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支链氨基酸在心血管疾病中的研究进展

朱浩然[1,2]，张亚茹[1,2]，尹晓荣[2]，崔　璐[1,2]，张　爽[1,2]，杨鹏飞[1,2]，明芙蓉[1,2]，申　程[2,3,4,5*]

[1]济宁医学院临床医学院(附属医院)，山东 济宁
[2]济宁医学院附属医院心内科冠心病二病区，山东 济宁
[3]山东省医药卫生心血管病学重点学科(济宁医学院附属医院)，山东 济宁
[4]山东省医药卫生心血管疾病诊疗重点实验室(济宁医学院附属医院)，山东 济宁
[5]济宁市冠脉介入精准治疗研究重点实验室，山东 济宁

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摘　要

支链氨基酸(Branched-chain amino acid, BCAA)作为必需氨基酸，不仅是蛋白质合成的基本单元，还作为重要的信号分子参与机体多种生理和病理过程。近年来，越来越多的证据表明，BCAA代谢紊乱与心血管疾病的发生发展密切相关。BCAA代谢通路中关键酶的缺陷可导致其在体内异常累积，通过激活哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)信号通路、影响能量代谢、加剧氧化应激等多种机制，促进高血压病、冠心病、心力衰竭、心律失常等疾病的进展。本文就BCAA及其代谢产物在多种心血管疾病中的作用及分子机制研究进展进行综述。

关键词

支链氨基酸，心血管疾病，代谢

Research Progress of Branched-Chain Amino Acids in Cardiovascular Diseases

Haoran Zhu[1,2], Yaru Zhang[1,2], Xiaorong Yin[2], Lu Cui[1,2], Shuang Zhang[1,2], Pengfei Yang[1,2], Furong Ming[1,2], Cheng Shen[2,3,4,5*]

[1]Clinical Medical College, Jining Medical University (Affiliated Hospital), Jining Shandong
[2]Coronary Heart Disease Ward II of Cardiology, Affiliated Hospital of Jining Medical University, Jining Shandong
[3]Shandong Provincial Key Medical and Health Discipline of Cardiology (Affiliated Hospital of Jining Medical University), Jining Shandong
[4]Shandong Provincial Key Medical and Health Laboratory of Diagnosis and Treatment of Cardiovascular Diseases (Affiliated Hospital of Jining Medical University), Jining Shandong
[5]Jining Key Laboratory of Precise Therapeutic Research of Coronary Intervention, Jining Shandong

*通讯作者。

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Abstract

Branched-chain amino acid (BCAA) is essential amino acids that serve not only as fundamental building blocks for protein synthesis but also as important signaling molecules involved in various physiological and pathological processes. In recent years, accumulating evidence has demonstrated that dysregulation of BCAA metabolism is closely associated with the development and progression of cardiovascular diseases. Deficiencies or dysfunctions of key enzymes in the BCAA metabolic pathway can lead to abnormal accumulation of BCAA and their metabolites, thereby promoting cardiovascular pathology through multiple mechanisms, including activation of the mammalian target of rapamycin (mTOR) signaling pathway, disruption of energy metabolism, and exacerbation of oxidative stress. These metabolic disturbances have been implicated in the progression of hypertension, coronary artery disease, heart failure, arrhythmias, and other cardiovascular disorders. This review summarizes the current advances in understanding the roles of BCAA and their metabolic products in cardiovascular diseases, with a particular focus on the underlying molecular mechanisms.

Keywords

Branched-Chain Amino Acids, Cardiovascular Diseases, Metabolism

1. 引言

支链氨基酸(Branched-chain amino acid, BCAA)包括缬氨酸、亮氨酸和异亮氨酸，由于其碳链中的支链结构而得名，具有重要的生理和生物学功能[1]-[3]。心血管疾病(Cardiovascular disease, CVD)是全球患病率及死亡率较高的疾病，在过去的二十年中，全球 CVD 的患病率几乎增加一倍[4]。过去几十年的大量研究已确定了一系列心血管疾病公认的危险因素，包括高收缩压、饮食风险、高低密度脂蛋白胆固醇、环境颗粒物污染、吸烟、空腹血糖升高、高体重指数等[5]。目前越来越多的研究表明 BCAA 代谢紊乱与多种 CVD 相关[6]，且有望成为新的潜在诊断和预后标志物。

2. BCAA 概述

2.1. BCAA 的来源与功能

BCAA 作为必需氨基酸，可在细菌、植物和真菌中从头合成，但在动物中不能合成，只能通过饮食获取[1]。BCAA 在哺乳动物营养物质中含量丰富，约占大多数膳食蛋白质的 20%~25%，约占哺乳动物必需氨基酸的 35% [7]。

