·综述·

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能量代谢在肝缺血再灌注损伤中的作用机制及靶向治疗

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摘要: 肝缺血再灌注损伤(HIRI)是肝移植、肝部分切除术等手术过程中不可避免的主要并发症,其防治也是临床上的热点与难点问题。本文重点综述肝缺血再灌注过程中由能量代谢障碍引发损伤的机制及治疗策略,并总结当前与代谢相关的治疗进展,旨在为进一步阐明HIRI的发生机制、探索临床有效的HIRI防治策略提供新的思路。

关键词: 再灌注损伤; 能量代谢; 肝疾病

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Mechanism of action of energy metabolism in hepatic ischemia-reperfusion injury and related targeted therapies

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Abstract: Hepatic ischemia-reperfusion injury (HIRI) is an inevitable major complication during surgical procedures such as liver transplantation and partial hepatectomy, and its prevention and treatment are hotspots and difficulties in clinical practice. This article reviews the mechanism of injury caused by energy metabolism disorders during liver ischemia-reperfusion and related treatment strategies and summarizes the current advances in metabolism-related therapies, in order to provide new ideas for further clarifying the onset mechanism of HIRI and exploring effective clinical prevention and treatment strategies for HIRI.

Key words: Reperfusion Injury; Energy Metabolism; Liver Diseases

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肝缺血再灌注损伤(hepatic ischemia-reperfusion injury, HIRI)是指各种原因导致肝脏血流中断或不足出现缺血状态后,当血供恢复时,肝脏结构和功能损伤并未减轻反而加重的现象。HIRI常见于多种临床病理生理和肝脏手术过程,如肝移植、肝部分切除术及心肺复苏后等,也可因创伤和休克引发。同时,HIRI是肝脏外科手术后引发肝功能不全乃至肝衰竭的关键风险因素,对肝移植手术的成败发挥着至关重要的作用[1]。HIRI由缺血损伤期和后续的再灌注损伤期构成。在缺血、缺氧的早期阶段,葡萄糖储存耗竭和三磷酸腺苷(adenosine triphosphate, ATP)生成量急剧下降等多种因素会导致局部肝细胞出现水肿变性,并逐步进展至不可逆的细胞坏死阶段[2];而再灌注期肝血供恢复后,会继发急性炎症级联反应,造成肝细胞和非实质细胞的显著损伤[3]。在HIRI的发生发展过程中,能量代谢占据关键地位。抑制能量代谢会导致ATP产生降低和自由基生成增强,两者共同促进炎症反应,加重肝损伤[4]。因此,探寻预防或抑制HIRI过程中能量代谢障碍的有效措施,对提高肝移植成功率和改善患者手术预后具有重要

意义。本文重点综述肝缺血再灌注（ischemia reperfusion，I/R）过程中能量代谢障碍引起损伤的机制，以及目前靶向能量代谢相关的HIRI治疗策略，旨在为深入探讨HIRI机制提供理论依据，以期从能量代谢角度为临床HIRI的防治提供新策略。

1 HIRI的发生机制

目前，HIRI的发生机制尚未完全阐明，可能与巨噬细胞极化、线粒体自噬及能量代谢障碍等存在内在联系[5-6]。其中，能量代谢紊乱是其发生发展的重要机制之一，任何导致能量代谢紊乱的因素均可造成肝细胞功能障碍。

