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SGLT-2抑制剂抗高血压作用及研究进展

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摘 要

钠－葡萄糖协同转运蛋白2抑制剂(sodium-glucose transporter 2 inhibitors, SGLT-2i)是一类较新颖的降糖药物，不依赖于刺激胰岛素分泌，通过尿糖来降低血糖，大量的证据表明其在心血管领域具有突出应用价值。高血压患病人群基数庞大，高血压不单是众多疾病的合并症，同时也是许多疾病的危险因素并影响相关预后。随着对SGLT-2i的深入了解及受试者临床试验的结果总结，降压作用受到关注，突显了该药物单纯降糖之外的潜在价值及多效性。现就SGLT-2i临床应用中的降压证据及可能的降压机制进行综述。

关键词

SGLT-2抑制剂，高血压，临床应用，作用机制

Antihypertensive Effects of SGLT-2 Inhibitors and Progress in Research

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Abstract

Sodium-glucose transporter 2 inhibitors (SGLT-2i) are a relatively new class of hypoglycemic agents that do not rely on stimulation of insulin secretion to lower blood glucose via urinary glucose, and a large body of evidence suggests that they have outstanding cardiovascular applications. With a large population base, hypertension is not only a comorbidity of many diseases, but also a risk factor for many diseases and affects the prognosis. With the deeper understanding of SGLT-2i and the summary of results from clinical trials in subjects, the antihypertensive effect has come under scrutiny, highlighting the potential value and multiplicity of the drug beyond glucose lowering alone. The evidence for antihypertensive effects and possible antihypertensive mechanisms in the clinical application of SGLT-2i are reviewed.

Keywords

Sodium-Glucose Transporter 2 Inhibitors, Hypertension, Clinical Application, Pharmacology

1. 引言

高血压是一种以全身动脉压持续升高为特征的疾病，伴随神经－内分泌系统的激活与适应性改变，是糖尿病(Diabetes mellitus, DM)、心力衰竭(Heart failure, HF)、慢性肾脏病(Chronic kidney disease, CKD)等患者心血管事件的一个公认的危险因素。难治性高血压(Resistant hypertension, RH)在上述患者人群中非常普遍[1] [2]，尽管许多患者已经接受常规降压药物单药甚至联合治疗，但仍未能达到指南推荐的理想血压目标(<130/80 mmhg) [3] [4]。越来越多的证据表明，降低血压至目标水平可以改善其临床预后[5]。SGLT-2 是一类主要位于近曲小管顶端膜上的协同转运蛋白，负责肾脏内 90%以上的葡萄糖重吸收[6]。SGLT-2i 最初被设想为降糖药物，独立于葡萄糖依赖的胰岛素途径，通过抑制葡萄糖在肾近端小管的重吸收，增加尿糖排泄降糖。在 SGLT-2i 的临床研究中观察到了受试者血压的降低，SGLT-2i 的出现弥补了一种兼有心肾益处及降压特性药物的空白。本文旨在总结 SGLT-2i 在 DM、HF、高血压、CKD 患者临床应用中降压的证据并阐述可能的降压机制。

2. SGLT-2i 的临床降压作用

2.1. 降低 DM 患者的血压

DM 与高血压常共存，血压得到最佳控制对 DM 患者的治疗至关重要，是预防血管并发症和降低相关死亡率的最有效方法之一。EMPA-REG OUTCOME 是 SGLT-2i 首个且具有里程碑意义的临床试验，结果发现恩格列净能够显著减少具有高心血管疾病风险的 2 型糖尿病(Type 2 diabetes mellitus, T2DM)患者的主要心血管不良事件。其中，有 90%以上的受试者应用降压药物，治疗 16 周后，恩格列净组收缩压较基线降低了 4~6 mmHg [7]。EMPA-REG OUTCOME 试验中观察到的降压效果，在随后 CANVAS [8]、DECLARE-TIMI 58 [9]、VERTIS CV [10]试验中得到进一步证实。SGLT-2i 针对 1 型糖尿病(Type 1 diabetes mellitus, T1DM)人群的应用价值仍在不断探索。其中，EASE [11]、DEPICT [12] [13] [14]、

inTandem [15] [16]等试验发现了 SGLT-2i 对 T1DM 患者的降收缩压作用。在一项针对 DEPICT 试验的事后分析中观察到，达格列净 5mg 组的降压效果最优，收缩压较基线下降 6.64 mmhg，该降压作用一直持续到 52 周[17]。

