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Hans汉斯

多疾病治疗潜能：二肽基肽酶4抑制剂的应用

李甜甜

山东大学齐鲁医院呼吸与危重症医学科，山东省呼吸道传染病重点实验室，山东 济南

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摘 要

二肽基肽酶4 (Dipeptidyl Peptidase-4, DPP4)是一种跨膜蛋白，具有多种生物学功能，如参与血糖调节、免疫调节和炎症反应。DPP4以膜结合和可溶形式存在，广泛分布于多种组织和体液中。而DPP4抑制剂通过延长胰高血糖素样肽-1 (Glucagon-like peptide-1, GLP-1)和葡萄糖依赖性促胰岛素多肽(Glucose-dependent insulinotropic polypeptide, GIP)的半衰期，有效控制2型糖尿病(Type 2 diabetes, T2DM)的血糖水平。此外，DPP4抑制剂在动脉粥样硬化(AS)、高血压、心力衰竭、血脂异常和神经退行性疾病等方面也展示出良好的治疗效果。本文综述了DPP4及其抑制剂在多种疾病中的作用机制和临床应用，探讨了其在现代医学中的潜在价值。

关键词

二肽基肽酶4，DPP4抑制剂，疾病

The Potential for Multi-Disease Treatment: Applications of Dipeptidyl Peptidase-4 Inhibitors

Tiantian Li

Department of Pulmonary and Critical Care Medicine, Qilu Hospital of Shandong University, Shandong Key Laboratory of Infectious Respiratory Diseases, Jinan Shandong

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Abstract

Dipeptidyl Peptidase-4 (DPP4) is a transmembrane protein with various biological functions, including involvement in glucose regulation, immune modulation, and inflammatory response. DPP4

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exists in both membrane-bound and soluble forms and is widely distributed across multiple tissues and body fluids. DPP4 inhibitors effectively control blood glucose levels in Type 2 diabetes (T2DM) by extending the half-life of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Additionally, DPP4 inhibitors have demonstrated promising therapeutic effects in conditions such as atherosclerosis (AS), hypertension, heart failure, dyslipidemia, and neurodegenerative diseases. This review summarizes the mechanisms and clinical applications of DPP4 and its inhibitors in various diseases, highlighting their potential value in modern medicine.

Keywords

Dipeptidyl Peptidase-4, Dipeptidyl Peptidase-4 Inhibitors, Disease

1. 引言

二肽基肽酶 4 (Dipeptidyl Peptidase-4, DPP4)是一种II型跨膜蛋白，隶属于丝氨酸肽酶亚家族 S9B，具有典型的 α/β 水解酶折叠结构[1]。DPP4 具有多种生物学功能，参与血糖调节，免疫调节和炎症反应[2]。DPP4 以两种形式存在，分别是膜结合蛋白和可溶形式(sDPP4)。sDPP4 由基质金属蛋白酶(Matrix metalloproteinase, MMP)裂解膜结合的 DPP4 产生，包含大部分细胞外 DPP4 蛋白。尽管 sDPP4 缺乏细胞内尾部和跨膜区域，但仍保留其催化活性[3]。膜结合的 DPP4 广泛表达于多种组织的细胞表面，如肠、肝、胰腺、肾、脾、肺和骨髓，而 sDPP4 则广泛分布于血清和体液中，如唾液、脑脊液、精液和胆汁[4]。循环中的活跃 sDPP4 确保其在细胞外环境中发挥 DPP4 介导的蛋白水解功能[5]。sDPP4 已被确定为一种新的脂肪因子，对多种副内分泌和内分泌作用有[6]。

