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·综述·

糖尿病性器官缺血再灌注损伤的研究进展

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【摘要】 缺血再灌注损伤发生于心、脑、肝、肾、肠等多种器官的疾病状态或手术过程中,是导致器官二次损伤、手术失败甚至死亡的重要原因。缺血状态下恢复血流以提供氧气及营养是必须的,但再灌注通常会增强局部或全身性的炎症反应,并加重缺血部位的损伤。为减少由于缺血再灌注损伤所造成的并发症及疗效损失,有必要对其机制进行研究。糖尿病是一种常见的基础性疾病,糖尿病患者身体长期处于高血糖及高血糖波动状态下,细胞应对病理状态的应激反应异常,发生器官缺血再灌注损伤往往更为严重,由于糖尿病的发病率逐年增高,对于糖尿病状态下的器官缺血再灌注损伤的研究迫在眉睫。本综述旨在总结糖尿病状态下各器官缺血再灌注损伤的研究进展。

【关键词】 缺血再灌注损伤;糖尿病;器官损伤;应激;炎症

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Research progress of diabetic organ ischemia-reperfusion injury. *XIA Kang, LIU Xiu-heng. Department of Urology, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei, CHINA*

【Abstract】 Ischemia-reperfusion injury occurs in the disease status or operation of heart, brain, liver, kidney, intestine and other organs, which is an important cause of secondary organ injury, failure of operation and even death. It is necessary to restore blood flow in order to provide oxygen and nutrition in the state of ischemia, but reperfusion usually enhances local or systemic inflammatory response and aggravates the injury of ischemic site. In order to reduce the complications and the loss of curative effect caused by ischemia-reperfusion injury, it is necessary to study its mechanism. Diabetes is a common basic disease and diabetic patients have been in hyperglycemia and hyperglycemia fluctuation for a long time. The stress response of cells to pathological state is abnormal, and organ ischemia-reperfusion injury is often more serious. Imminent research on the organ ischemia-reperfusion injury in diabetes is due to the increasing incidence rate of diabetes. The purpose of this review is to summarize the research progress of ischemia-reperfusion injury of various organs in diabetic state.

【Key words】 Ischemia-reperfusion injury; Diabetes; Organ damage; Stress; Inflammation

缺血和再灌注是一种病理状况,其特征是最初限制了器官的血液供应,随后是灌注的恢复和伴随的再氧合。其会引起各种病理类型的发病和死亡,包括心肌梗塞、中风、急性器官损伤、镰状细胞病、睡眠呼吸暂停、创伤等。缺血再灌注损伤也是器官移植及外科手术期间的主要挑战[1]。缺血器官内代谢供需的不平衡会导致严重的组织缺氧和微血管功能障碍,随后的再灌注进一步增强了先天性和适应性免疫反应以及细胞死亡程序的激活[2]。

糖尿病的特征是慢性高血糖症以及胰岛素分泌和/或胰岛素作用完全或部分不足引起的碳水化合物,脂质和蛋白质代谢受损。其发病率在世界范围内稳步增长,并且近年来急剧增加。不仅很多潜在的糖尿病患者并没有得到诊断,还有大量糖耐量异常的患者[3]。由于体内异常的代谢反应,糖尿病会加重身体的氧化应激与炎症反应[4]。

因此,糖尿病患者在发生缺血再灌注时器官的损伤更为严重,随着糖尿病患者基数的不断增大,全球对于糖尿病患者器官缺血再灌注损伤的研究需求越加迫切。本综述旨在总结糖尿病患者各器官发生缺血再灌注损伤的研究进展。

1 糖尿病的脑缺血再灌注损伤

糖尿病被证明是脑缺血的危险因素,而且研究表明,脑缺血相对危险性糖尿病患者大约是非糖尿病患者的两倍[5]。炎症是糖尿病(DM)加剧缺血性脑血管疾病的主要机制之一。降低大脑皮层中促炎因子肿瘤坏死因子α (TNF-α)和核因子-κB (NF-κB)的表达水平可以减少炎症反应从而减轻糖尿病性脑缺血/再灌注损伤[6]。内质网应激也在糖尿病性脑缺血再灌注损伤中扮演重要角色,糖尿病通过增强内质网应激,激活CHOP/GADD153和Caspase-12,诱导细胞凋亡,从而加剧脑缺血再灌注损伤[7]。

近年来,大脑中GLP-1受体的激活也在该领域被广泛研究,GLP-1受体激活是通过蛋白激酶B (Akt)/内皮型一氧化氮合酶(eNOS)的磷酸化途径,抑制了缺血再灌注损伤增强的NF-κB/ICAM-1信号传导、内质网应激和凋亡,从而对糖尿病大鼠脑缺血再灌注提供神经保护作用[8]。