作为人体必需氨基酸中含量最丰富的一种，BCAA 不仅是合成含氮化合物的底物，还可通过哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)信号通路，作为信号分子调节葡萄糖、脂质和蛋白质的合成代谢，调节肠道健康和免疫功能[8]-[11]。在上游感应层面，溶质载体家族 7 成员 5 (SLC7A5)/SLC3A2 溶质载体家族 7 成员 5/溶质载体家族 3 成员 2 (Solute Carrier Family 7 Member 5/Solute

Carrier Family 3 Member 2, SLC7A5/SLC3A2)异二聚体作为主要的细胞膜 BCAA 转运蛋白，其表达与活性直接影响细胞内 BCAA 浓度，从而调控 mTORC1 的定位与激活[12]。Sestrin2 作为亮氨酸的关键感应器，可通过与 GATOR2 复合物结合，解除 GATOR2 对 GATOR1 的抑制作用，进而促进 mTORC1 定位于溶酶体膜并被激活[13] [14]。在下游效应层面，通过激活 mTORC1 下游的核糖体蛋白 S6 激酶(Ribosomal Protein S6 Kinase, S6K)和真核起始因子 4E 结合蛋白(Eukaryotic Translation Initiation Factor 4E-Binding Protein, 4E-BP)，促进蛋白质翻译，在心肌中可导致病理性心肌肥厚[15]。mTORC1 磷酸化并抑制自噬起始关键复合物 ULK1，损害细胞清除受损细胞器与蛋白质的能力，在心血管细胞中累积氧化损伤[16]。

2.2. BCAA 的分解与调控

BCAA 在人体内主要在肝脏、心脏、骨骼肌中分解，并受多种酶调节，其中大多数过程在线粒体中进行。首先，亮氨酸、异亮氨酸、缬氨酸经过 BCAA 转氨酶(Branched-chain aminotransferase, BCAT)催化，可逆地生成相应的支链 α 酮酸(Branched-chain α-ketoacid, BCKA)。因此，1 种 BCAA 水平变化伴随着其他 2 种 BCAA 水平变化，具有相同的方向性和幅度，反映了 BCAA 相似的化学性质和代谢[17]。然后三种 BCKA 通过线粒体支链 α-酮酸脱氢酶(Branched-chain α-keto acid dehydrogenase, BCKD)复合物进行不可逆的氧化脱羧，释放 CO_2，并将辅酶 A 基团共价添加到氧化的 BCKA 产物中[18]。最终，亮氨酸生成乙酰辅酶 A、缬氨酸生成丙酰辅酶 A，异亮氨酸可同时生成乙酰辅酶 A 与丙酰辅酶 A 进入三羧酸循环。

作为三种 BCAA 分解的关键酶，BCKD 复合物位于线粒体内膜的内侧，因此所有 BCAA 分解均在线粒体基质内进行[19]。BCKD 复合物受到磷酸化(失活)/去磷酸化(激活)以及 Ppm1k 编码的线粒体蛋白磷酸酶 2C (mitochondrial protein phosphatase 2C, PP2Cm)去磷酸化(激活)的调节的严格调控[20]。这一通量控制步骤是一个关键的调节点：营养、运动和激素可以通过 BCKD 激酶调节 BCAA 代谢，该激酶磷酸化 BCKD 的 e1 亚基以抑制其活性[21]，相反，蛋白磷酸酶 1K 去除这种磷酸化以促进 BCKD 活性，进而调控体内 BCAA 的代谢[22]。

因此，BCAA 代谢稳态的失调与多种代谢性疾病如肥胖、2 型糖尿病及心血管疾病的发生发展紧密相连。

3. BCAA 与心血管疾病

3.1. BCAA 与高血压病

高血压是导致心血管疾病和过早死亡的主要危险因素。近年来的多项大规模人群研究揭示了 BCAA 与高血压之间的密切联系。一项前瞻性队列研究[23]表明，较高的 BCAA 膳食摄入量，尤其是缬氨酸，与高血压的发病风险呈正相关。另一项基于代谢组学的研究[24]也发现，血浆中 BCAA 的浓度是高血压发病的强风险标志物，其预测能力独立于传统的危险因素。尽管确切的分子机制尚不完全清楚，但现有研究提示了几个可能的途径。BCAA 代谢紊乱常伴随胰岛素抵抗，而胰岛素抵抗可通过多种机制(如交感神经系统激活、肾脏钠重吸收增加)导致血压升高[25] [26]。此外，BCAA 及其代谢物也可能直接影响血管内皮细胞功能和血管张力，从而参与血压的调节[27]。上述研究表明高浓度 BCAA 与高血压之间存在密切关系，为从代谢角度理解高血压的病理生理学提供了新的视角，未来循环 BCAA 水平可作为新的生物标志物评估高血压发病风险。

