

氨基酸调控糖脂代谢在脂肪肝形成中的作用

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摘要: 氨基酸是蛋白质的基本组成单位和重要的代谢信号分子, 在糖脂代谢调控中发挥关键作用。研究表明, 支链氨基酸(BCAAs)、芳香族氨基酸和含硫氨基酸的代谢紊乱与非酒精性脂肪肝(NAFLD)的发生发展密切相关。BCAAs通过激活 mTOR 信号通路, 诱导氧化应激和线粒体功能障碍, 促进胰岛素抵抗和肝脏脂质沉积。此外, 亮氨酸缺乏可通过氨基酸感应器 GCN2 通路增强胰岛素敏感性, 减少肝脏葡萄糖生成; 而蛋氨酸缺乏则通过 FGF21 信号调控脂质代谢。临床研究发现, 血清 BCAAs 水平与脂肪肝严重程度显著相关, 提示其作为潜在生物标志物的价值。尽管靶向氨基酸代谢的干预策略, 例如 BCAA 限制饮食、支链 α -酮酸脱氢酶激酶(BCKDK)抑制剂在改善肝脏代谢方面展现出良好前景, 但 mTORC1 抑制剂等治疗手段的代谢副作用提示氨基酸感知网络的复杂性。临床主要挑战包括: 氨基酸代谢网络的动态平衡调控、干预措施的双重性验证, 以及个体化治疗反应差异的预测等。未来研究需结合多组学技术, 阐明氨基酸感知信号通路的组织特异性机制, 开发基于代谢分型的个体化治疗方案, 为 NAFLD 的精准防治提供新思路。

关键词: 氨基酸; 糖脂代谢; 非酒精性脂肪肝

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Role of amino acids in regulating glucose and lipid metabolism in the development of fatty liver disease

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Abstract: Amino acids, as the basic building blocks of proteins and important metabolic signalling molecules, play a key role in the regulation of glycolipid metabolism. Studies have shown that metabolic disorders of branched-chain amino acids (BCAAs), aromatic amino acids and sulphur-containing amino acids are closely related to the development of non-alcoholic fatty liver disease (NAFLD). BCAAs induce oxidative stress and mitochondrial dysfunction through activation of the mTOR signalling pathway, which promotes insulin resistance and hepatic lipid deposition. In addition, leucine deficiency enhances insulin sensitivity and reduces hepatic glucose production through the GCN2 pathway, while methionine deficiency regulates lipid metabolism through FGF21 signalling. Clinical studies have found that serum BCAAs levels significantly correlate with fatty liver severity, suggesting their value as potential biomarkers. Although intervention strategies targeting amino acid metabolism, including BCAA-restricted diets, Branched-Chain α -Ketoacid Dehydrogenase Kinase (BCKDK) inhibitors, have shown promising results in improving hepatic metabolism, the metabolic side effects of treatments such as mTORC1 inhibitors suggest the complexity of the amino acid perception network. Current challenges include the regulation of the dynamic balance of amino acid metabolic networks, the long-term safety validation of interventions, and the prediction of differences in response to individualised treatments. Future studies need to incorporate multi-omics techniques to elucidate the tissue-specific mechanisms of amino acid sensing signalling pathways, develop individualised treatment plans based on metabolic typing, so as to provide new ideas for the precise prevention and treatment of NAFLD.