2.2. 降低 HF 患者的血压

基于大量研究与荟萃分析的研究结果，SGLT-2i 显著减少了稳定性心血管疾病和急性心力衰竭患者 HF 住院次数，降低了心血管疾病风险[18] [19]。欧洲心脏病学会推荐 SGLT-2i 作为 HF 的基线治疗药物，意味着肾素－血管紧张素系统抑制剂、β 受体阻滞剂、醛固酮受体拮抗剂和 SGLT-2i 治疗“新四联”时代的到来[20] [21]。面对射血分数降低性 HF 患者，DAPA-HF 结果显示，达格列净组在干预第 2 周时收缩压显著降低 2.54 mmHg，这种作用一直持续到试验结束——32 周后收缩压较基线降低 1.41 mmHg [22]。然而，EMPEROR-Reduced 试验[23]发现恩格列净组受试者收缩压与基线相比没有变化。在慢性(射血分数保留性/中间范围射血分数)HF 患者中，EMPEROR-Preserved 结果显示恩格列净 10 mg 组受试者在 52 周后，收缩压下降了 1.2 mmHg [24]。李敏等[25]人对纳入的 16 项有关 HF 患者的随机对照试验的 meta 分析表明——与对照组相比，受试者经 SGLT-2i 治疗后收缩压降低 1.68 mmHg 且有统计学意义($p = 0.001$)，舒张压降低 1.06 mmHg 而没有统计学意义($p = 0.33$)。

2.3. 降低高血压患者的血压

Baker 等[26]人总结了之前致力于了解 SGLT-2i 在高血压患者中降压特性的临床试验，试验中均监测患者的 24 小时动态血压，SGLT-2i 组受试者收缩压显著降低 3.76 mmhg，舒张压降低 1.83 mmHg。RH 作为一种特殊类型的高血压，更易并发靶器官损害，且预后差。RH 的治疗方案较为局限，对传统降压药物不断提出新挑战，SGLT-2i 的出现似乎带来了新的希望。Amira Obeid 等人[27]报道了一名 68 岁男性高血压患者，尽管联合了三种降压药(雷米普利、非洛地平和阿替洛尔)并服用最大耐受剂量，血压也未能得到良好的控制(平均日间血压为 168/99 mmHg)。当把卡格列净加入该患者降压方案后发现血压显著降低，最佳临床读数为 137/80 mmHg。在 EMPA-REG OUTCOME 的事后分析中，定义假定 RH 患者为基线时使用 ≥ 3 类抗高血压药物，至少包括利尿剂，且血压不受控制(收缩压 ≥ 140 和/或舒张压 ≥ 90 mmHg)。恩格列净治疗 12 周后，假定难治性高血压组收缩压下降 4.5 mmHg，无假定难治性高血压组收缩压下降 3.7 mmHg，血压的下降在随访期间持续存在[28]。

2.4. 降低 CKD 患者的血压

DAPA-CKD [29]旨在评估达格列净对 CKD 肾脏结局和心血管死亡率的影响，该试验发现，无论有无 DM，达格列净均可减少 CKD 患者的肾脏不良结局并降低心血管死亡率。CKD，特别是合并高血压时，预示着进展为心肾功能衰竭的风险急剧增加。SGLT-2i 的降糖作用在一定范围内随着应用者肾功能下降而下降，但其降压作用几乎不受影响[30]，可有效降低 CKD 患者的血压[31]。CREDENCE 试验发现，相对于安慰剂组，卡格列净组收缩压在第 3 周时显著降低约 3.5mmHg，该降压作用持续整个试验期间，最终收缩压、舒张压平均差异分别−3.30 mmHg，−0.95 mmHg [32]。SCORED 试验招募了有心血管疾病风险的 CKD3 期患者。受试者经索格列净干预 4 周后收缩压降低 2.4 mmHg，舒张压降低 0.80 mmHg [33]。EMPA-KIDNEY [34]在对 CKD 人群随访中同样观察到恩格列净组较对照组收缩压的降低。

