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中性粒细胞 NADPH 氧化酶与组织缺血再灌注关系的研究进展*

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摘要:缺血再灌注损伤为心肌梗死,器官移植,肠道灌注不足,脑中风等疾病或手术的常见并发症,是导致危重病人死亡的重要因素,然而至今临床上仍未有十分理想的治疗方法。在组织缺血再灌注过程中,中性粒细胞通过 NADPH(Nicotinamide-adenine dinucleotide phosphate)氧化酶的活化产生大量活性氧(Reactive oxygen species,ROS),一方面参与氧化应激,另一方面进一步招募中性粒细胞,扩大炎症反应,造成组织损伤。本文综述了国外期刊报道的中性粒细胞 NADPH 氧化酶与组织缺血再灌注损伤的相关研究进展,以期为中心脑血管等重大疾病防治提供一定线索。

关键词:中性粒细胞;NADPH 氧化酶;缺血再灌注

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Advances in Study on Relationship between Neutrophil NADPH Oxidase and Tissue Ischemia Reperfusion*

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ABSTRACT: Ischemia reperfusion injury is a common complication of diseases or surgeries such as myocardial infarction, organ transplantation and stroke. It is a leading cause of death of critical patients while satisfying treatments still remains to be developed. During ischemia and reperfusion, neutrophils release a large amount of reactive oxygen species (ROS) to contribute to oxidative stress and recruit more neutrophils to ischemic tissue which expands the inflammatory response and results in tissue injury. Research progresses published in foreign journals on the connection between neutrophil Nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase and tissue ischemia reperfusion injury have been reviewed in this review, so as to provide evidences for the prevention and treatment of major diseases such as cardiovascular and cerebrovascular diseases.

Key words: Neutrophil; NADPH oxidase; Ischemia reperfusion

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前言

缺血再灌注损伤,指组织缺血后导致氧气供应不足,随后恢复血流供应,导致的不可逆组织损伤。多种组织的缺血再灌注损伤病理机制涉及氧化应激、细胞凋亡、炎症反应、钙离子超载、兴奋性氨基酸毒性等因素^[1-5]。组织缺血再灌注引起中性粒细胞活化并产生大量活性氧(Reactive oxygen species,ROS)造成组织损伤,这一过程称为“呼吸爆发”,主要通过烟酰胺腺嘌呤二核苷酸(Nicotinamide-adenine dinucleotide phosphate, NADPH)氧化酶的活化实现^[6]。同时,中性粒细胞分泌的促炎因子和趋化因子将进一步加剧中性粒细胞的聚集,形成一个中性粒细胞活化和聚集的正反馈循环^[7-8]。已有研究表明,中性粒细胞 NADPH 氧化酶参与了心肌^[9]、肝脏^[10]、肠道^[11]、脑^[12,13]、肾^[14]等

组织缺血再灌注的病理过程。同时,一些天然产物^[15,16]、重组生物制品^[17]及非药物治疗手段如肢体后适应^[12]等,能够调节中性粒细胞 NADPH 氧化酶改善组织缺血再灌注损伤。可见中性粒细胞 NADPH 氧化酶有可能成为防治组织缺血再灌注损伤的关键干预环节。基于以上背景,本文综述了中性粒细胞 NADPH 氧化酶与组织缺血再灌注关系研究进展,为以中性粒细胞 NADPH 氧化酶为靶点的组织缺血再灌注的防治提供一定的线索和理论依据。

