

• 综述 •

支链氨基酸与母子间超重肥胖代际传递的关系

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摘要: 儿童超重肥胖问题日趋严峻,可能来源于母亲超重肥胖的代际传递。支链氨基酸(BCAAs)包括亮氨酸、异亮氨酸和缬氨酸,是人体必需氨基酸,参与能量代谢和蛋白质合成,且与超重肥胖风险密切相关,但其在母子代际传递中的作用尚待探讨。研究表明,肥胖孕妇体内的 BCAAs 水平升高,并可通过胎盘转运至胎儿,激活哺乳动物雷帕霉素靶蛋白复合物 1(mTORC1),上调氨基酸转运蛋白的表达,促使更多 BCAAs 向胎儿转移。过高的 BCAAs 可通过促进脂肪合成及干扰胰岛素信号等途径,导致糖脂代谢异常,增加子代肥胖风险。鉴于 BCAAs 在母子间肥胖代际传递中扮演的关键角色,本文综述了 BCAAs 与母子间超重肥胖代际传递的现有证据及机制,旨在探讨其作为干预靶点的可能性,并为儿童肥胖预防策略提供科学依据。

关键词: 支链氨基酸; 超重; 肥胖; 母婴; 代际传递

中图分类号: R179

文献标识码: A

文章编号: 1008-6579(2025)09-0992-05

doi: 10.11852/zgetbjzz2024-0937

Relationship between branched-chain amino acids and mother-offspring overweight/obesity transmission

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Abstract: The escalating prevalence of childhood overweight and obesity may stem from the intergenerational transmission of maternal overweight and obesity. Branched-chain amino acids (BCAAs), including leucine, isoleucine, and valine, are essential amino acids involved in energy metabolism and protein synthesis. While BCAAs are closely associated with the risk of overweight and obesity, their role in mother-offspring intergenerational transmission remains unclear. Studies indicate that obese pregnant women exhibit elevated BCAA levels, which can be transferred to the fetus via placental transport. This process activates the mammalian target of rapamycin complex 1 (mTORC1), upregulating the expression of amino acid transporters and further facilitating fetal BCAAs uptake. Excessive BCAAs may disrupt glucose and lipid metabolism by promoting lipogenesis and impairing insulin signaling, thereby increasing offspring obesity risk. Given the critical role of BCAAs in the intergenerational transmission of obesity, this review synthesizes current evidence and mechanistic insights into the relationship between BCAAs and mother-offspring overweight/obesity transmission, in order to explore their potential as an intervention target and provide a scientific foundation for childhood obesity prevention strategies.

Keywords: branched-chain amino acids; overweight; obesity; mother and infant; intergenerational transmission

儿童超重肥胖问题在全球范围内日趋严峻,2022 年 5 岁以下儿童超重已达 3 700 万,5~19 岁学龄儿童和青少年肥胖人数为 12 790 万^[1-2]。据最新研究报告,我国 2019 年 7~18 岁儿童青少年超重和肥胖总患病率为 23.4%,预计到 2030 年儿童肥胖患病率将飙升至 15.1%^[3-4]。研究表明,母亲孕前超重/肥胖及孕期增重过多,对子代的健康状况有显著影响,是增加子代肥胖风险的关键因素之

一^[5-6]。在探讨超重和肥胖问题的代际传递机制时,支链氨基酸(branched-chain amino acids, BCAAs)的作用逐渐受到关注。BCAAs 包括亮氨酸、异亮氨酸和缬氨酸。众多证据表明,BCAAs 水平升高与肥胖密切相关,这一关联在孕妇和儿童中也受到广泛关注^[7-8]。尽管已有研究揭示了 BCAAs 与超重肥胖的联系,但其在母子间代际传递的路径探索尚存在空白。鉴于此,探讨 BCAAs 在超重肥胖代际传递

基金项目:江西省自然科学基金资助项目(20232BAB216103)

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中的作用机制及其在肥胖预防和干预中的潜在应用显得尤为重要。因此,本综述旨在梳理 BCAAs 与母子间超重肥胖代际传递的现有研究证据,为降低子代超重肥胖风险提供科学依据。

1 支链氨基酸与超重肥胖的关系

BCAAs 是人体的必需氨基酸,主要来源于肉类、奶制品等富含蛋白质的食物,主要代谢场所是肝脏和骨骼肌^[9]。动物实验和人群研究均发现 BCAAs 的异常升高与超重肥胖之间存在密切关联。动物实验表明,高脂饮食诱导的肥胖小鼠血浆 BCAAs 水平显著升高^[10]。人群研究也指出,血浆 BCAAs 水平与肥胖之间存在显著的正相关(OR 为 $0.06 \sim 0.07$, $P < 0.001$),减肥手术可以降低 BCAAs 水平^[10-12]。但目前仍不清楚肥胖人群的 BCAAs 水平升高是营养摄入增加的直接结果,还是由肥胖个体本身的代谢异常导致^[13-14]。