Keywords: amino acids; glycolipid metabolism; non-alcoholic fatty liver disease

葡萄糖、脂类和氨基酸是维持生命活动的主要物质。氨基酸不仅是蛋白质的基本组成单位, 也是

合成肽类激素及其他小分子的重要底物。除了参与蛋白质代谢外, 氨基酸还在糖脂代谢中发挥着关键

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的调控作用。氨基酸作为调节糖脂代谢稳态的重要信号分子,已取得一定研究进展:支链氨基酸(branched-chain amino acids, BCAAs),包括缬氨酸、亮氨酸和异亮氨酸,被多项研究证实是糖脂代谢紊乱的潜在生物标志物。BCAAs 及其相应的支链酮酸(branched-chain α -ketoacids, BCKAs)能够激活 mTOR 信号通路,诱导氧化应激,引起线粒体功能障碍,并可能进一步促进胰岛素抵抗的进展^[1-3]。多项研究发现芳香族氨基酸(如酪氨酸和苯丙氨酸)上调能够预测 2 型糖尿病(type 2 diabetes mellitus, T2DM)发生^[4],而甘氨酸和谷氨酰胺下调则与 T2DM 发生呈负相关^[5-6]。同时,研究发现赖氨酸降解产物 2-氨基己二酸(2-aminoadipic acid, 2-AA)水平升高也与糖尿病风险增加相关^[7]。2-AA 与脂肪生成和胰岛素抵抗密切相关,可作为糖尿病风险的标志物。鉴于氨基酸内稳态在糖脂代谢调控中的关键作用,其在人群脂肪肝发生中的调控机制显得尤为重要。近年来氨基酸调控在脂肪肝生成中的作用引起了广泛关注。在脂肪肝进展中氨基酸的主要功能包括促进蛋白质合成和能量代谢。例如,氨基酸水平的升高会通过 mTORC1 依赖的方式增强肝脏脂肪酸生物合成基因的表达,同时削弱胰岛素对糖异生的抑制作用^[8]。相反,氨基酸缺乏则会抑制肝脏糖异生和脂肪细胞分化等过程^[9]。此外机体对氨基酸水平变化的响应依赖于精密的调控网络:当氨基酸供应充足时,氨基酸感知信号会激活合成代谢和储存途径;反之,在氨基酸缺乏时,则会启动分解代谢过程^[10-11]。基于以上证据,本文将重点探讨脂肪肝发生前期氨基酸感知信号通路如何响应氨基酸水平波动,以及这些感知信号通路如何通过调节糖脂代谢诱导脂肪肝的发生。

1 氨基酸在脂肪肝形成中的糖代谢信号通路

近年研究表明,下丘脑内侧基底核(mediobasal hypothalamus, MBH)的亮氨酸作为 mTORC1 和 S6K1 磷酸化的强效激活剂,在葡萄糖代谢调控中发挥关键作用。肖斐等^[12]发现亮氨酸缺乏能够使小鼠胰岛素分泌减少但血糖浓度维持不变,通过激活 GCN2 和下调 mTOR/S6K1 信号通路增强胰岛素敏感性从而减少肝脏葡萄糖生成。进一步研究发现,肝脏特异性敲除 *Tsc1* 基因(mTORC1 信号通路抑制因子)导致 mTORC1 持续激活的小鼠,因转录因子 PPAR α 受抑制而在空腹期间无法生成酮体^[13]。此外, mTORC1 的持续激活还会为糖异生提供游离氨基酸的关键过程^[8]。Xu 等^[14]研究发现,全身或肝脏特异性敲除 GCN2 的小鼠,空腹期间维持葡萄

糖稳态的能力显著受损,但其胰岛素水平和敏感性正常,表明 GCN2 主要通过调控糖异生维持葡萄糖稳态。进一步机制研究表明,GCN2 缺陷小鼠在空腹 24h 后肝脏转录因子 C/EBP β 表达诱导失败,而肝脏特异性 C/EBP β 敲除小鼠表现出与 GCN2 缺陷相似的表型,提示 GCN2 可能通过 C/EBP β 调控糖异生。也有研究进一步证实异亮氨酸或缬氨酸缺乏 7d 可显著降低野生型和胰岛素抵抗小鼠的血糖水平,其机制可能与糖异生限速酶葡萄糖-6-磷酸酶表达下调有关^[15]。

2 氨基酸在脂肪肝形成中的脂代谢信号通路

研究表明,亮氨酸缺乏可显著上调野生型动物肝脏中成纤维细胞生长因子 FGF21 表达,同时伴随脂肪生成相关基因的下调,而 FGF21 基因敲除小鼠则表现出脂肪生成增强和肝脏脂肪变性表型^[16]。生酮饮食条件下,蛋氨酸缺乏可特异性诱导 FGF21 显著升高。值得注意的是,蛋氨酸/胆碱缺乏饮食可诱导野生型小鼠出现脂肪肝表型,并最终发展为非酒精性脂肪性肝炎样病理表型,同时伴随肝脏 FGF21 表达和血清水平显著升高^[17]。低蛋白饮食也可显著促进小鼠肝脏 FGF21 的产生,而 FGF21 敲除小鼠则对低蛋白饮食的代谢效应表现出显著拮抗性^[18]。这些研究结果充分表明, mTORC1、GCN2 和 FGF21 信号通路参与脂质代谢调控,并可能形成复杂的调控网络。进一步机制研究表明, mTORC1 的激活能够显著促进脂肪细胞形成并增强脂质合成,这一现象在脂肪细胞特异性 Raptor 敲除(Ad-Rap KO)小鼠模型中得到了验证:该模型表现出进行性脂肪营养不良和脂肪肝表型。值得注意的是, Ad-Rap KO 小鼠对高脂饮食(high-fat diet, HFD)诱导的肥胖具有显著抗性,这主要归因于脂肪生成过程受到抑制,提示脂肪组织中 mTORC1 信号通路的抑制可能具有双重效应^[19]。在分子机制层面, mTORC1 信号通路的下游效应分子 S6K1 和 4E-BPs 在脂肪生成调控中扮演早期关键角色,其中 S6K1 通过调控早期促脂肪生成因子的基因表达参与胚胎干细胞向脂肪生成祖细胞的定向分化过程,而 4E-BP1 和 4E-BP2 通过翻译水平调控主要促脂肪生成因子 PPAR γ 的表达,进而影响脂肪细胞分化^[20]。与此同时,GCN2 信号通路在氨基酸感知与脂质代谢调控中的作用也逐渐受到关注。活化的 GCN2 磷酸化 eIF2 α 的 Ser51 位点,导致 eIF2-GTP-tRNA Met 复合物形成受阻,抑制全局翻译起始。研究发现,蛋氨酸等氨基酸缺乏时,ATF4 还可通过 GCN2/eIF2 α 非依赖途径激活 CARE 基因^[21]。