二肽基肽酶抑制剂(Dipeptidyl peptidase-4 inhibitors, DPP-4 抑制剂)是一类起初被广泛研究和应用于糖尿病治疗的药物[7]。它们通过抑制二肽基肽酶(DPP-4)的活性，从而增加胰岛素的释放和血糖的降解，有助于管理糖尿病的症状[8]。这些抑制剂已经成为糖尿病治疗的重要组成部分，并且在临床上得到了广泛应用。二肽基肽酶可以降解胰高血糖素样肽-1 (glucagon-like peptide-1, GLP-1)和葡萄糖依赖性胰岛素性多肽(glucose-dependent insulinotropic polypeptide, GIP) [9]。这两种激素在调节胰岛素分泌和血糖稳态中发挥着重要作用。通过抑制 DPP-4 的活性，DPP-4 抑制剂能够延长 GLP-1 和 IGF-1 的半衰期，从而增强它们的生物学效应[3]。这种机制使得 DPP-4 抑制剂能够有效地降低空腹和餐后血糖水平，减少糖尿病患者的胰岛素需求。目前市场上已经有多种 DPP-4 抑制剂，如西格列汀[10]、沙格列汀[11]、利格列汀[12]等。这些药物在治疗 2 型糖尿病方面显示出了良好的疗效和安全性[13]。它们通常作为口服药物使用，方便患者服用，并且具有较少的副作用和相对简单的用药方案。除了在 2 型糖尿病治疗中的应用，DPP-4 抑制剂还显示出了一定的潜力用于其他疾病的治疗一些研究表明 DPP-4 抑制剂可能对心血管疾病具有保护作用，并且在肾脏疾病、肥胖等方面也有一定的研究价值[12] [14]。

2. DPP4 抑制剂与多种疾病

2.1. DPP4 抑制剂和 2 型糖尿病

GLP-1 是一种已知能够通过增强胰腺 β 细胞的葡萄糖依赖性胰岛素分泌并抑制胰高血糖素释放来维

持葡萄糖稳态的肽激素。DPP4 抑制剂是一类针对 2 型糖尿病的药物，其作用机制主要是通过增强肠促胰岛素–胰岛素通路来有效控制血糖水平[15]。在 DPP4 可以快速将 GLP-1 裂解成无活性片段 GLP-1 (9–36/37)，从而阻止其与 GLP-1 受体(GLP-1R)结合并发挥作用[16]。除了 GLP-1，DPP4 还可以降解其他肠促胰岛素激素，如葡萄糖依赖性促胰岛素多肽 GIP [17]，其在调节葡萄糖和胰岛素方面发挥与 GLP-1 类似的作用。

DPP4 抑制剂起初作为降糖药物，已被批准用于临床治疗 2 型糖尿病(Type 2 diabetes, T2DM) [18]，可以降低 DPP4 酶活性并进一步增加 DPP4 底物的浓度。DPP-4 抑制剂通过抑制 DPP-4 酶的活性，延长了 GLP-1 和 GIP 在体内的半衰期，使它们能够更长时间地发挥作用[19]。胰岛素的释放被增强同时抑制胰高血糖素的分泌，有效地降低了血糖水平。因此，DPP-4 抑制剂被广泛应用于 2 型糖尿病的治疗中。目前市场上常见的 DPP-4 抑制剂包括西格列汀、沙格列汀、利格列汀和阿格列汀[20]。它们被广泛应用于 2 型糖尿病患者的治疗中[21]，单独或与其他降糖药物联合使用，有效控制血糖水平，改善患者的生活质量，并降低了糖尿病并发症的发生风险。有研究发现使用 DPP-4 抑制剂(西格列汀)治疗 24 周后，患者的 HbA1c 水平平均降低了 0.7%~1.0% [22]。这表明 DPP-4 抑制剂对空腹血糖和餐后血糖均有显著的降低效果。二甲双胍与 DPP-4 抑制剂联合研究显示，二甲双胍与 DPP-4 抑制剂(如西格列汀)联合使用，可以将 HbA1c 水平进一步降低 1.5%~2.0% [23]。

