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钠－葡萄糖共转运蛋白2抑制剂改善病理性心脏重塑的研究进展

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摘　要

心脏重塑是心脏在持续性压力、代谢等刺激下发生的适应性形态结构变化过程，其中病理性心脏重塑是心血管不良事件独立危险因素。新型降糖药物钠－葡萄糖协同转运蛋白-2 (sodium-glucose cotransporter 2, SGLT2)抑制剂除了能够降低容量负荷、减少心血管死亡及住院风险外，还展现出改善心脏结构和功能、逆转心脏重构的潜力。本文旨在对SGLT2抑制剂在改善心脏重塑方面的研究进展进行综述。

关键词

钠－葡萄糖共转运蛋白2抑制剂，心脏重塑，心力衰竭，分子机制

Progress in the Treatment of Pathological Cardiac Remodeling with Sodium-Glucose Cotransporter 2 Inhibitors

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Abstract

Cardiac remodeling, a process of adaptive morphological and structural alterations in the heart triggered by sustained stress, metabolic, and other stimuli, among which pathological cardiac re-

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modeling serves as an independent predictor of adverse cardiovascular outcomes. Recently, novel hypoglycemic agents, specifically sodium-glucose cotransporter 2 (SGLT2) inhibitors, have emerged as potential therapeutics that not only alleviate volume overload but also reduce the risk of cardiovascular mortality and hospitalization. Additionally, these agents exhibit promising effects in improving cardiac structure and function, as well as reversing pathological cardiac remodeling. This article aims to comprehensively review the progress made in investigating the therapeutic benefits of SGLT2 inhibitors in ameliorating cardiac remodeling.

Keywords

Sodium-Glucose Cotransporter 2 Inhibitors, Cardiac Remodeling, Heart Failure, Molecular Mechanisms

1. 引言

心血管疾病严重威胁人类健康，是全球死亡的主要原因，而心脏重塑在其中扮演着重要角色。心脏重塑可分为生理性和病理性两种类型。生理性重塑是对生长、运动和妊娠等外部变化的有益适应，而病理性重塑则是在炎症、缺血再灌注(ischemia reperfusion, I/R)损伤、血流动力学改变、神经体液过度激活等病理刺激下，心脏结构和功能逐渐恶化的过程，是心力衰竭病程进展的重要因素[1]。钠－葡萄糖协同转运蛋白-2 (sodium-glucose cotransporter 2, SGLT2)抑制剂作为新型口服降糖药物不仅具有显著的降糖效果，还能带来心血管获益，包括改善心肌能量代谢和逆转心肌重构[2]。然而，SGLT2 抑制剂对于临床结局及心脏结构的改善不能仅通过降糖作用解释，其具体作用机制尚不清楚。因此，本文将对 SGLT2 抑制剂在改善病理性心脏重塑方面的研究进展作一综述，以期为发现新治疗靶点、逆转心脏重塑、改善心脏功能及预后提供帮助。

2. SGLT2 抑制剂对心脏重塑的影响

SGLT2 抑制剂是一种治疗 2 型糖尿病(Type 2 Diabetes Mellitus, T2DM)的新型口服降糖药物。它主要通过阻断近端肾小管中葡萄糖的重吸收，从而发挥非胰岛素依赖性的降血糖作用，可显著降低心血管不良事件发生风险[3] [4]。研究表明，SGLT2 抑制剂在逆转病理性心脏重塑方面起着重要作用，而改善心脏重塑可能是 SGLT2 抑制剂心脏获益的核心机制[5] [6]。

2.1. SGLT2 抑制剂在动物实验中对心脏重塑的影响

在小鼠模型中，通过组织学改变显示出 SGLT2 抑制剂对心脏重塑的改善。Zhang 等[7]发现，恩格列净(Empagliflozin, EMPA)能够改善心肌肥大和纤维化。Moellmann 等[8]也观察到，在心脏肥大小鼠模型中，经过 10 周的厄格列净治疗，左室纤维化减少，左室功能改善。

在大鼠模型中，研究者通过超声心动图更直观地观察到心脏重塑的改善。在代谢综合征大鼠模型中，EMPA 使左室容积和心脏质量减少[9]。进一步研究表明，SGLT2 抑制剂独立于降糖作用外发挥逆重构作用。在射血分数保留的心力衰竭(heart failure with preserved ejection, HFpEF)大鼠模型中，无论血糖水平如何，EMPA 使左室容积和室壁应力显著降低[10]。伊格列净同样可使非糖尿病心肌病大鼠左室质量和间隔