3.2. BCAA 与动脉粥样硬化及冠心病

动脉粥样硬化是多种 CVD 的基础，冠状动脉粥样硬化可有效预测心血管事件。一项前瞻性队列研究[28]通过测定女性的血浆 BCAA 代谢物，并在随访中对心血管事件分析发现，基线 BCAA 的单次随机血

浆测定与心血管事件呈正相关，并且独立于多个已确定的危险因素。多项流行病学和基础研究已证实，循环中 BCAA 水平升高与冠心病风险独立相关。一项针对接受心脏导管插入术患者的研究[29]验证了 BCAA 代谢谱与冠心病严重程度之间的关联。BCAA 代谢紊乱可能通过多种途径促进动脉粥样硬化的病理过程。高浓度的 BCAA 可通过激活 mTORC1 信号，促进人外周血单核细胞的氧化应激、炎症和迁移，而单核细胞的迁移和分化是动脉粥样硬化斑块形成的关键环节[30]。Xu 等[31]研究发现 BCAA 代谢产物可以通过增强血小板中蛋白的丙酰化修饰，促进血小板活化和血栓形成风险，而血栓形成是急性冠脉综合征的直接原因。此外，BCAA 及其代谢物还与内皮功能障碍、胰岛素抵抗和脂质代谢紊乱多重危险因素密切相关，共同促进了动脉粥样硬化的发生与发展[32] [33]。

3.3. BCAA 与心肌缺血再灌注损伤

心肌缺血/再灌注(Ischemia/reperfusion, I/R)损伤是急性心肌梗死血运重建后面临的主要挑战，其病理过程复杂，涉及能量代谢紊乱、氧化应激、炎症和细胞凋亡等[34]。BCAA 在 I/R 损伤中的作用呈现出显著的双面性，这取决于其暴露的持续时间和浓度。一方面，慢性 BCAA 累积会加重心肌 I/R 损伤。在 BCAA 分解代谢缺陷(如 PP2Cm 基因敲除)的动物模型中，心脏内 BCAA 的慢性蓄积会通过直接抑制丙酮酸脱氢酶活性，从而干扰心肌的葡萄糖氧化，削弱心脏在缺血应激下的代谢适应能力，使心脏对 I/R 损伤更加敏感[35]。Li 等[36]研究揭示，BCAA 可通过激活 GCN2/ATF6/PPAR-α 信号通路，异常增强心肌的脂肪酸氧化，在 I/R 期间加剧脂毒性产物的积累和氧化应激，从而加重损伤。另一方面，短期补充 BCAA 可能具有心肌保护作用。一项研究显示，在缺血前给予亮氨酸预处理，可通过激活 mTOR 信号通路，改善线粒体功能，减少心肌细胞死亡，显著缩小梗死面积，发挥出类似缺血预适应的心肌保护效应[37] [38]。此外，Cai 等[39]研究发现，empagliflozin 等药物可能通过激活 AMPK/ULK1 通路来调控线粒体自噬，从而保护心脏微血管免受 I/R 损伤，这也间接反映了能量代谢调控在 I/R 损伤中的重要性。

3.4. BCAA 与心力衰竭

心力衰竭是各种心脏病的终末阶段，其核心特征之一是显著的心肌能量代谢重构[40] [41]。大量证据表明，BCAA 分解代谢障碍是心力衰竭的重要特征和驱动因素[42] [43]。Sun 等[44]的一项开创性研究明确指出，由 PP2Cm 基因敲除导致的 BCAA 分解代谢缺陷会直接促进病理性心肌重构和心力衰竭的发生。其机制被认为与 BCAA 及其代谢产物 BCKA 在心肌中的蓄积有关。这些累积的 BCKA 可以被重新氨基化以激活蛋白质合成，持续激活 mTOR 信号通路，导致心肌细胞肥大、纤维化和心功能障碍。在心肌梗死后的心衰模型中，同样观察到 BCAA 分解代谢受损，进一步加剧了心室重构[45]。通过药物激活 BCKD 恢复 BCAA 的正常分解代谢，可以改善压力超负荷诱导的心力衰竭。这些研究共同揭示了 BCAA 代谢通路作为心力衰竭潜在治疗靶点的重要性。

3.5. BCAA 与心律失常

心律失常，尤其是恶性室性心律失常和心房颤动，是导致心脏性猝死和脑卒中的主要原因[46] [47]。最近的研究首次揭示了慢性 BCAA 水平升高与心律失常之间的直接因果关系。Portero 等[48]通过构建 Bcat2 基因突变小鼠模型，发现血浆和心肌中 BCAA 的慢性累积可导致心肌细胞动作电位时程显著延长、静息膜电位去极化，并诱发早后除极和迟后除极等促心律失常事件。这种电生理异常与心肌细胞内钙稳态的严重失调有关，进一步的机制研究发现，这些促心律失常效应是通过 mTOR 信号通路的过度激活介导的，使用 mTOR 抑制剂雷帕霉素可以有效逆转这些电生理异常。此外，在德国的一个大型人群队列研究中也观察到，血浆 BCAA 水平与心电图中的 PR 间期和 QTc 间期呈正相关[48]，进一步证实了 BCAA