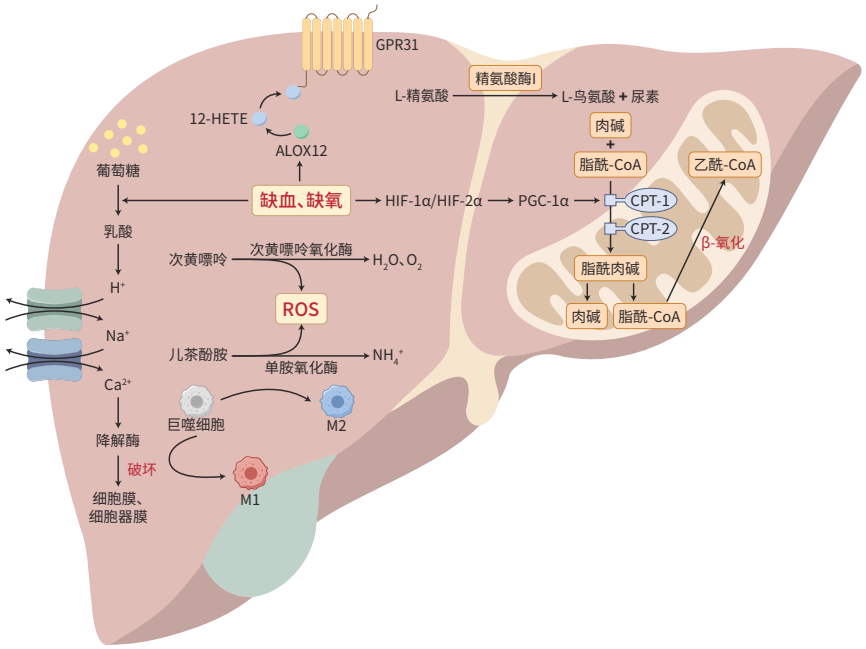
HIRI包括早期缺血和后续再灌注两个连续阶段。在缺血期，局部组织细胞的代谢活动发生紊乱，具体表现为供氧不足及糖原的持续耗竭。此外，血管闭塞会降低线粒体ATP合酶亚基δ的表达，进而影响ATP合成，同时伴随乳酸和酮体堆积，引发代谢性酸中毒。在再灌注阶段，肝损伤被显著放大。在肝血供恢复的初始阶段，肝巨噬细胞被激活以诱导氧化应激；而再灌注后6～24 h，大量肝非实质细胞被激活、积聚，释放炎症介质、细胞因子和补体[7]。次黄嘌呤在次黄嘌呤氧化酶的酶促作用下分解形成水和分子氧，产生并释放活性氧（ROS）成分[8]。因此，再灌注期间代谢紊乱现象显著，且伴有一系列严重的后续炎症反应，这些反应涉及直接的细胞毒理机制及由介质介导的间接损伤途径。

综上所述，肝缺血期间因缺氧导致ATP水平下降，而再灌注期血液供应的重建促进ROS的产生，进而诱导炎症反应和细胞死亡[9]。能量代谢产物的变化（如ATP下调和ROS生成）以及调控代谢途径的酶类直接参与HIRI的发生发展，因此深入探讨能量代谢在肝脏I/R中的变化特点尤为重要。

2 肝I/R过程中能量代谢变化的特点

在肝I/R的病理生理过程中，糖代谢、脂质代谢、氨基酸代谢等多种代谢途径的紊乱，经由代谢产物及调控代谢途径酶类的变化共同推动HIRI的发生发展（图1）。

2.1 糖代谢 有氧条件下，葡萄糖依次经糖酵解、氧化脱羧、三羧酸循环和氧化磷酸化等过程生成ATP，以满足肝脏的能量需求。但在肝缺血期间，氧气和能量供应中断，氧化磷酸化受阻，导致葡萄糖转向无氧糖酵解供能，ATP合成减少而乳酸累积增加。Ding等[10]的研究表明，过量乳酸堆积使胞质pH值从7.4降至6.6，从而诱导酸性微环境产生肝细胞毒性作用。酸性微环境会抑制调节性T细胞生成，打破免疫平衡，加重HIRI[11]。此外，低氧通过阻碍线粒体呼吸链电子传递、破坏膜电位，诱导氧化磷酸化功能障碍，由此引发的ATP合成锐减，促



注：ALOX12，花生四烯酸12-脂氧合酶；12-HETE，12-羟基二碳四烯酸；GPR31，G蛋白偶联受体31；HIF-1α/HIF-2α，缺氧诱导因子1α/2α；PGC-1α，过氧化物酶体增殖物激活受体γ共激活因子1α；CPT-1，肉碱棕榈酰转移酶1；CPT-2，肉碱棕榈酰转移酶2；ROS，活性氧；M1/M2，M1/M2型巨噬细胞。

图1 肝脏I/R过程中能量代谢的变化

Figure 1 Changes in energy metabolism during I/R in the hepatic

使Na^+-H^+交换或电压依赖性Na^+通道活性上调，经Na^+-Ca^{2+}交换机制触发钙超载。最终，钙信号失衡激活膜磷脂降解酶系，造成膜脂质过氧化与双分子层结构解体[12]。当血供恢复、肝脏重新获得氧后，缺血激活的中性粒细胞暴发性耗氧，产生大量ROS，引起脂质过氧化、细胞凋亡和坏死。缺血释放的ROS会促进中性粒细胞胞外诱捕网形成，促进炎症发展，从而加剧肝损伤[13]。在HIRI进程中，调控糖代谢途径的酶类也展现出显著的功能性作用。Zhang等[14]研究发现，GSK-3β（糖原合成酶激酶-3）的抑制性磷酸化在I/R的早期和晚期恢复阶段均有所增加，表明其与HIRI的早期激活和晚期稳态修复相关。此外，GSK-3β的缺失能够诱导骨髓源性巨噬细胞向M2型（修复表型）分化，从而减轻HIRI。