2.2. DPP4 抑制剂和动脉粥样硬化

动脉粥样硬化(Atherosclerosis, AS)作为血管衰老的一种表现，是与衰老相关的心血管疾病的主要原因[24]。其特征是血管壁中脂质和纤维成分的积累，导致血管壁变厚、变硬，最终引发各种心血管事件[25]。AS 是一个复杂的过程，伴随着不同细胞、脂质和炎症调节因子的相互作用。近年来，越来越多的实验和临床研究证实了 DPP4 抑制剂在 AS 中的良好作用[26]。

研究发现 DPP4 抑制剂对动脉粥样硬化的进展具有显著的抑制作用[26]。DPP4 抑制剂能够显著抑制巨噬细胞的浸润，并减少胆固醇喂养兔子的动脉硬化斑块体积[27]。巨噬细胞在动脉壁内浸润并吞噬氧化低密度脂蛋白，形成泡沫细胞，从而促进斑块的形成和进展。DPP-4 抑制剂通过减少趋化因子和黏附分子的表达，抑制巨噬细胞的招募和浸润，进而减轻斑块的炎症反应[28]。在肥胖 T2DM 小鼠和患者中，特力利汀已被证明可显著抑制氧化低密度脂蛋白(Oxidized low-density lipoprotein, ox-LDL)的摄取和巨噬细胞泡沫细胞的形成[18]。此外，西格列汀被发现能够负向调节 MMP2 和 MMP9 的水平，降低斑块中的 MMP9 表达[29]。西格列汀在 ApoE 基因敲除小鼠中增加了斑块中的胶原蛋白含量，这有助于动脉粥样硬化病变的稳定性[30]。DPP4 抑制剂和钠-葡萄糖协同转运蛋白 2 (Sodium-glucose cotransporter 2, SGLT2)抑制剂的联合应用也显示出对糖尿病小鼠主动脉根部斑块病变的协同抑制作用[31]。在接受 20 周药物管理的 ApoE−/−小鼠中，特力利汀通过减少巨噬细胞积累、脂质沉积和单核细胞趋化蛋白-1 (MCP-1)表达，抑制了主动脉弓中 AS 的进展。

DPP4 抑制剂作为抗动脉粥样硬化药物，在临床研究中得到越来越多的应用[32]。在一项前瞻性、随机、开放标签平行组试验中，DPP4 抑制剂通过减少日常炎症和氧化应激，逆转了用西格列汀和维格列汀治疗 12 周的 T2DM 个体颈动脉 AS 的发生和进展[33]。通过超声描记术评估内膜中层厚度(Intima-media thickness, IMT)变化，结果表明 DPP4 抑制剂治疗能够显著降低颈动脉 IMT。一项名为 SPIKE 的随机对照试验进一步表明，西格列汀治疗 104 周后，受试者的平均和左侧最大 IMT 均有更大程度的降低[34]。阿格列汀在糖尿病动脉粥样硬化预防作用研究中也显示出显著效果，研究结果表明阿格列汀能够改变颈动脉的最大和平均 IMT [35]。另一项随机研究分析发现西格列汀能够使 T2DM 患者的颈动脉 IMT 显著消退[36]，与 SPIKE 试验结果一致。主动脉脉搏波速度(Pulse wave velocity, PWV)是早期 AS 的标志。在接受

利格列汀治疗 26 周的 T2DM 受试者中，PWV 显著降低[37]。然而，PROLOGUE 随机对照试验的结论是，与常规治疗相比，西格列汀给药组的颈动脉 IMT 发生率没有显著差异[38]。PROLOGUE 研究的进一步分析与这一观点一致，西格列汀对内皮功能和动脉僵硬度没有显著的有益作用，而这可能有助于 AS 的进展。

2.3. DPP4 抑制剂和高血压

高血压是一种日益严重的全球性疾病，尤其在老年人中发病率较高[39]。随着年龄增长，血管老化如动脉硬化和 AS 现象可能是高血压的重要原因。大量研究发现 DPP4 抑制剂不仅在糖尿病治疗中具有重要作用，也能有效降低血压水平[40]。

