), 其中 p38 MAPK 活性与 PDGFR- α 激活后的 BBB 完整性特别相关[12]。PDGF-AA 可与 PDGFR- α 直接结合促进少突胶质细胞增殖和存活、参与中枢神经系统髓鞘形成, 其信号传导通路同时参与 TGF- β 调节平滑肌细胞的生长过程[13][14]。

PDGF-BB 是与 BBB 联系最紧密、目前研究最深入的生长因子之一, 其表达水平可作为血脑屏障完整性的指标[15]。PDGF-BB 主要在血管平滑肌细胞和周细胞中高度表达[16][17], 其受体 PDGFR- β 在血管周围壁细胞上表达, 主要参与调节周细胞迁移, 还调节紧密连接蛋白和粘附连接蛋白表达, 并在胚胎期及出生后的中枢神经系统发育过程中对周细胞和血管平滑肌细胞发挥重要作用[18][19]。在 Leon C. D. Smyth 等人研究中证实, PDGF-BB 通过 ERK 途径保护周细胞免受凋亡, 同时激活 PI3K 通路促进神经营养因子分泌, 保证了血管的稳定性以及 BBB 正常结构的形成[20]。另外通过使用 PDGF-BB 基因缺陷小鼠模型, 观察到在小鼠胚胎时期即出现微血管系统的损害, 引起脑血管破裂和出血而死亡; 同时由于中枢神经系统中周细胞覆盖率及数量明显减少, 致使 BBB 的完整性及稳态的破坏[21][22]。此前认为对于成年大脑 PDGF-BB 对维持 BBB 正常功能不是必需的。然而, 相关研究中通过使用成体诱导的 PDGF-BB 缺陷小鼠模型, 观察到持续的内皮源性 PDGF-BB 缺失可导致周细胞覆盖率降低、BBB 通透性增加[23]。因此 PDGF-BB 在出生及成年后对 BBB 正常功能的维持皆是必不可少的。

而 PDGF-CC 因其独特的结构, 需通过组织纤溶酶原激活物(tissue plasminogen activator, tPA)、纤溶酶等进行蛋白水解加工后, 移除 CUB 结构域释放出活性生长因子部分, 与 PDGFR- α 相结合发挥神经保护作用。在胚胎发育过程中, PDGF-CC 主要分布在平滑肌和骨骼肌的间充质细胞中; 在成人中, 主要局限在血管及内脏平滑肌[24]。相关研究表明, PDGF-CC 作为神经保护因子, 与 PDGFR 结合发挥作用, 进一步发现 PDGF-CC 通过调节糖原合成酶激酶 3 β (glycogen synthase kinase 3 β , GSK3 β)磷酸化, 使得受损的颅内神经元免于凋亡结局; 同时也参与保护帕金森病中多巴胺能神经元[25]。另一项研究中, Su 等人通过给小鼠脑室内注射 PDGF-CC 及 tPA, 观察到 BBB 的通透性明显增加, 反之予以注射中和 PDGF-CC 的抗体可减少 tPA 所诱导的 BBB 功能障碍, 因此目前认为 tPA 作为 PDGF-CC 的潜在激活剂, 通过促进 PDGFR- α 胞内结构域的磷酸化破坏 BBB 的通透性[26][28]。

PDGF-DD 和 PDGF-CC 均显示出与血管内皮生长因子家族高度相似, PDGF-DD 被尿激酶型 PA 或基质蛋白酶裂解后激活, 活化的 PDGF-DD 与 PDGFR- β 的同源二聚体结合发挥作用[29], 通过对血管内皮细胞及平滑肌细胞的直接作用发挥血管生成作用, 并可上调其他生长因子的表达改善心脏功能及结构[30][31]。目前对 PDGF-DD 与 BBB 之间的联系相关研究较少, 未来可进一步探索在神经系统中的作用。