1 中性粒细胞 NADPH 氧化酶

中性粒细胞,是外周血白细胞中比例最高的细胞,也是机体免疫防御的重要效应细胞。在正常情况下,中性粒细胞主要存在于外周血并保持静息状态;当局部有细菌入侵时,中性粒

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细胞随即被招募到炎症部位,通过产生 ROS,并脱颗粒释放蛋白水解酶,同时分泌各种趋化因子诱导其它免疫细胞进入感染部位杀伤细菌^[18]。然而,在一定条件下也会导致组织炎症损伤^[19]。在大多数组织缺血再灌注损伤过程中,缺血组织分泌的趋化因子白细胞介素-8(Interleukin-8, IL-8),白细胞介素-6(Interleukin-6, IL-6),肿瘤坏死因子 α (Tumor necrosis factor- α , TNF- α),补体 3a(Complement 3a, C3a), C5a(Complement 5a, C5a),氧自由基等将中性粒细胞激活并招募到缺血部位^[20]。中性粒细胞在粘附分子作用下特异性粘附于血管内皮细胞而造成微循环障碍,同时在血管内皮细胞上发生滚动,粘附,伸展,最终穿过紧密连接浸润到组织中^[8];其可通过脱颗粒作用释放弹性蛋白酶,胶原酶,髓过氧化物酶(Myeloperoxidase, MPO)等多种蛋白酶;也可通过其膜上 NADPH 氧化酶的激活产生大量氧自由基如超氧阴离子,羟自由基,次氯酸等来介导组织缺血再灌注损伤。研究已证实中性粒细胞在心^[21]、肝^[22,23]、脑^[24]等组织的缺血再灌注病理过程中的重要作用。

在组织缺血再灌注过程中,中性粒细胞的呼吸爆发导致缺血组织的氧化应激及炎症反应,造成组织缺血再灌注损伤,这一过程主要由 NADPH 氧化酶实现^[6]。NADPH 氧化酶首先被发现于中性粒细胞和巨噬细胞,后来,在大脑神经元、血管内皮细胞、星形胶质细胞、小胶质细胞中均发现它的存在。在哺乳动物中,根据分布、表达水平、释放的活性氧种类等因素的不同, NADPH 氧化酶被分为七个亚型,分别为 Nox1, Nox2, Nox3, Nox4, Nox5, Duox1 和 Duox2^[25]。据报道, Nox1 主要分布于结肠,平滑肌,内皮,子宫等; Nox2 高表达于吞噬细胞,在 B 淋巴细胞,神经元,心肌细胞,骨骼肌中均有表达,中性粒细胞中的 NADPH 氧化酶即为 Nox2 亚型; Nox3 主要分布于内耳、胎肾、胎脾、脑等; Nox4 常见于肾,血管,破骨细胞,内皮细胞等; Nox5 主要分布于淋巴组织和睾丸; Duox1 和 Duox2 均高表达于甲状腺^[26]。NADPH 氧化酶由两种膜结合蛋白和数种可溶性胞浆蛋白组成。在刺激下,胞浆成分向膜转移并结合形成酶的激活形式,即一个电子传递系统。该系统能将胞浆内 NADPH 的电子传递给氧分子形成超氧化物,与随后的反应产物一同表现出杀菌作用及细胞毒性^[27]。

综上所述,在正常激活状态下,中性粒细胞主要通过呼吸爆发和脱颗粒而发挥杀菌作用;组织缺血再灌注时,在炎症因子作用下过度激活的中性粒细胞,主要通过 NADPH 氧化酶而释放过量的 ROS,扩大炎症反应,导致组织损伤。因此,中性粒细胞 NADPH 氧化酶参与了组织缺血再灌注损伤的关键病理环节,阐明两者关系,有助于更加深入理解组织缺血再灌注损伤病理机制,并通过抑制中性粒细胞 NADPH 氧化酶的过度活化作为临床上治疗此类疾病的重要手段。

2 中性粒细胞 NADPH 氧化酶与各组织缺血再灌注

2.1 中性粒细胞 NADPH 氧化酶与心肌缺血再灌注

急性心肌梗塞是指冠状动脉血流供应不足而导致的心肌衰弱,影响心室功能,在世界范围内有极高的发病率^[28]。针对急性心肌梗塞的初始治疗是通过冠状动脉血管成形术恢复血流再通,改善心肌功能^[29-31]。然而再灌注在恢复血流和营养供应的同时也增加了缺血后的炎症反应和氧化应激^[32,33]。研究发现,在

