·综　述·

PAI-1与颅脑损伤相关性的研究进展

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【关键词】颅脑损伤;纤溶酶原激活剂抑制剂-1(PAI-1);继发性脑损伤
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颅脑损伤(traumatic brain injury,TBI)是导致青壮年死亡、残疾的主要死因[1]。TBI后继发性损伤,包括炎症、脑水肿、血脑屏障破坏和氧化应激等,严重影响病人预后[2]。研究表明,纤溶酶原激活剂抑制剂-1(plasminogen activator inhibitor-1,PAI-1)在TBI继发性损伤中起重要作用,TBI后脑组织或血清PAI-1明显升高,抑制PAI-1活性可减轻继发性损伤。本文就PAI-1与TBI相关性研究进展做一综述。

1 PAI-1

PAI-1是丝氨酸蛋白酶抑制超家族成员,人类PAI-1基因位于7号染色体,由9个外显子和8个内含子组成[3]。PAI-1是体内组织型纤溶酶原激活剂(tPA)和尿激酶型纤溶酶原激活剂(uPA)的天然抑制剂,通过调节tPA和uPA的活性阻止纤维蛋白溶解的持续状态。PAI-1在体内以三种不同的形式存在:活性、非活性-潜伏和分裂,以活性形式发挥作用,但由于缺乏半胱氨酸,活性构象不稳定,在生理环境中,活性PAI-1的功能半衰期在1~2 h,然后迅速转化为热力学稳定的潜在形式[4]。PAI-1在体内可以实现自身调节,以降低血栓形成的风险[5]。

1.1 PAI-1的合成及其影响因素　正常情况下,PAI-1由肝细胞、血小板、脂肪细胞、血管平滑肌细胞、成纤维细胞和巨噬细胞/单核细胞产生;在病理条件下,肿瘤细胞和炎症细胞也可成为PAI-1来源[6]。PAI-1的表达和释放受到多种因素的调控,包括生长因子(如转化生长因子-β、表皮生长因子)、炎性细胞因子(如肿瘤坏死因子-α和白细胞介素-1β)、激素(如胰岛素、糖皮质激素和血管紧张素Ⅱ)、葡萄糖、胰岛素、血管紧张素和血管紧张素,革兰氏阴性菌内毒素[7]。研究表明,PAI-1的表达受遗传变异的影响,PAI-1基因启动子区-675位点的4G/5G多态性(rs1799889)与血浆PAI-1水平升高有关[8]。

1.2 PAI-1的功能　PAI-1与tPA和uPA形成共价键,并通过阻止非活性纤溶酶原转变成纤溶酶,从而阻止活性纤维蛋白的降解[9],因此PAI-1可直接影响血栓的形成和降解,是动脉血栓形成的危险因素。Chen等[4]研究表明动脉粥样硬化的主要事件是由于PAI-1水平升高抑制纤溶,因纤溶无效而导致血栓形成增加。van de Craen等[10]研究发现,中年人PAI-1水平升高与心肌梗死风险增加存在很强的相关性。近年来研究表明,PAI-1参与许多疾病和代谢紊乱有关,例如肥胖[4]、胰岛素抵抗及代谢异常[11]、肾母细胞瘤[12]、骨骼肌再生过程[13,14]。另外,PAI-1不仅是细胞衰老和机体衰老的标志物,而且是一个关键的调节因子[15]。

2 PAI-1与TBI

tPA是中枢神经系统最具特征的丝氨酸蛋白酶之一,主要由神经元和小胶质细胞产生。TBI后,小胶质细胞过度激活及神经元去极化导致tPA在细胞外积聚,加剧神经退行性病变,破坏血脑屏障。PAI-1通过与tPA的催化残基形成复合物,抑制tPA活性,减少中枢神经系统因丝氨酸蛋白酶活性过高而产生的有害影响[16]。PAI-1主要由星形胶质细胞产生,TBI后PAI-1的表达增加,机制是TBI后损伤部位炎性因子的释放及局部缺血缺氧会刺激星形胶质细胞PAI-1表达增加,其中TGF-β是PAI-1表达最重要的调节因子之一[17]。

脑血管通透性增加是导致TBI后短期和长期脑损伤的原因之一[18]。Maruyama等[19]应用小鼠TBI模型研究发现,tPA与PAI-1复合物诱导基质金属蛋白酶-3表达,并和损伤严重程度成正比,MMP3是一种能有效降解神经血管单位基膜的蛋白酶,因此

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MMP3升高增加神经血管单位的通透性，使用MMP3抑制剂可显著降低白蛋白外渗的程度，并改善急性期神经功能。

PAI-1是纤维蛋白溶解的关键内源性抑制物，可促进创伤后血栓的形成。TBI后，纤溶失调可能导致持续的微血栓形成并加速病变扩展。研究表明，脑损伤区域周围微血栓最早于损伤后1 h形成[20]。Griemert等[21]研究显示，小鼠TBI后抑制PAI-1活性后，激活纤溶途径，防止伤后早期向促凝血状态的转变，降低脑微血管微血栓形成的风险，减轻继发性损伤。

TBI后早期判定损伤程度并指导进一步诊疗极为重要。Condron等[22]研究显示，孤立性脑损伤后（简明损伤量表头部AIS≥2分），入院8 h内血清PAI-1水平显著升高，并且与ISS水平成正比，即损伤越重，PAI-1水平越高。

研究指出，轻型TBI后常出现生长激素缺乏和中枢性甲状腺功能减退[23]。Frendl等[24]研究指出，与垂体功能正常的轻型TBI相比，晚期垂体功能低下病人入院时PAI-1水平显著降低，PAI-1有望作为轻型TBI后晚期垂体功能障碍的生物标志物，从而帮助识别随后可能出现永久性垂体障碍的病人。

总之，TBI导致脑实质机械性损害，其中脑血管系统损伤引起一系列病理生理反应，促使原发性病变扩展到周围的健康组织，血小板和白细胞的聚集范围进一步扩大，损害脑血流，导致脑缺血[25]。为了抑制血栓形成导致的血管闭塞，大量tPA从受损的内皮中释放，内源性抑制剂PAI-1，明显降低tPA的表达。这表明PAI-1有可能作为TBI的生物标志物，并有望成为治疗靶点减少继发性损伤。

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