3. PDGF 与缺血性脑卒中

脑卒中是一种常见的神经系统疾病, 以缺血性脑卒中最为常见, 具有高发病率、高致残率的特点[32], 目前急性期最主要的治疗方式是输注组织纤溶酶原激活物等行溶栓治疗。脑组织发生缺血性损伤后极易出现脑水肿, 研究表明, BBB 的破坏参与脑水肿发生及进展、影响神经组织的修复。首先内皮细胞间紧密连接结构发生破坏, 与转运蛋白功能障碍共同引起细胞旁途径通透性增加, 导致组织水肿并加剧脑损伤[33], 其次外周免疫细胞和炎症因子向脑组织中浸润, 进一步加剧 BBB 的渗透性, 同时加重组织水肿程度[34]。

3.1. PDGF-CC/PDGFR- α 信号通路

研究显示急性缺血性脑卒中发生后 PDGF-AA 及 BB 主要表达于半暗带区神经元和大血管中, 发挥

促神经再生作用, 保护 BBB 免受破坏[35]。上文所述 tPA 作为 PDGF-CC/PDGFR- α 的下游介质, 因此在脑缺血急性期时使用溶栓治疗时, 其信号通路介导 BBB 损伤并增加梗死区域出血转化风险[36]。在 PDGFR- α 基因敲除小鼠中, 脑梗死亚急性期周围血管细胞中的 PDGFR- α 下调, 增加了出血转化、IgG 渗漏风险; 进一步研究发现血管壁上所表达的 PDGFR- α 通过诱导 TGF- β 1 及 MMP9 对卒中亚急性期 BBB 的破坏产生特异性保护性作用并预防缺血性卒中的出血转化[37]。除此之外, 在一项关于小鼠脑缺血后采用远端缺血处理(Remote ischemic conditioning, RIC)的研究中, 他们通过在不同时间点给予重组组织型纤维蛋白酶原激活剂(Recombinant tissue plasminogen activator, rtPA)溶栓治疗后的小鼠血栓栓塞性卒中模型, 发现 RIC 可以保护 BBB 功能结构从而使颅脑免出血转化损伤, 同时表明血清中 PDGF-CC 含量水平与脑梗死体积呈正相关, 其表达上调可消除 RIC 对 BBB 的保护作用[38], 因此 PDGF-CC 在一定程度可增加缺血性卒中后 BBB 的通透性并导致继发性损伤, 对神经内环境有不同程度的损害, 当前活化的 PDGF-CC 如何介导 BBB 损伤仍不清楚。与脑卒中不同的是, 在急性脑出血情况下, 研究人员发现使用酪氨酸激酶抑制剂伊马替尼抑制 PDGFR- α 活性后, 在脑出血 24~72 小时后可防止神经功能缺损、脑水肿的形成, 其结果可能与 PDGFR- α 信号传导通过调节 MMP9 活性而引起 BBB 损伤有关[39]。

3.2. PDGF-BB/PDGFR- β 信号通路

在缺血性脑卒中的动物模型中, PDGFR- β 在梗死周围的周细胞中特异性表达上调, PDGF-BB/PDGFR- β 信号传导通路通过诱导周细胞中 Akt 磷酸化促进梗死区周边周细胞增生, 以及上调神经营养因子、神经生长因子和神经营养素-3 等的表达, 共同维持 BBB 正常结构及神经功能恢复[21]。同时研究表明, 在脑卒中亚急性期, 周细胞向梗死区迁移, 通过促进星形胶质细胞增生介导梗死组织纤维化修复, 梗死区域的周细胞进一步分泌促进星形胶质细胞增生因子(如白介素-6), 促进神经功能恢复。还参与内皮细胞紧密连接蛋白及粘附连接蛋白的调节, 并且分泌神经营养因子保护 BBB 的完整性[40] [41]。还有相关研究发现碱性成纤维细胞生长因子、转化生长因子参与梗塞周围区域的 PDGFR- β 表达上调, 从而减轻脑卒中后 BBB 通透性, 缓解脑组织水肿及神经功能障碍[42]。