心肌梗塞阶段,中性粒细胞 p47^{phox} 磷酸化位点 Ser 345 已经开始磷酸化,且该作用与上游细胞外信号调节激酶(Extracellular signal-regulated kinase, ERK)的活化有关^[16]。许多研究表明缺血再灌注后,组织中活性氧快速生成并大量增加,中性粒细胞及 NADPH 氧化酶在其中的作用也分别得到了证实^[32-35]。中性粒细胞因其通过本身的 NADPH 氧化酶进行呼吸爆发并由此产生大量的活性氧,可能成为治疗心肌缺血再灌注损伤的切入点。Ikeda Y^[9]等采用离体大鼠心肌缺血再灌注,同时给予中性粒细胞液灌流的方法,发现中性粒细胞引起离体心脏的收缩功能障碍,而给予一种可通过干预 NADPH 氧化酶的组装而抑制其活性的抗菌肽 PR-39 后,可显著改善该模型下的左心室充盈压及其最大变化速率,并显著减少中性粒细胞对血管的粘附及对缺血心肌组织的浸润,减少中性粒细胞活性氧的产生。上述报道均提示中性粒细胞 NADPH 氧化酶的活化在心肌缺血再灌注损伤过程中发挥了重要作用。

2.2 中性粒细胞 NADPH 氧化酶与肝脏缺血再灌注

肝脏缺血再灌注导致大量中性粒细胞浸润及 ROS 产生^[36]。早有研究^[37]证实,肝脏缺血再灌注过程中的超氧化物主要来源于以中性粒细胞为主导的氧化应激。而中性粒细胞主要通过 NADPH 氧化酶来产生超氧化物^[38]。活化的中性粒细胞 Nox2 产生的活性氧在肝细胞死亡中具有重要作用^[39]。近年来也有研究表明,在肝脏缺血再灌注过程中,中性粒细胞活化引起 NADPH 氧化酶的活化,该酶氧化 NADPH,释放的电子传递给 O₂ 形成超氧阴离子(O₂^{•-})。O₂^{•-}通过随后的反应进一步产生过氧化氢(H₂O₂),羟自由基等^[40]。中性粒细胞嗜苯胺蓝颗粒释放的 MPO 在卤化物如氯离子存在的条件下,通过酶促反应将过氧化氢转化为又一强氧化剂次氯酸(HOCl)。这些氧化剂的产生将直接损伤肝细胞,也会通过影响蛋白酶而介导肝损伤^[41]。同时,中性粒细胞 NADPH 氧化酶也参与肝脏缺血再灌注时中性粒细胞与血小板的细胞间相互作用,且其对 Ca²⁺ 的调控与 Akt, ERK 和 p38 丝裂原活化蛋白激酶(Mitogen-activated protein kinase, p38 MAPK)的磷酸化有关^[42]。Tadashi Hasegawa 等^[38]应用大鼠肝脏缺血再灌注模型证实,中性粒细胞通过 NADPH 氧化酶产生,经 MPO-H₂O₂-Cl⁻ 系统作用进而产生 HOCl。HOCl 在中性粒细胞介导的再灌注损伤阶段扩散至肝细胞,引起细胞内酪氨酸残基的氧化修饰和氯化作用,而 NADPH 氧化酶抑制剂可改善肝脏氧化型谷胱甘肽(Oxidized glutathione, GSSG)和蛋白结合型 MDA 水平。Lu Zhou 等^[10]发现在肝脏缺血再灌注时,中性粒细胞的大量浸润伴随着 Nox2 和 Nox4 蛋白水平及 Rac1, p22^{phox}, p47^{phox} 和 gp91^{phox} mRNA 水平的升高,ROS 可能来源于浸润的中性粒细胞。其机制可能为胰岛素样生长因子结合蛋白 3 (Insulin-like growth factor binding protein-3, IGFBP-3)降低过氧化氢酶活性,同时使 MPO 活性增加,于是中性粒细胞 NADPH 氧化酶产生的 O₂^{•-}传递给过氧化氢,后者为 MPO 提供充足的反应底物以生成 HOCl,最终导致肝损伤。