厚度减少，且不影响血糖水平[11]。

在心衰猪模型[12] [13]中，EMPA 可降低左室质量和球形度并减少左室扩张。此外，组织学及心脏磁共振还观察到心肌细胞肥大和间质纤维化减少，提示 SGLT2 抑制剂对心脏重塑有改善作用。各类动物模型研究表明，无论是否合并糖尿病，使用 SGLT2 抑制剂均可改善心肌细胞肥大和心肌纤维化。

2.2. SGLT2 抑制剂在人体研究中对心脏重塑的影响

体外研究表明，SGLT2 抑制剂显著减轻心肌间质纤维化，并可能对结构重塑产生有利影响。Kang 等[14]研究显示，从人心房组织中分离出的心脏成纤维细胞在接受 EMPA 治疗后，显著减弱了转化生长因子 β1 (TGFβ1)诱导的成纤维细胞活化。此外，形态学显示，暴露于 EMPA 的肌成纤维细胞呈现更静止的表型，且细胞介导的细胞外基质重塑显著减少。最后，基因谱显示，EMPA 显著抑制促纤维化标志物表达。

在 T2DM 患者中，SGLT2 抑制剂能减少心脏病理性重塑。EMPA-HEART Cardiolink-6 试验[15]发现，在 T2DM 合并冠状动脉疾病患者中，接受 EMPA 治疗 6 个月后，左室质量指数显著降低，且与血压变化无关。同样，DAPA-LVH 试验[16]证明达格列净(Dapagliflozin, DAPA)具有类似效果。

针对心衰人群，EMPA-TROPISM 试验[17]通过心脏磁共振观察到，EMPA 显著降低了射血分数降低的心力衰竭患者的左室容积、质量及球形度，减少了心肌纤维化。Empire HF 试验[18]同样观察到类似结果，并通过更大的样本量增加了结果的可靠性。

目前，关于 SGLT2 抑制剂对人心脏重塑的研究较少，普遍随访时间短，长期效果不明确，且针对非糖尿病、HFpEF 患者的研究较少，仍需进一步研究。

3. SGLT2 抑制剂逆转病理性心脏重塑的潜在机制

病理性心脏重塑是各种心脏疾病的普遍终点。SGLT2 抑制剂对病理性心脏重塑的改善显示了其在心血管疾病中的重要影响，但其潜在作用机制尚不明确。当前研究表明，这种积极效果可能涉及以下几个方面。

3.1. 心肌效应：维持心肌细胞稳态、抑制心肌纤维化

SGLT2 抑制剂引起的生酮作用和红细胞增多反映了对营养不足和缺氧的典型反应[19]。该反应提示 SGLT2 抑制剂的心血管益处可能与营养剥夺信号的激活有关，从而促进自噬、改善线粒体功能、减少活性氧产生、减少细胞凋亡、抑制炎症和纤维化，并增强心肌细胞的活力。

3.1.1. 自噬

适度激活自噬有助于保护心脏免受压力超负荷、缺氧和心脏毒性物质的损伤[20] [21]。自噬不足或过度会影响病理性心脏重塑的进程。心脏逆重构的患者自噬得到改善，而自噬的持续降低是不良预后的因素之一[22] [23]。

SGLT2 蛋白是一种营养过载传感器，应用 SGLT2 抑制剂会导致尿糖增加，从而引发饥饿状态，激活沉寂信息调节因子 1 (SIRT1)及其下游效应因子单磷酸腺苷激活的蛋白激酶(AMPK)，从而促进自噬的上调[24]。增强自噬活性可以减少心脏纤维化及重塑，并改善心脏功能[25] [26]。此外，苄氯素 1 (BECN1)介导的内质网应激也是调节自噬的途径之一。研究显示，EMPA 能够调节心肌细胞中基于 BECN1 的自噬，并通过 BECN1-Toll 样受体 9-SIRT3 轴发挥心肌保护作用[27] [28]。此外，EMPA 还可通过靶向心肌细胞上的钠/氢交换蛋白 1 (NHE1)来调节过度的自噬[29]。多项研究表明，SGLT2 抑制剂通过多种途径调节自噬的活性来发挥心脏保护作用。