4. PDGF 及其受体的临床应用

PDGF/PDGFR 信号通路参与体内多种疾病的发生发展, 在不同疾病状况下 PDGF 家族发挥着负性及正性作用。针对不同的受体及配体进行药物研发。目前临床已有多种针对 PDGFR- α 及 β 拮抗剂 - 酪氨酸激酶抑制剂(Tyrosine Kinase Inhibitor, TKI), 包括 olaratumab、甲磺酸伊马替尼、舒尼替尼、马西替尼等药物, 目前主要应用在恶性肿瘤、血液系统疾病、泌尿系统疾病等方面的治疗[43]。

在神经系统疾病中, 应用最为广泛的即为伊马替尼及马西替尼, 可以显著抑制 PDGFR- α 及 β 两种受体, 在不同的病理情况下发挥不同的生理作用。在急性缺血性脑卒中, 伊马替尼通过阻断 PDGF-CC 信号传导抑制 tPA 的神经毒性作用, 减少了 BBB 的渗漏以及神经元的损伤, 证明可能有助于延长安全溶栓时间[44]。随后进行了一项 II 期随机试验, 在急性缺血性卒中患者中进行静脉溶栓治疗, 受试者口服伊马替尼, 研究结果显示伊马替尼是安全且耐受的, 可以减少缺血性卒中后静脉溶栓治疗患者的神经功能障碍, 早期予以伊马替尼治疗降低出血转化风险, 并在一定程度上延长 tPA 溶栓时间(长达 5 小时) [45]。马西替尼与其发挥相似作用, 被认为是一种合适的神经保护剂, 共同用于与 rt-PA 联合溶栓治疗, 以改善缺血性卒中的最终结局[46]。除此之外, 还在多发性硬化、急性脊髓炎、肌萎缩性侧索硬化症等神经系统变性疾病中通过改善 BBB 的完整性, 修复神经炎症[47]。除使用受体拮抗剂抑制负性反应, 还有外源性补充 PDGF 配体促进其在体内的正性作用。已有临床研究显示经脑室注射重组 PDGF-BB 可以小程度改善帕金森患者症状[48]。

安全有效的药物递送是当前治疗的主要障碍, 目前研究着重于以纳米颗粒、外泌体作为递送方式。纳米技术目前已较为成熟, 多功能纳米载体可以同时携带成像剂、治疗药物和主动及被动靶向配体, 但如何将 TKI 与纳米载体整合, 同时有机纳米粒子在生物体内稳定性差, 如何使其顺利到达 BBB 后发挥作用仍需进一步研究[49], 而外泌体作为天然纳米囊泡, 具有稳定性、高递送效率和可自主穿过血脑屏障等特性, 作为中枢神经系统药物递送方式受到极大关注[50][51], 但目前外泌体提取纯度低、产量少, 仍没有完美的外泌体纯化方式, 相应的大规模生产成本昂贵, 开发外泌体新的纯化方式将是未来着重研究方向[52]。另外还有研究使用磁共振引导聚焦超声达到局灶性临时 BBB 的开放, 从而实现输送药物至颅内并尽快达到治疗所需血药浓度[53], 研究主要以帕金森病为介导, 临时开放中脑、黑质部分是安全且有效的, 目前仍需要更多循证医学证据。综上, TKI 作为小分子化合物, 在胃肠道中吸收良好, 尽管其具有高亲脂性, 能够充分渗透 BBB, 但在健康个体中的 CNS 分布较低。目前及未来研究需进一步考虑药物有效治疗剂量、给药途径和进入脑组织的途径。

5. 讨论及展望

PDGF/PDGFR 在神经元、少突胶质细胞、血管内皮细胞、周细胞等多种细胞成分中广泛表达, 直接参与生长发育过程。相关药物未来的开发将面向选择性靶向阻断 PDGFR- α / β 信号通路, 以及进一步研究 PDGF 作为中枢神经系统疾病治疗药物的安全给药方式, 这些新疗法有望改善脑血管病急性期脑水肿、出血转化以及神经退行性疾病的患者预后, 如何能最大程度发挥 PDGF/PDGFR 信号通路的正性作用仍需未来研究。

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