2.3 中性粒细胞 NADPH 氧化酶与肠道缺血再灌注

一些疾病如外伤/出血性休克、烧伤及败血症能够引起肠道缺血及肠道通透性的变化;手术如肠移植,腹主动脉瘤手术和心肺转流术等,也会引起肠道缺血再灌注^[43,44]。在此病理情况下,肠淋巴液中来自于缺血肠道的毒性及炎症因子又将进一步

导致急性肺损伤,骨髓功能障碍,内皮细胞损伤,内皮粘附分子表达上调,中性粒细胞活化等,造成多器官功能障碍综合征^[45,46]。Zaets S B等^[44]证实,在肠系膜上动脉栓塞诱导的大鼠肠道缺血再灌注模型中,肺血管通透性增加,肺和肠道组织中的中性粒细胞浸润伴随呼吸爆发活性升高,造成回肠黏膜损伤并影响肝微脉管血流。Sener G等^[47]也在大鼠肠道缺血再灌注模型中观察到TNF- α 产生,回肠内丙二醛(Malondialdehyde,MDA)含量及MPO活性升高,中性粒细胞呼吸爆发活性增加,提示NADPH氧化酶活力的增加。

虽然中性粒细胞产生的ROS是大多数组织或器官缺血再灌注损伤的主要病理机制之一,然而,其在肠道中亦会发挥保护作用。由于缺血再灌注还会导致粘膜屏障损伤,肠道细菌移位,进而引起感染并发症,这时的中性粒细胞NADPH氧化酶活化对机体体现为一种保护作用。Yen-Zhen Lu^[11]等证实大鼠肠道缺血再灌注后出现明显的肠道细菌移位,粘膜组织病理学变化及上皮屏障功能的缺失;而给予低氧预适应手段干预(每天17h,持续3周)后再对其进行造模,结果发现能活化中性粒细胞,其胞浆成分p47phox和p67phox向膜转移增多,超氧化物和过氧化氢生成增加,进而使中性粒细胞的杀菌和吞噬作用得到加强,同时上皮完整性得到改善,细菌移位被抑制,提示中性粒细胞NADPH氧化酶的活化在此过程中呈现保护作用。

2.4 中性粒细胞NADPH氧化酶与脑缺血再灌注

中性粒细胞NADPH氧化酶与脑缺血再灌注的关系已有研究报道。Chen G^[12]等采用大鼠大脑中动脉栓塞模型证实了中性粒细胞NADPH氧化酶与脑缺血再灌注的关系。其研究表明,脑缺血再灌注引起中性粒细胞聚集并活化NADPH氧化酶,表现为中性粒细胞p47^{phox}膜位移现象增加,p47^{phox} mRNA水平、蛋白表达及Ser 304,345磷酸化均显著升高,给予肢体后适应手段干预可显著抑制中性粒细胞NADPH氧化酶的活化并改善脑缺血再灌注损伤,其机制与中性粒细胞髓系分化因子88(Myeloid differentiation factor 88,MyD88)/肿瘤坏死因子受体相关因子6(Tumor necrosis factor receptor-associated factor 6,TRAF6)/p38 MAPK途径对p47^{phox}磷酸化的调控有关。