3.1.2. 氧化应激

氧化应激是病理性心脏重塑发展的关键因素[30]。多项研究表明，SGLT2 抑制剂通过减少体内氧化应激来保护心肌细胞。Li 等[31]在 KK-Ay 糖尿病小鼠模型中发现，EMPA 通过激活核因子样红系因子 2/抗氧化反应元件信号传导抑制心脏氧化应激，从而减少心肌肥大。在非糖尿病模型中，EMPA 通过增强线粒体的氧化磷酸化和减少活性氧的产生减少氧化应激，改善心脏功能并减少重塑[32] [33]。Kondo 等[34]首次证明，卡格列净(Canagliflozin, CANA)通过 SGLT1/AMPK/Rac1 信号通路抑制心肌 NADPH 氧化酶活性，从而减轻氧化应激，对人心肌产生保护作用。然而，现有研究主要集中在高血糖或糖尿病状态下，对正常血糖及涉及人类组织的研究仍然相对较少。

3.1.3. 细胞凋亡

SGLT2 抑制剂可通过抑制细胞凋亡途径减少心脏重塑并改善心脏功能。Liu 等[35]发现 EMPA 可抑制心肌梗死早期心肌细胞凋亡并改善心脏重塑。此外，DAPA 可使线粒体裂变正常化，并减少心肌细胞凋亡，从而改善急性心肌梗死后的心脏重塑[36]。Ren 等[37]研究表明，DAPA 还通过激活 SIRT1 来抑制内质网应激诱导的细胞凋亡，并改善心脏重塑。尽管目前已有多项研究表明 SGLT2 抑制剂可通过调节线粒体途径减少细胞凋亡，但对于死亡受体通路的研究仍较少，未来需要进一步深入研究。

3.1.4. 铁死亡

铁死亡是由大量脂质过氧化介导的膜损伤从而引起铁依赖性调节坏死，在多种心血管疾病的发生和进展中发挥作用[38] [39]。目前已有多项研究表明，SGLT2 抑制剂可以减少铁死亡，而铁死亡与心脏重塑及功能影响有关。研究表明，通过使用铁抑素-1 抑制铁死亡，可以预防晚期糖基化产物诱导的心脏重塑和功能障碍，并通过增强谷胱甘肽过氧化物酶 4 信号传导来减轻心脏纤维化和病理重塑[40] [41]。Ma 等[42]研究表明，CANA 可通过减少铁的摄入和铁超负荷以及抑制氧化应激来调节铁死亡以治疗 HFpEF。此外，DAPA 可通过丝裂原活化蛋白激酶信号通路减少铁死亡，并发挥心脏保护作用[43]。减少铁死亡可能是 SGLT2 抑制剂改善心脏重构的一种途径，但仍需进一步探索。

3.1.5. 心肌细胞肥大及纤维化

在许多心血管疾病中，心肌细胞肥大和心肌纤维化与病理性心脏重塑密切相关[1]。在纤维化的信号通路中，TGFβ1/Smad 对诱导和维持胶原合成以及激活心脏成纤维细胞至关重要，并在一定程度上介导了血管紧张素 II 引起的结构重塑[44]。研究证实，EMPA 能够减轻由 TGFβ1 介导的人类成纤维细胞活化和细胞介导的胶原重塑[14]。进一步的研究显示，DAPA 以血糖非依赖性方式调节 TGFβ1/Smad 信号传导，并减弱心肌纤维化和胶原合成，改善了心脏重塑[45]。Zhang 等[7]研究表明，EMPA 还通过下调 Toll 样受体 4 的表达并抑制转录激活因子 3 的磷酸化，来缓解心肌肥大和纤维化。总之，SGLT2 抑制剂能够调节多种信号通路，从而抑制心肌细胞肥大和心脏纤维化。

3.2. 间质效应：减轻炎症

炎症显著影响心脏重塑和心衰的进展[46]。越来越多的证据表明 SGLT2 抑制剂具有广泛的抗炎作用，且主要归因于它能抑制炎症小体的激活[47]。靶向特定的细胞因子或炎症途径可以有效减轻心脏的病理性重塑。