3. SGLT2i 可能的降压机制

3.1. 利钠、利尿

SGLT-2 是一种主要位于近端小管 S1 段的转运蛋白，具有低亲和力、高容量的特性，主要负责经肾

小球自由滤过的葡萄糖在近端小管绝大部分的重吸收。小管基底膜外侧的钠钾泵使小管上皮细胞内 Na^+ 浓度低于管腔滤液的 Na^+浓度，并维持这一钠电化学浓度梯度。钠离子沿电化学浓度梯度协同葡萄糖以1:1 比例被转移到细胞内，然后通过基底膜外侧葡萄糖转运体 2 重新入血，借此完成对小管液中钠和葡萄糖的重吸收[6]。因此基于以上生理机制，抑制 SGLT-2 可减少肾脏近端小管对钠和葡萄糖的重吸收，进而利钠、利尿，降低血压。对于 SGLT-2i 的利尿、利钠作用，在部分试验中得到了证实[35] [36]，EMPA-KIDNEY 试验通过对 660 例 CKD 患者的研究发现，恩格列净组“细胞外液”平均流失 0.24 L，该效果持续并超过 18 个月[37]。另有动物试验表明，SGLT-2i 可以减低非糖尿病 CKD 大鼠的盐敏感性[38]。Kawasoe 等人通过 SGLT-2i 对 T2DM 合并肥胖患者降压潜在机制的研究发现，早期血压的下降与 SGLT-2 渗透性利尿作用有关，而长期血压降低可能与利钠作用更密切[39]。然而部分试验并未出现上述作用[40] [41]，DAPASALT 试验观察到肾功能保留的 T2DM 患者在标准化钠摄入期间，达格列净组 24 小时动态收缩压下降，而尿钠排泄没有明显变化，这表明存在利钠作用以外的降压因素[40]。研究之间的差异可以由研究设计的不同、受试者特征、或使用潜在干扰药物作为背景治疗产生，但在大多数研究中，早期使用 SGLT-2i 治疗会导致尿钠浓度和尿量的增加，最大利钠作用出现在干预后的前 3 天，即使其会随着时间的推移逐渐恢复至基线水平[42]。

3.2. 改善动脉硬化

动脉硬化，即血管壁硬度的增加，是血管功能障碍和衰老的重要标志[43]。动脉硬化与血压存有较密切的关系。随着管壁僵硬度的增加，动脉随血压变化而扩张和收缩的能力下降，久而久之，这种弹性的降低会导致收缩压升高、舒张压降低，脉压差增大。而收缩压的升高反而加剧内皮细胞的损伤，诱发炎症、氧化应激、纤维化、钙化进一步升高血压，致使脑、肾脏、心脏等低阻终末器官损伤。Solini 等人首次在人类试验中证实，达格列净能够改善动脉硬化，即使校正了平均血压[44]。在动物实验中同样发现，相较于对照组，达格列净改善了 DM 小鼠的动脉僵硬度[45] [46]。多数研究均发现 SGLT-2i 降低 T2DM 患者血压的同时改善了动脉的僵硬度[47] [48] [49] [50]，尽管部分研究未能观察到[51] [52]。SGLT-2i 改善动脉硬化的确切机制不甚明了，但相关研究发现 SGLT-2i 可通过改善内皮细胞功能[53] [54]、增加 NO 利用度[55]、改善内皮炎症[56]等在一定程度上发挥血管保护作用。