2.5 中性粒细胞NADPH氧化酶与其他组织缺血再灌注

肾缺血再灌注由急性肾损伤引起,对肾移植后肾功能早期的恢复和预后都有可能造成影响。肾缺血导致组织低氧,严重时影响组织正常代谢与能量供应。虽然再灌注后血流组织功能恢复,但再灌注也会带来组织损伤和炎症反应。因此肾缺血再灌注也是一个涉及多因素如低氧,炎症反应,自由基损伤的复杂病理过程^[48]。有研究表明,大鼠肾缺血再灌注后血液中肌苷酸,尿素氮,乳酸脱氢酶,TNF- α 及中性粒细胞呼吸爆发显著升高,肾组织中MDA含量和MPO活力增加,同时谷胱甘肽水平和Na⁺/K⁺-ATP酶活力受到影响,表明肾缺血再灌注也伴随着中性粒细胞的浸润与活化^[14]。

动脉手术有可能导致肾,心脏或肺微血管的缺血再灌注损伤,主要表现为局部损伤或系统性炎症反应,这种损伤在一定程度上由中性粒细胞介导。活化的中性粒细胞与血管内皮发生粘附,并浸润到组织中,释放活性氧和细胞因子,导致间质损伤。在大鼠腹主动脉缺血再灌注诱导的急性肺损伤模型中出现

肺部微血管渗漏和中性粒细胞浸润的情况,且外周血中性粒细胞呼吸爆发活力增加,而使用抗氧化剂维生素C干预后此现象得到改善^[49]。在颈静脉抽血90min/输血4h引起的创伤失血性休克大鼠模型中,大鼠肠系膜淋巴液的中性粒细胞也表现出呼吸爆发活性的升高^[17]。

3 小结与展望

综上所述,中性粒细胞NADPH氧化酶参与了多个组织的缺血再灌注损伤。大量研究证实,多种药物及非药物的治疗方法可通过对中性粒细胞NADPH氧化酶的调节而减轻缺血再灌注损伤(见表1),这些研究中多采用天然产物进行干预,天然产物因其多来源于中草药,有来源广泛、毒副作用低的优势,具有一定的研究潜力和深远的应用前景,而重组生物制品具有用量低、药效高的特点。目前药物治疗及低氧预适应治疗,均为造模前进行干预,即预防性治疗,而由于临床上组织缺血的不可预测性,预防性治疗的应用受到一定限制;肢体后适应为再灌注的同时给予干预操作,更符合临床应用的需要。多种治疗手段的结合有望有效防治组织缺血再灌注损伤。基于以上研究现状,开发安全有效并符合临床需要的治疗手段以防治组织缺血再灌注损伤是当前科研工作者面临的重要课题。

目前针对中性粒细胞NADPH氧化酶与组织或器官缺血再灌注的研究多集中在肝脏、心肌和肠道等,针对与脑缺血再灌注关系的研究较少。通过调节中性粒细胞NADPH氧化酶而减轻脑的缺血再灌注损伤,很可能成为相关研究新的切入点^[12]。在针对中性粒细胞NADPH氧化酶与组织或器官缺血再灌注的研究手段方面,目前多采用相关动物模型考察外周血中性粒细胞呼吸爆发和组织中性粒细胞的浸润,以及采用体外实验考察中性粒细胞NADPH氧化酶的活化,其指标多侧重在p47^{phox}的磷酸化水平或膜位移情况,而针对NADPH氧化酶其他亚基的研究相对较少。采用免疫共沉淀、邻位连接技术,通过检测各亚基间相互作用来反映NADPH氧化酶的活化,以及在整体动物研究水平使用相关基因敲除动物,或在细胞水平研究中采用基因干扰或过表达细胞,将会使相关研究更全面深入。总之,对中性粒细胞NADPH氧化酶与组织缺血再灌注关系的研究及对相关机制的阐释,将有助于进一步理解组织缺血再灌注的病理机制,并为相关疾病的实验及临床研究提供新的切入点。

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表 1 组织缺血再灌注的治疗方法
Table 1 Treatments to tissue ischemia reperfusion