DPP4 抑制剂降低血压的潜在机制复杂且多样化。DPP4 抑制剂通过增强 GLP-1 的活性抑制近端肾小管的钠重吸收，减少钠潴留，从而对血压产生有益影响[27] [41]。其次，维格列汀通过激活电压依赖性钾通道和肌浆网/内质网钙 ATP 酶泵(Sarcoplasmic reticulum/endoplasmic reticulum calcium ATPase pump, SERCA)，诱导血管舒张[42]。DPP4 抑制剂增加内皮一氧化氮合酶(Endothelial nitric oxide synthase, eNOS)的活性，导致一氧化氮的释放，进而引起血管壁扩张[43]。此外，乙酰胆碱和硝普钠引起的血管扩张效应似乎归因于利格列汀降低血管收缩相关酶的表达，如血管紧张素转换酶(Angiotensin converting enzyme, ACE) [44]。

多项研究支持 DPP4 抑制剂对高血压的疗效。一项随机、双盲、安慰剂对照的三期交叉研究表明，西他列汀对非糖尿病患者具有适度的抗高血压功能[45]，该研究发现西他列汀可小幅降低 24 小时动态血压，这一效果与血糖控制和体重指数无关。一些试验观察到西他列汀显著降低血压水平。在一项双盲、随机、对照研究中，2000 名未接受过药物治疗的 T2DM 受试者每天服用维格列汀一次或两次，剂量为 50 毫克，持续 24 周[46]。研究结果发现维格列汀显著降低了受试者的收缩压和舒张压。另有研究发现恩格列净和利格列汀的联合应用相比于二甲双胍和胰岛素的组合，显著改善了中枢血压和血管功能[47]。

2.4. DPP4 抑制剂和心力衰竭

血管老化是动脉硬化的主要原因，动脉硬化会导致心室后负荷增加和左心室形态变化，这些因素是心力衰竭的重要病理机制[48]。越来越多的实验和临床研究表明 DPP4 抑制剂在心力衰竭的进展中具有潜在的可能，并改善心血管状态[49]。

研究发现 DPP4 抑制剂可以改善糖尿病和冠心病患者的心功能[50]。通过磁共振成像评估，阿格列汀被发现能够改善 T2DM 和冠心病患者的冠状动脉血流储备和左心室射血分数[49]。西格列汀也被证明在多巴酚丁胺应激期间改善了 T2DM 和 CAD 患者的左室功能障碍，并减少了缺血后的惊厥反应[51]。动物研究也进一步证明了 DPP4 抑制剂在改善心力衰竭方面的作用[52]。在胰岛素抵抗和肥胖啮齿动物模型中，利格列汀显著改善了心力衰竭相关的舒张功能障碍[53]。

在 T2DM 患者中，DPP4 抑制剂显著降低了二尖瓣多普勒早期充盈速度与组织多普勒舒张早期二尖瓣环速度(E/e')的比率，并增加了早期舒张末期峰值充盈速度(E/A)的比率，显示出对左心室舒张功能的有益作用[54]。DPP4 抑制剂还通过增加基质细胞衍生因子-1，促进骨髓干细胞在缺血区域的积累，从而改善急性心肌梗死后的心功能。

2.5. DPP4 抑制剂和血脂异常

血脂水平与动脉硬化密切相关，最终导致血管老化[55]。甘油三酯(Triglyceride, TG)/高密度脂蛋白胆固醇(High density lipoprotein cholesterol, HDL-C)比率是致动脉粥样硬化指数，这是早期血管老化的预测因

子[56]。各种 DPP4 抑制剂可显著降低动物和患者的低密度脂蛋白(Low-density lipoprotein, LDL)胆固醇、TG、总胆固醇(Total cholesterol, TC)和游离脂肪酸(Free fatty acid, FFA)水平，并增加 HDL-C 水平[57]。