多种促炎细胞因子通过影响心肌细胞、成纤维细胞和免疫细胞来介导心脏重塑。Zhang 等[48]发现，DAPA 能降低 HFpEF 猪的 IL-6 和 TNF-α 水平，并逆转心脏重塑。Yan 等[49]观察到，DAPA 降低了促炎细胞因子水平，促进巨噬细胞向 M2 极化，并激活转录激活因子 3 信号通路，从而发挥抗炎作用并减少心脏损伤。此外，研究表明 EMPA 通过减少细胞内 Ca2+水平，抑制炎症小体的激活和细胞因子的表达，

从而减轻炎症反应和心脏纤维化，改善心衰小鼠心脏重塑及功能[50]。

在慢性炎症等病理情况下，心外膜脂肪组织(EAT)中合成的促炎细胞因子可直接分泌到心肌中，导致心肌炎症和纤维化。多项研究表明，SGLT2 抑制剂可降低 EAT 厚度并改善心外膜脂肪细胞的分化，减少 EAT 炎症趋化因子和炎症标志物的产生[51]-[53]。Takano 等[54]首次证明，SGLT2 主要在人 EAT 的前脂肪细胞中表达，EMPA 可能通过调节 IL-6 的表达来抑制前脂肪细胞的成熟和分化，以及 EAT 中炎症因子的表达和分泌。然而，SGLT2 介导的 EAT 旁分泌谱变化机制尚不清楚，仍需体外机制研究来探索复杂的细胞内信号传导。

越来越多的证据表明，SGLT2 抑制剂在减轻炎症方面具有重要意义，这可能部分解释了其改善斑块形成、内皮功能障碍、心脏纤维化和心脏重塑风险的原因[55]。然而，未来仍需进一步研究以确定这些抗炎作用是否与其降低心衰住院率和心血管死亡有关。

3.3. 血管效应：改善内皮功能，保护微血管系统

内皮功能障碍常伴有心脏肥大和纤维化，并与各种心血管疾病的发展相关。促进血管生成可增加微血管和小动脉的密度，从而减少心脏重塑[56] [57]。Juni 等[58]首次证明，EMPA 可以直接作用于心脏微血管内皮细胞，改善微血管功能紊乱。Nakao 等[59]发现，EMPA 通过激活 Akt/NOS/NO 通路防止内皮细胞凋亡，并维持毛细血管形成，从而改善收缩功能障碍。然而，仅使用电子显微镜观察微血管的结构变化难以全面评估其功能，Adingupu 等[60]应用无创多普勒超声成像监测冠状动脉血流速度储备和右室面积变化分数的改变，进一步证实 EMPA 可改善冠状动脉微血管功能。各类研究表明，SGLT2 抑制剂可能通过改善内皮功能和血管生成，保护微血管系统，从而改善心脏重塑。

3.4. 神经系统：交感神经系统活动减少

交感神经系统(SNS)在心脏重塑中发挥重要作用，SGLT2 抑制剂降低血压而没有代偿性增加心率，表明其可能抑制 SNS。Herat 等[61]研究发现，用 6-羟基多巴胺对 SNS 进行化学去神经支配会降低肾脏 SGLT2 的表达，且 DAPA 治疗显著减少了心肾酪氨酸羟化酶及去甲肾上腺素水平，降低了 SNS 活性。因此，SGLT2 抑制与 SNS 活性之间可能存在双向关系。EMBODY 试验[62]显示，EMPA 显著改善了交感神经和副交感神经活动的参数，但研究中 123I-间碘苄胍心肌闪烁显像的延迟期 H/M 比值和洗脱率的改善在 EMPA 组和安慰剂组之间没有差异，这可能表明 SGLT2 抑制剂能降低整体交感神经张力，而非心脏局部效应。Raza 等[63]综合相关研究后得出类似结论，即 SGLT2 抑制剂可能通过降低肾传入神经活性和抑制全身 SNS 激活而发挥心血管保护作用。