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另外，GSK-3β的激活也是糖尿病加重脑缺血再灌注损伤的一个重要机制[9]。通过AMP依赖的蛋白激酶(AMPK)介导的APN-LKB1途径下游的GSK-3β磷酸化可以保护糖尿病的脑缺血再灌注[10]。胰岛素在治疗糖尿病性脑I/R中有显著效果。例如高血糖会加重脑缺血再灌注损伤，增加脑梗死和神经功能缺损，抑制葡萄糖摄取和葡萄糖转运蛋白1的膜转运活性，并降低大脑中蛋白激酶B (Akt)和内皮型一氧化氮合酶(eNOS)磷酸化。使用胰岛素治疗可以逆转这个过程，但依赖eNOS的激活[11]。

2 糖尿病的心肌缺血再灌注损伤

抗心律失常和抗炎作用在糖尿病心脏I/R损伤的心脏保护中提供关键的作用[12]。高血糖诱导的NLRP3炎症反应活化是一个ROS依赖的过程，NLRP3炎症反应诱导的炎症反应加重了糖尿病大鼠MI/R损伤[13]。表观遗传学修饰在糖尿病的心肌缺血再灌注损伤中也起着关键作用，并且是当前的研究热点。糖尿病和MI/R损伤均会增加心脏HDAC的活性。在高血糖条件下，通过Akt调节的线粒体凋亡途径通过Foxo3a/Bim通路抑制HDAC，触发了针对MI/R和H/R损伤的保护作用[14]。

选择性抑制蛋白活化激酶C (PKC)家族在糖尿病的心肌缺血再灌注中扮演重要角色，抑制PKC β_2活化可改善线粒体质量减轻高糖和H/R诱导的心肌细胞损伤[15]。另外减轻高葡萄糖诱导的PKC家族的PKC-ε过表达可通过激活STAT3来减轻糖尿病心脏I/R损伤[16]。

自噬也是糖尿病性心肌缺血再灌注的重要机制，糖尿病通过损害自噬通量增强MI-R损伤。ADIPOR激活可恢复AMPK介导的自噬体的形成和抗氧化剂介导的自噬体的清除，代表了一种针对糖尿病情况下对MI-R损伤有效的新型干预措施[17]。

另外，一些非编码RNA (lncRNA)及微小RNA (miRNA)参与糖尿病性心肌缺血再灌注损伤过程。例如长链非编码RNA心肌梗死相关转录本1 (MIRT1)的下调通过抑制NF-κB信号通路的活化来改善糖尿病大鼠的心肌I/R损伤[18]。LncRNA NEAT1通过靶向miR-27b调节PINK1加剧糖尿病性心肌缺血再灌注损伤[19]。这些研究展现了RNA在糖尿病性心肌缺血再灌注损伤研究中的巨大潜力。

3 糖尿病的肾缺血再灌注损伤

糖尿病通过增加炎症反应而加重肾缺血/再灌注(I/R)损伤，并钝化各种措施的保护作用。丙酮酸乙酯(EP)通过抑制高迁移率族1号框蛋白(HMGB1)释放提供抗I/R损伤的抗炎作用[20]。氧化应激也是糖尿病加重肾缺血再灌注损伤的重要机制。抗氧化剂预处理可以减轻糖尿病患者的I/R [21]。因此，一些具有抗炎和抗氧化特性的药物，在改善糖尿病的肾脏I/R损伤中发挥巨大作用[22]。糖尿病患者更容易受到肾脏I/R损伤，还与ICAM-1、E-选择素的表达增加和免疫细胞浸润、肾髓质血管阻塞和肾髓质缺血时间延长有关[23]。

右美托咪定(DEX)是一种高度选择性的α2-肾上腺素受体激动剂，在最近的研究中发现其对肾脏缺血再灌注损伤显示出肾脏保护作用。DEX治疗减弱了缺血再灌注诱导的NLRP3、Caspase-1、IL-1β、磷酸化AKT和磷酸化ERK信号转导的增加。此外，氧化应激损伤、炎症反应、细胞凋亡和肾小管损伤可以通过DEX治疗得到很好的调节。另外，在调节NLRP3炎性体、AKT和ERK信号转导以及氧化应激方面，DEX再灌注后治疗比治疗前有效得多[24]。

胱硫醚γ-裂合酶(CSE)是转硫途径中的主要酶，可催化哺乳动物组织中的H_2S产生。近端小管中的CSE表达也可能通过H_2S产生来调节小管间质微循环。H_2S可能代表了预防糖尿病性肾病缺血性损伤进展的治疗目标[25]。糖尿病还可以通过在体内和体外抑制线粒体功能和PINK1/Parkin介导的线粒体吞噬来加重肾I/R损伤[26]。

4 糖尿病的肝缺血再灌注损伤

在非糖尿病小鼠中，内皮型一氧化氮合酶(eNOS)基因的过度表达导致肝脏保护。相反的，在糖尿病患者中，eNOS以“非耦合”状态存在，db/db小鼠肝脏eNOS功能紊乱，eNOS基因表达增加导致过氧亚硝酸盐产生增多，加重肝缺血再灌注损伤。在糖尿病患者中，只有施以辅助因子和eNOS酶的“重新结合”才能恢复其保护作用[27]。