2.2 脂质代谢 肝脏在脂质生物合成与分解代谢中发挥着至关重要的作用。在I/R进程中，缺血阶段的脂质合成紊乱构成早期关键性触发因素，其通过调控信号转导途径，诱导后续炎症反应、氧化应激及细胞凋亡的发生。研究显示，缺血应激通过上调肝细胞ALOX12（花生四烯酸12-脂氧合酶）的表达，驱动12-HETE（12-羟基二碳四烯酸）合成累积并与G蛋白偶联受体-31结合，触发促炎通路，加重肝损伤[15]。此外，I/R组织中过量的ROS和炎性因子可激活神经酰胺合成酶，导致促凋亡介质神经酰胺异常蓄积，加速细胞凋亡及组织破坏[16]。脂质分解代谢也在I/R进程中受到显著抑制，缺氧微环境通过遏制缺氧诱导因子1α/2α调控的脂肪酸氧化关键基因转录，致使脂肪酸β-氧化活性减弱，引发代谢通路受阻及脂质异常蓄积[17]。进一步研究表明，脂质代谢旁路紊乱同样推动HIRI的发生发展。例如，I/R过程中肝心磷脂氧化显著增强，其氧化产物通过诱发氧化应激加剧肝损伤[18]；铁死亡抑制蛋白1通过调控烟酰胺腺嘌呤二核苷酸-二氢泛醌通路清除脂质过氧化物，增强抗氧化防御以对抗铁死亡[19]；乳酸激活的赖氨酸乙酰转移酶-8则直接作用于线粒体磷酸烯醇式丙酮酸羧激酶-2，重塑脂代谢并加速HIRI进展[20]。这些脂质代谢障碍均可促使脂质稳态网络发生适应性重构，增加移植后高脂血症及脂肪性肝病风险[21]。由此可见，脂质代谢从多层次、多水平调控HIRI的发生和发展，有望成为防治HIRI的重要靶向代谢通路。

2.3 氨基酸代谢 氨基酸代谢异常在HIRI的触发中同样占据重要地位。Zhu等[22]研究发现，在HIRI进程中，损伤肝细胞释放的精氨酸酶通过大量水解L-精氨酸产生L-鸟氨酸和尿素，导致精氨酸耗竭，从而加速HIRI发展。此过程中释放的GGT促使谷胱甘肽降解增强，通过诱导ROS生成增加和氧化应激加剧放大肝损伤效应[23]。同时，犬尿氨酸通路在I/R进程中发生代谢重塑，该代谢流重编程通过扰乱NAD^+（烟酰胺腺嘌呤二核苷酸）稳态平衡加剧肝损伤[24]。部分因素在HIRI进程中发挥关键保护作用，例如肠道菌群代谢产物谷氨酰胺及α-酮戊二酸可通过驱动巨噬细胞向M2型极化、促进组织修复来减轻HIRI[25]。

2.4 其他代谢 缺血期琥珀酸脱氢酶的酶活性逆转导致细胞内琥珀酸盐蓄积，再灌注期琥珀酸盐则经由琥珀酸脱氢酶介导的氧化再生途径与线粒体呼吸链复合体逆向电子传递，驱动ROS生成[26]。此外，I/R应激下肝细胞胆汁酸代谢发生重编程，促进三羟基化胆汁酸合成，通过抑制巨噬细胞炎性体激活来减轻HIRI炎症反应[27]。

3 靶向肝脏代谢的相关治疗研究进展

肝脏是代谢的主要器官，具有良好的自我修复能力，而HIRI首先破坏肝脏的代谢稳态。因此，在肝I/R的早期阶段进行代谢干预能够缓解初始损伤和后期炎症，有望减轻组织损伤程度和免疫调节负担。目前，多种相关治疗方法已展现出良好的应用前景。