GCN2 缺失或抑制可改善高脂饮食/链脲佐菌素和 db/db 小鼠的高血糖、胰岛素抵抗及脂肪肝。机制研究表明,GCN2 抑制通过调节葡萄糖代谢、抑制脂肪生成基因和激活 Nrf2 通路发挥保护作用^[22-23]。

3 氨基酸代谢与脂肪肝病的临床相关研究

Batch 等^[24]通过代谢组学分析 1 872 名受试者(按瘦/超重/肥胖分组),发现 BCAAs 相关代谢物簇在代谢差异组间差异显著,且可独立于体质量指数(body mass index, BMI)区分代谢状态,提示其作为潜在生物标志物的价值。当前多数临床研究聚焦于血清氨基酸(amino acid, AA)水平,尤其是 BCAAs 水平,与脂肪肝密切相关^[3, 25-26]。也有研究发现肝脏和脂肪组织中 BCAAs 代谢的组织特异性变化(而非肌肉中的变化)可能导致肥胖个体血浆 BCAAs 水平升高^[27]。全氟辛烷磺酰基化合物(per-fluorooctane sulphonate, PFOS)暴露通过扰乱甘氨酸、丝氨酸和苏氨酸等氨基酸的代谢途径,影响糖代谢和脂质代谢,导致关键代谢物(如 3-磷酸甘油和乳糖基神经酰胺)的变化以及相关基因(如 *Ppp1r3c*、*Abcd2*、*Ogdh* 和 *Ppp1r3g*)的表达异常。这些代谢和基因表达的扰动可能与空腹血糖水平的升高和脂肪肝的形成密切相关^[28]。

4 临床展望与挑战

可以预见的是,氨基酸调控信号组分失衡与多种病理状态相关。氨基酸感知网络组分的效率可能对治疗具有重要意义,而对这些组分的了解对于制定针对脂肪肝相关表型的氨基酸干预计划至关重要。近年来,针对氨基酸代谢通路的靶向药物研发为脂肪肝病的治疗提供了新的方向^[23]。研究表明,通过调控 BCAAs、芳香族氨基酸(aromatic amino acids, AAAs)及含硫氨基酸代谢途径中的关键酶或信号分子,可有效改善肝脏代谢紊乱^[29-30]。例如,肝脏特异性敲除 BCKDK 可抑制肝糖生成和糖异生关键酶表达,但不影响基础糖代谢。BCKDK 抑制剂 BT2 通过减弱 CREB 信号通路和促进 FOXO1 蛋白降解来调控糖异生,揭示了 BCKDK 调控肝糖代谢的新途径,为糖尿病治疗提供了潜在靶点^[31]。与此同时,基于患者个体化氨基酸代谢特征的精准干预策略也展现出良好的应用前景。通过限制 BCAAs 摄入或补充特定功能性氨基酸(如精氨酸)等个性化营养干预手段,可有效改善部分脂肪肝患者的代谢紊乱和肝脏功能^[32]。然而,目前关于氨基酸感知机制的研究仍存在不足,特别是许多已提出的氨基酸感知机制是否具有生理相关性仍需验证。以

mTORC1 为例,作为对氨基酸水平最敏感的感知器,其已被证实是代谢性疾病治疗的潜在靶点^[29]。但在啮齿动物模型中使用 mTORC1 抑制剂(雷帕霉素)进行治疗时,却意外观察到代谢状态恶化的现象^[33]。这一发现提示,有必要深入探究生理状态下关键的氨基酸感知器及其响应信号激活的具体分子机制。此外,为了解释细胞如何感知氨基酸可用性以协调细胞代谢和生长,需要更全面地探索氨基酸感知网络信号之间的串扰。未来研究需要整合多组学技术和精准医学策略,开发基于代谢分型的个体化治疗方案,同时探索氨基酸代谢调控与其他治疗手段的协同效应,为脂肪肝的防治提供新思路。

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