对心脏传导和复极的调节作用。有研究表明，心房组织中 BCAA 的分解代谢缺陷会加剧心房纤维化和线粒体氧化应激，从而增加心房颤动的易感性[49] [50]。通过药物增强 BCAA 分解代谢或使用褪黑素激活 PKG-CREB-KLF15 信号通路，可以改善心房 BCAA 代谢并减轻心房颤动的病理重构[49]。这些发现为理解代谢紊乱与心律失常之间的联系开辟了新方向，并提示靶向 BCAA/mTOR 通路可能成为防治心律失常的新策略。

4. 争议与讨论

尽管 BCAA 与心血管疾病的关联性得到广泛认可，但该领域仍存在若干核心争议，这些问题对准确理解其病理角色至关重要，后续还需要更多研究进一步证实。

4.1. BCAA 与 BCKA：谁是真正的致病分子？

BCAA 代谢障碍常伴随其转氨产物 BCKA 的累积。有观点认为，BCKA 在心肌和血小板中的异常蓄积，可能直接干扰线粒体代谢并诱发异常翻译后修饰，从而对心血管系统产生不利影响[31]。也有研究发现，高水平的支链氨基酸，而不是它们的代谢物，通过直接抑制丙酮酸脱氢酶复合体的活性选择性地干扰线粒体丙酮酸的利用，抑制了葡萄糖代谢，并使心脏对缺血损伤敏感[51]。未来研究需利用能在时空上精准调控 BCAA 与 BCKA 水平的模型，以进一步解析它们在心血管疾病不同阶段的具体影响。

4.2. BCAA 的致病性：独立于抑或依赖于胰岛素抵抗？

胰岛素抵抗是心血管疾病的重要危险因素，且常与 BCAA 代谢紊乱并存，因此 BCAA 的致病作用是否独立于胰岛素抵抗存在较大争议。在支链氨基酸分解代谢受损的小鼠模型中，支链氨基酸分解代谢缺陷不会导致胰岛素抵抗，且心脏中参与胰岛素信号转导的蛋白质，在分解代谢受损的小鼠模型与野生型小鼠心脏中的表达相似，这些结果表明，支链氨基酸分解代谢缺陷抑制了葡萄糖摄取，而不是依赖于胰岛素信号[51]。也有研究表明支链氨基酸有助于胰岛素抵抗，提示氨基酸在心血管疾病中的作用可能与胰岛素抵抗和 2 型糖尿病存在共同的机制[52] [53]。而胰岛素抵抗本身可通过影响 BCAA 分解代谢关键酶(如 BCKD 激酶)的活性，导致 BCAA 累积[54]。因此，BCAA 紊乱与胰岛素抵抗很可能构成一个恶性循环，在不同个体或疾病阶段，其主导驱动因素可能不同。未来可通过分别调控胰岛素敏感性和 BCAA 代谢，明确两者在心血管疾病发生中的因果关系和交互作用。

5. 总结与展望

综上，支链氨基酸代谢紊乱已被证实广泛参与多种心血管疾病的发生与进展过程，其潜在机制涉及能量代谢重构、炎症反应、氧化应激、血小板功能异常及心肌电生理稳态破坏等多个层面。近年来，随着代谢组学和基础研究的深入，BCAA 逐渐被认为是连接营养状态、代谢调控与心血管病理生理过程的重要代谢节点。尽管相关研究取得了显著进展，但该领域仍存在若干亟待解决的关键科学问题。首先，循环 BCAA 水平同时受膳食摄入和内源性代谢调控影响，如何精确区分膳食 BCAA 摄入增加与 BCAA 分解代谢障碍在心血管风险形成中的相对贡献，仍缺乏明确结论。其次，心肌细胞、血管内皮细胞、免疫细胞及血小板在 BCAA 代谢酶表达及信号应答方面可能存在显著差异，心血管系统是否存在组织或细胞类型特异性的 BCAA 代谢调控机制，有待进一步研究。此外，性别、年龄及激素状态等因素可能影响 BCAA 代谢通量及其下游效应，但相关分层研究仍明显不足。总之，通过调控 BCAA 代谢，不仅能够深化对代谢与心血管疾病交互关系的理解，也有望为心血管疾病的治疗提供新的靶点和策略，为心血管疾病的预防、诊断和治疗提供新的视角和方法。

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