DPP4 抑制剂降低肠道富含 TG 的脂蛋白的分泌，并改变参与脂质合成和氧化的肝酶的活化[58]。其次，DPP4 抑制剂通过胰 GLP-1)和 GLP-2 途径阻止脂质吸收。此外，DPP4 抑制剂通过交感神经系统的激活促进餐后脂质氧化[59]。餐后高甘油三酯血症在内皮细胞功能障碍中发挥重要作用，并加速 AS 的发展[60]。研究发现维格列汀可降低糖尿病大鼠主动脉中的循环 TC 并逆转内皮细胞功能障碍[61]，这得益于血管生成素 3 和甜菜碱同型半胱氨酸 S-甲基转移酶表达的减少以及对氧磷酶 1 激活的升高。

阿格列汀已被证明能够下调血脂，从而延缓动脉粥样硬化(AS) [62]。有研究发现在非禁食状态下，特力利汀的单次和重复治疗都会降低血浆中的 TG 和 FFA 水平[63]。维格列汀表现出一种有益的空腹脂质颗粒，与轻微的体重减轻有关。在接受维格列汀/二甲双胍治疗的参与者中，与格列美脲/二甲双胍治疗组相比，他们的 TC 和 TG 显著降低，HDL-C 水平显著升高[47]。维格列汀还被证明可以降低接受富含脂肪膳食治疗的患者的 TG 和载脂蛋白 B-48 [64]。多中心、随机研究的证据证实使用阿格列汀会导致空腹载脂蛋白 B-48 水平降低[62]。一项前瞻性、随机、多中心研究发现，西他列汀减少了冠状动脉中的脂质斑块体积[65]，非高密度脂蛋白胆固醇水平的显著下降可以解释这种现象。

2.6. DPP4 抑制剂和神经退行性疾病

DPP4 抑制剂在神经退行性疾病和脑血管疾病中的应用展示了广阔的潜力，如神经退行性疾病，如帕金森病(Parkinsonism, PD) [66]和阿尔茨海默病(Alzheimer's disease, AD) [67]。PP4 抑制剂成为治疗这些疾病的新方法，其通过靶向特定的病理生理学蛋白已经在临床上得到了应用。

对于 PD 和 AD 等神经退行性疾病，DPP4 抑制剂通过调节核受体相关 1、PTEN 诱导的推定激酶 1 和核因子 E2 相关因子 2 (Nuclear Factor Erythroid 2—related Factor 2, Nrf2)等蛋白的表达来保护神经[68]。DPP4 抑制剂通过包含 PI3K-Akt 和 MAPK 的 GLP-1 信号通路，逆转了受损的学习和记忆，并且减轻了 AD 样神经变性[69]。沙格列汀的研究表明其对 AD 的神经保护作用，如抗炎、抗氧化、抗凋亡和神经保护功能[70]。DPP4 抑制剂如利格列汀还通过增加 CX3CR1 单核细胞数量，对患有神经退行性疾病的 2 型糖尿病患者发挥神经保护作用[71]。在糖尿病小鼠模型中利格列汀也被认为可以恢复由短暂性脑缺血引起的认知功能受损和脑萎缩[72]。这些发现突显了 DPP4 抑制剂在神经保护方面的潜在作用。针对脑血管疾病，如缺血性脑卒中等，DPP4 抑制剂也显示出有利的影响[73]，DPP4 抑制剂对改善受损的脑血管结构和功能具有潜在的有利影响。

3. 总结

DPP4 是一种具有多功能性的酶，通过多种形式参与生理和病理过程。DPP4 抑制剂在 T2DM 治疗中的已经得到了广泛应用，其通过延长 GLP-1 和 GIP 的活性，增强胰岛素释放和抑制胰高血糖素分泌，显著降低血糖水平。此外，DPP4 抑制剂在心血管疾病、神经退行性疾病和代谢紊乱等多领域也表现出潜在的治疗效果。DPP4 抑制剂能抑制动脉粥样硬化斑块的形成和发展，降低血压，改善心功能，调节血脂，并对神经系统疾病具有保护作用。尽管 DPP4 抑制剂在不同疾病中的具体机制尚需进一步研究，但其多功能性和广泛应用前景无疑为临床治疗提供了新的选择。

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