有研究表明糖尿病还可通过促进M1极化和抑制M2极化而特异性地触发S1P/S1PR3信号传导并加剧肝脏IRI。氨醇-1-磷酸(S1P)和鞘氨醇-1-磷酸受体(S1PRs)已知与代谢和炎性疾病有关，S1PR3组合键可显着恢复高血糖调节的M1/M2极化并减轻炎症[28]。

蛋白激酶C (PKC)-β抑制剂治疗可预防糖尿病大鼠的肝脏I/R损伤。其机制可能涉及微血管损伤的减轻，损伤相关因子的运输减少以及NF-κBp65激活的减少[29]。白藜芦醇(RSV)是具有抗氧化作用的天然多酚化合物，通过调节炎性反应和氧化应激减轻糖尿病大鼠中肝I/R损伤[30]。

5 糖尿病的其他器官缺血再灌注

在其他器官如肺、肠等中，糖尿病性缺血再灌注损伤的研究相对比较少。糖尿病可以通过激活p38 MAPK途径使肺缺血再灌注损伤恶化[31]。脂联素(APN)具有抗炎、抗氧化和抗凋亡的作用，但APN处理的糖尿病大鼠的保护作用会消失，肺缺血再灌注损伤反而加重[32]。糖尿病状态会增强肠道缺血再灌注损伤后的炎症反应[33]。在诱导的局部肠缺血再灌注模型里，糖尿病与依赖于PAF和白三烯的缺血再灌注反应增强有关。糖尿病患者对PAF的敏感性增加，CD11a的表达增加，可能是糖尿病患者对缺血再灌注过度炎

症反应的原因[34]。嗜中性粒细胞活性改变导致糖尿病对局部肠道和全身损伤的敏感性增加[35]。

6 总结

糖尿病加重器官缺血再灌注损伤涉及炎症反应、氧化应激、内质网应激、线粒体损伤、细胞活性物质产生以及葡萄糖代谢等多种复杂机制，目前该领域的研究还很宽泛，大部分的防治措施也是通过调节相关途径来改善糖尿病对器官再灌注损伤的影响。随着糖尿病患者基数的不断增加，糖尿病相关器官缺血再灌注损伤的深入研究迫在眉睫，仍需更多的基础及临床实验探究来找到防治糖尿病性器官缺血再灌注损伤的有效措施，为糖尿病患者带来福音。

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·综述·

CD123靶向治疗母细胞性浆细胞样树突状细胞肿瘤的研究进展与思考

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【摘要】 母细胞性浆细胞样树突状细胞肿瘤(BPDCN)是一种罕见的侵袭性血液系统恶性肿瘤,异质性强,可累及皮肤、淋巴结和骨髓,预后不佳。目前,对BPDCN的治疗尚无统一标准,主要采用急性髓系白血病、急性淋巴细胞白血病和淋巴瘤为主的方案,针对化疗有很高的反应,但中位无事件生存期通常很短,一般不到两年。2018年,SL-401被批准为首个针对2岁及以上BPDCN患者的靶向治疗,靶向治疗的出现为患者的生存提供了希望。本文将重点探讨靶向治疗的优势及最新的思考。

【关键词】 母细胞性浆细胞样树突状细胞肿瘤;恶性肿瘤;CD123;SL-401;靶向治疗

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Research progress and consideration of CD123 targeted therapy for blastic plasmacytoid dendritic cell neoplasm.

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【Abstract】 Blastic plasmacytoid dendritic cell tumor (BPDCN) is a rare and invasive hematological malignancy with strong heterogeneity. It may involve the skin, lymph nodes and bone marrow, and has a poor prognosis. At present, there is no unified standard for the treatment of BPDCN, and the main regiments are acute myeloid leukemia, acute lymphoblastic leukemia and lymphoma. There is a high response to chemotherapy, but the median eventless survival time is usually very short, generally less than two years. In 2018, SL-401 was approved as the first targeted therapy for BPDCN patients aged 2 years and older, and the emergence of targeted therapy offers hope for patient survival. This article will focus on the advantages of targeted therapy and the latest thinking.

【Key words】 Blastic plasmacytoid dendritic cell tumor (BPDCN); Malignant tumor; CD123; SL-401; Targeted therapy

母细胞性浆细胞样树突状细胞肿瘤是一种临床侵袭性血液恶性肿瘤,来源于树突状前体细胞,其典型特征是CD4、CD56和CD123的表达,没有共同的淋巴或髓系标记物,预后极差[1]。2008年,世界卫生组织分类将其分为急性髓性白血病(AML)和相关前体肿瘤[2]。2016年,世界卫生组织(WHO)造血及淋巴组织肿瘤分

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