3.5. 生理学效益：维持离子稳态

钠、钙平衡失调是导致心脏重塑的关键因素，其中晚期钠电流(INaL)的病理性增加和 NHE1 活性升高起主要作用[64]。在心力衰竭小鼠模型中，EMPA、DAPA、CANA 均表现出对 INaL 选择性抑制作用，且效果相当；且在单个心肌细胞中，EMPA 能可逆性地降低 INaL 诱导的钙紊乱的发生率[65]。此外，Baartscheer 等[66] [67]提出，SGLT2 抑制剂可降低心肌中的 Na+、Ca2+浓度并抑制 NHE。同时在使用 NHE1 抑制剂对细胞进行预处理时，观察到 EMPA 的效果减弱，因此推测 SGLT2 抑制剂可能通过抑制 NHE1 发挥心脏保护作用。然而，Li 等[68]并未发现 EMPA 能与 NHE1 直接相互作用，且 NHE1 抑制剂处理心肌细胞可观察到收缩力降低和钙瞬变，但 EMPA 没有类似变化，提示 NHE1 抑制剂并不能模拟 SGLT2 抑制剂对心肌细胞的作用。因此，SGLT2 抑制剂的心脏获益是否与直接抑制心脏 NHE1 相关，有待进一步深入研究。

3.6. 代谢效应：改善能量代谢

心脏是人体代谢最活跃的器官之一，日常活动需要消耗大量三磷酸腺苷(ATP)，并可利用脂肪酸、葡萄糖等多种能量底物。心肌能量代谢的变化可促进病理性心脏重塑的发展[69]。心脏代谢重塑通常表现为在各种病理生理条件下，从以脂肪酸代谢为主转变为以葡萄糖代谢为主。虽然糖酵解使心脏对缺血的耐受性更强，但由于胰岛素抵抗和葡萄糖氧化减少，糖酵解不能为患病的心脏提供足够的能量，进一步加重心脏重塑。因此，改善心脏能量代谢，提高能量底物利用效率可能是治疗心力衰竭和心脏重塑的有效策略。

Li 等[68]的研究发现，EMPA 可通过与葡萄糖转运蛋白结合，减少过度糖酵解，恢复脂肪酸摄取并改善线粒体氧化磷酸化。此外，葡萄糖摄取减少还可激活 AMPK，以减少病理性心脏重塑。相反，Trang 等[70]发现，EMPA 通过减少脂肪酸代谢、增加葡萄糖代谢，改善糖尿病心肌病大鼠的心脏重塑。这些实验结果的差异可能与糖尿病心肌病中脂肪酸增加导致的脂毒性和胰岛素抵抗相关，后续尚需进一步研究。此外，Yurista 等[33]研究发现，EMPA 通过增加酮体的利用率以及葡萄糖和脂肪酸的氧化，使心脏 ATP 生成增加并改善了心脏代谢。然而，这项研究未提供直接证据表明 EMPA 的心脏益处与酮体氧化增加有关，也未量化酮体氧化与心肌 ATP 水平升高之间的关系。Santos-Gallego 等[12]研究进一步表明，EMPA 可通过将心肌底物利用从葡萄糖转向酮体、支链氨基酸和游离脂肪酸的氧化来减轻心脏重塑。酮体为心脏提供了额外的燃料来源并改善心脏功能，但与葡萄糖氧化相比，酮体氧化并不是一种更有效的能量底物来源，因此并不会提高心脏的效率。目前，酮体氧化增加对心脏功能的长期影响及对其他潜在不良途径的干扰仍存在争议，心肌酮体氧化与 EMPA 的心脏保护作用之间的关系仍未明确，需进一步深入研究。综合而言，一系列研究表明，SGLT2 抑制剂可能不会提高心脏的效率，但为心脏提供了额外的能量底物来源，改善了心脏能量代谢，从而减轻心脏重塑。

4. 总结和展望

SGLT2 抑制剂是一种重要的心血管药物，可以显著降低心血管不良事件发生风险。多项基础研究和临床试验表明，SGLT2 抑制剂具有抗心脏重塑的作用。当前的理论认为，它可能通过多种机制逆转病理性心脏重塑，包括维持细胞稳态、减少炎症反应、改善血管重塑、抑制交感神经系统、维持离子稳态和优化能量代谢等。然而，SGLT2 抑制剂在心脏中的具体作用机制及潜在分子机制仍需进一步探索。此外，很少有研究比较 SGLT2 抑制剂对不同人群(如糖尿病与非糖尿病人群、缺血性与非缺血性心脏病人群)心脏重塑的影响及所涉及的分子途径是否相同。近年来，表观遗传学在疾病发展中的作用受到广泛关注，但 SGLT2 抑制剂在心脏重塑中的表观遗传机制尚未明确。总之，未来需要更多研究以探索 SGLT2 抑制剂改善心脏重塑的潜在治疗靶点，为临床诊疗提供新方案和策略。

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