3.3. 改善胰岛素抵抗

胰岛素抵抗是指机体对胰岛素敏感性的降低，表现为胰岛素促使葡萄糖经细胞膜上的葡萄糖转运蛋白摄入胞内能力的下降。早在 1966 年，Welborn 等[57]人通过对 19 例糖耐量正常的原发性高血压患者的临床观察中发现，这些患者血浆胰岛素浓度明显高于血压正常的对照组。后有研究对 1933 名非高血压志愿者进行了 4 年的随访，旨在评估这些参与者胰岛素敏感性与高血压发病率以及高血压进展情况的关系，结果发现胰岛素抵抗与高血压的发生、发展密不可分[58]。研究人员在动物实验中发现，达格列净组小鼠较对照组血糖和胰岛素水平降低，肌肉和脂肪组织胰岛素抵抗得到改善[59]。此外，有研究发现恩格列净可以通过抑制大鼠骨骼肌中甘油三脂的累积，从而提高胰岛素的敏感性，促进肌肉对葡萄糖的摄取和利用[60]。在 T2DM 患者中同样发现，应用 SGLT-2i 后血糖降低的同时，胰岛素抵抗得到了改善[61]。另一项研究表明，经鲁格列净治疗的 T2DM 患者，胰岛素抵抗指数从第 12 周开始得到显著改善，并持续到治疗期结束[62]。可能的机制有抑制葡萄糖毒性[61]、改善脂质代谢[63]、改善 β 细胞功能[64] [65]、抗炎和抗氧化应激[66]等。

3.4. 减轻体重

体重指数和血压几乎呈线性相关，该结果在不同的群体中可重复，尤其是超重或肥胖患者，有研究

表明肥胖受试者罹患高血压的可能性增加 2~3 倍[67] [68]。SGLT-2i 可以减轻 T2DM 患者的体重[69]，一项关于 SGLT-2i 与减重的综述中总结发现，DM 受试者接受 SGLT-2i 干预后平均体重下降 0.591~2.1 kg [70]。一项在加拿大开展的回顾性队列研究中，1052 名 T2DM 受试者在接受达格列净单药治疗 3~6 个月后体重下降 2.2 ± 3.1 kg ($p < 0.01$) [71]。随后的研究表明，SGLT-2i 对 T1DM 患者同样有减轻体重的作用[72]。综上，当减轻体重作为治疗目标的一部分时，美国糖尿病学会推荐 SGLT-2i 作为初始降糖治疗药物[73]。在一项汇总 8 项随机对照试验的系统综述中，对纳入的 750 名超重或肥胖非 DM 患者数据分析显示 SGLT-2i 单药治疗组体重显著降低 2.32 kg，而安慰剂组降低 1.01 kg，两组平均差异为−1.31 kg ($p < 0.0001$) [74]。可认为，无论有无糖尿病，SGLT2i 均可以减轻应用者体重。SGLT-2i 的减重作用得益于糖尿—尿中葡萄糖的排泄导致体液减少(主要是细胞外液)和渗透性利尿水分的排出[75]。SGLT-2i 所致糖尿或直接、或间接改善胰岛素抵抗，从而使胰高血糖素/胰岛素比值升高，加速脂肪分解和脂质氧化[76]，减少身体脂肪含量进一步减轻体重。一项在日本 2 型 DM 的研究发现，应用伊格列净 24 周后，受试者内脏、身体脂肪含量显著降低[77]。在一项关于身体脂肪组成的观察性研究中，发现 SGLT-2i 组受试者内脏脂肪组织减少[78]。此外有研究认为，SGLT-2i 的减重机制可能与促进脂肪褐变[79]、线粒体形态转变及功能改善[80]、交感神经系统受抑/副交感神经系统兴奋增加有关[81]。

4. 小结

起初，SGLT-2i 作为一种降糖药被开发，但大规模随机试验显示了其超越单纯降糖的多效性。SGLT-2i 的适应症正在迅速扩大，虽然目前不作为降压药物使用，但是相当多的证据表明，它通过利钠、利尿、改善动脉硬化、改善胰岛素抵抗、减轻体重等可能机制降低应用者血压。虽然这种降压效应背后的确切作用机制仍有待探索与明确，但总的证据表明，SGLT-2i 作为一种有巨大潜力价值的药物类别，丰富了我们治疗多种疾病患者高血压的方法，为 RH 患者降压带来新的希望。

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