治疗类型	名称	组织	模型	作用	途径
天然产物	川芎嗪 ^[50]	心肌	体内:心肌缺血 45 min, 再灌注 1 h	增加大鼠心肌 HO-1 表达;	/
			体外:fMLP 刺激人外周血中性粒细胞活化	抑制 fMLP 刺激下中性粒细胞迁移及呼吸爆发	
	己酮可可碱 ^[47]	肠道	大鼠肠系膜上动脉栓塞 1 h,再灌注 2 h	降低大鼠回肠 MDA 及 GSH 水平,抑制大鼠回肠 MPO 活力,提示该作用与抑制中性粒细胞呼吸爆发活性有关	/
	维生素 C ^[49]	肺	体内:大鼠主动脉缺血 30 min,再灌注 2 h	减少大鼠腹主动脉缺血再灌注引起的中性粒细胞对肺的浸润	/
			体外:大鼠外周血中性粒细胞与大肠杆菌共孵育	抑制中性粒细胞呼吸爆发活性	
	迷迭香酸 ^[51]	肝脏	体内:大鼠肝脏缺血 45 min,再灌注 2 h	降低大鼠肝脏缺血再灌注后血清 AST, ALT 和 LDH 水平	/
			体外:PMA 刺激人外周血中性粒细胞活化	抑制中性粒细胞呼吸爆发活性	
	桦木酸 ^[14]	肾脏	体内:大鼠肾脏缺血 45 min,再灌注 6 h	降低肾缺血再灌注大鼠血清肌酐酐,尿素氮, LDH 活力;血浆 TNF- α 水平;肾组织 MDA, GSH 水平,MPO 及 Na ⁺ -K ⁺ -ATP 酶活力	/
			体外:fMLP 和 PMA 刺激外周血中性粒细胞活化	抑制中性粒细胞呼吸爆发活性	
药物 治疗	生物来源	心肌	大鼠心脏离体缺血 20 min,再灌注 45 min	改善离体心肌缺血再灌注后的 LVDP 及其最大变化速率;抑制中性粒细胞对血管的粘附及对缺血心肌组织的浸润	与 p47phox 结合,抑制 NADPH 氧化酶的组装
	重组 IL-37 ^[36]	肝脏	体内:小鼠肝脏缺血再灌注模型:缺血 90 min,再灌注 1 或 8 h;	改善肝脏缺血再灌注小鼠肝细胞损伤,抑制肝脏中性粒细胞聚集及 ROS 生成	/
			体外:TNF- α 刺激中性粒细胞的炎症模型	减少 TNF- α 刺激下中性粒细胞活化及呼吸爆发	
	重组凝血因子 XIII A2 ^[44]	肠道	体内:大鼠肠系膜上动脉栓塞 45 min,再灌注 3 h	降低肠道缺血再灌注大鼠肺通透性,肺及回肠 MPO 活力,抑制中性粒细胞呼吸爆发活性;	/
			体外:凝血酶刺激 HUVECs 的内皮屏障损伤模型	抑制凝血酶引起的 HUVECs 通透性改变	
	重组人乳铁蛋白 ^[17]	肠道	大鼠外伤 - 出血性休克模型:颈静脉抽血 90 min,输血 4 h	改善回肠损伤,抑制中性粒细胞呼吸爆发活性	/
非药 物治 疗	低氧预适应 ^[11]	肠道	大鼠肠系膜上动脉栓塞 20 min,再灌注 1 h	改善肠粘膜通透性,增加中性粒细胞浸润及呼吸爆发活性	增加 p47 ^{phox} 和 p67 ^{phox} 的膜位移
	肢体后适应 ^[12]	脑	大鼠大脑中动脉栓塞 1.5 h,再灌注 24 h	改善脑缺血再灌注损伤,减少外周血中性粒细胞数量和活化,增加中性粒细胞对被操作后肢的浸润;减少中性粒细胞对脑组织的浸润	调节中性粒细胞 MyD88/IRAK1/p38 MAPK 途径减少 p47phox 磷酸化

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