3.1 药物干预 在HIRI的治疗中，中成药和中药方剂因多靶点作用受到关注。例如，丹参酮ⅡA通过抑制代谢异常诱导的HMGB1（高迁移率族蛋白B1）上调，降低TLR-4（Toll样受体4）/NF-κB（核因子κB）信号通路活性发挥肝保护作用[28]；甘草次酸同样具备下调HMGB-1表达的能力，并通过阻断TLR-4活化，有效减少炎症因子的产生与释放[29]；紫草酸镁B可通过抑制Jak2/Stat3（Janus激酶/信号转导和转录激活因子）通路减轻肝损伤[30]；地黄通过调节脂质代谢改善HIRI，黄芩素作为抗氧化成分可阻断氧化应激介导的肝凋亡[31]。

西药方面，酸性神经酰胺酶预处理可通过双向调节神经酰胺代谢（降低神经酰胺水平并提升保护性鞘氨醇-1-磷酸水平）显著缓解肝损伤[32]；重组成纤维细胞生长因子-21可通过改善脂质代谢，抑制先天性免疫炎症，缓解HIRI，罗伊氏乳杆菌则通过纠正代谢物失衡发挥肝保护效应[33-34]；熊去氧胆酰溶血磷脂酰乙醇酰胺可抑制胞质磷脂酶A2对线粒体膜磷脂的水解，调控磷脂代谢与线粒体的交互串扰，从而恢复线粒体功能并改善I/R损伤[35]；缺血阶段联合5-氨基乙酰丙酸和几丁质酶样蛋白-3治疗，可促进脂质代谢及ATP生成[36]。此外，胆汁酸类药物通过促进牛磺-β-鼠胆酸合成，抑制巨噬细胞炎性小体激活以缓解I/R的炎症损伤[27]。

3.2 基因治疗 多基因位点及相关信号通路在I/R代谢调控中发挥核心作用,针对相应基因进行沉默或强化干预,可有效缓解代谢紊乱导致的肝损伤。胰岛素诱导基因-2通过上调抗氧化磷酸戊糖途径重塑糖代谢,有效减轻HIRI[37]。肝细胞过表达热休克蛋白A12A可显著改善I/R所致肝损伤,提示靶向强化该蛋白对HIRI患者具有治疗潜力[38]。人胎盘间充质干细胞来源的外泌体对HIRI具有缓解作用,其低氧条件下的糖酵解供能可被Lin28蛋白增强,肝保护效应进一步强化[39]。

3.3 缺血预处理 缺血预处理(ischemic preconditioning,IPC)策略涉及在长期缺血再灌注前对目标器官进行短暂且重复的缺血-再灌注循环,提升器官对后续持续缺血的耐受力。具体而言,IPC可通过减缓肝缺血期ATP消耗速率并遏制乳酸堆积以纠正代谢紊乱,实现肝保护效应[40]。大量研究证实,IPC能够减轻HIRI程度,其机制包括抑制脂质过氧化过程、调节免疫反应、促进自噬功能恢复以及加速肝I/R后胆汁流量恢复[41]。

3.4 机械灌注 近年来,肝肿瘤及肝硬化等疾病广泛采用肝切除和肝移植技术,而机械灌注技术作为肝移植供肝保存的重要策略,可有效缓解HIRI并维持离体肝脏功能[42-43]。该技术利用机械装置构建循环灌注系统,以脉冲方式向肝血管灌注保存液,延长器官存续时间[44-45]。在此过程中,灌注液提供的代谢底物可满足I/R肝脏的代谢需要,同时清除代谢产物和自由基,缓解因I/R代谢紊乱引发的肝损伤。其优势包括保护肝脏微循环、改善移植物功能,且可通过添加细胞保护剂及免疫调节剂进一步增强HIRI改善效果。

4 小结与展望

能量代谢调控在HIRI的发生发展中发挥重要作用。本文综述糖代谢、脂质代谢及氨基酸代谢在肝I/R中的变化特点,上述代谢过程主要通过代谢物生成紊乱、信号通路异常激活和相关代谢酶调动等方式参与肝I/R进程。然而,目前对HIRI机制的认知仍存在局限,有待深入研究。此外,针对HIRI治疗药物的研究多处于基础实验阶段,相关临床研究和临床转化有待推进。未来研究仍需深入探究能量代谢在HIRI中调控网络的复杂机制,加强治疗药物的临床转化,突破生物利用度优化及脱靶效应控制等技术瓶颈,以实现代谢通路的精准干预。综上所述,能量代谢的调控为HIRI的防治提供了新方向,深入理解其相关机制,并研发靶向能量代谢更有效的药物,以期从能量代谢角度为HIRI提供新型治疗策略。

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