BCAAs 可通过多种途径导致肥胖的发生^[15]。例如,BCAAs 能通过促进脂质合成、减少能量消耗等,造成体内脂质堆积,增加肥胖风险^[15-16];另外,BCAAs 还可通过激活哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)信号通路,上调脂质生成相关基因过氧化物酶体增殖物激活受体 γ (peroxisome proliferators-activated receptors, PPAR γ)和固醇调节元件结合蛋白-1c(sterol regulatory element binding protein-1c, SREBP-1c)的表达,促进脂质合成^[17]。此外,BCAAs 代谢紊乱还与肥胖相关的胰岛素抵抗形成恶性循环^[18-19]。BCAAs 水平升高会激活哺乳动物雷帕霉素靶蛋白复合物 1(mTOR complex 1, mTORC1),引起胰岛素抵抗,而通过雷帕霉素阻断该通路可缓解这一效应^[20]。此外,胰岛素抵抗相关的基因变异(如 PPM1K 基因),可抑制 BCAAs 分解酶的活性,减缓 BCAAs 分解,致其水平上升^[11]。总之,BCAAs 通过促进脂质合成、干扰胰岛素信号等途径,在肥胖发展中起重要作用,而这些机制同样适用于儿童。研究表明,儿童体内 BCAAs 水平的异常升高是超重肥胖的一个显著标志^[8];而这又可能与母亲体内的 BCAAs 水平升高有关^[7-8]。这种关联提示了 BCAAs 可能在儿童肥胖发生过程中扮演关键角色,本文将从 BCAAs 对母体孕期及其胎儿的影响阐述其在肥胖代际传递中的作用。

2 支链氨基酸代际传递的研究进展

2.1 母体孕期支链氨基酸水平与其自身肥胖的关联

2.1.1 母体孕期 BCAAs 水平变化及其机制 通

常情况下,母孕期的血浆 BCAAs 水平在孕早期相对较低,在孕晚期会有所增加^[21]。这种变化部分归因于胎儿生长和发育过程中对蛋白质需求的增加,以及相应的母体代谢适应^[21]。随着胎儿生长,其对氨基酸(包括 BCAAs)的需求也相应增大,促使母体通过饮食或内源性代谢的调整来满足这些需求^[22-23]。此外,母体血浆中 BCAAs 水平的上升还受到母体自身代谢状态、胰岛素抵抗程度等因素的影响。孕早期母体胰岛素敏感性较高,胰岛素抵抗现象较少,随妊娠进程,胰岛素抵抗增强,导致葡萄糖利用下降和血糖升高^[24]。为稳定血糖,机体抑制脂肪酸和氨基酸氧化,减少能量供应,从而导致 BCAAs 氧化速率降低,循环 BCAAs 水平升高^[25]。

2.1.2 母体体重情况与孕期 BCAAs 水平的关系

动物研究结果显示,肥胖导致母体在怀孕之前就出现不利的代谢状态^[26]。如在高脂饮食诱导肥胖小鼠模型中,与正常喂养的小鼠相比,肥胖小鼠的平均葡萄糖水平在受孕前显著升高^[26]。人群研究也发现,孕前超重/肥胖的孕妇与体重正常的孕妇相比,整个孕期的 BCAAs 水平均较高;且与超重孕妇相比,肥胖孕妇的血清 BCAAs 水平更高($P < 0.01$)^[7,27-28]。另有研究发现,孕期体重增加过多与其较高的缬氨酸、异亮氨酸水平有关($P < 0.01$)^[29-30]。目前关于孕前 BCAAs 水平的研究较少,但基于体内的 BCAAs 水平与体质量指数之间的密切关联^[7,12,27-28],综合以上证据提示,孕前、孕期超重肥胖以及孕期体重过度增加均对母体 BCAAs 产生显著影响。

2.1.3 肥胖母体孕期 BCAAs 水平升高及机制

动物实验显示,肥胖母鼠孕期 BCAAs 水平高于体重正常母鼠^[31]。肥胖母鼠在孕早期的 BCAAs 代谢状态与正常母鼠孕晚期相似,表现为 BCAAs 分解代谢酶活性低、BCAAs 转酮酸效率低^[31]。这种代谢状态不仅提高母体内 BCAAs 水平,还使后代过早暴露于孕晚期的代谢信号,影响胎儿正常发育^[31]。肥胖母体体内 BCAAs 的积累与多种因素有关。正常妊娠中,氨基酸(包括 BCAAs)被用于生成胎儿发育所需的葡萄糖和酮体^[32],但在母体超重肥胖状态下,过多的脂质使脂肪酸成为主要能量来源,减少了氨基酸(包括 BCAAs)和葡萄糖的分解代谢,导致 BCAAs 累积^[33-34]。此外肥胖状态下的 BCAAs 分解酶(如线粒体支链氨基酸转氨酶和支链 α -酮酸脱氢酶)活性降低,以及肠道微生物群(如普氏拟杆菌)增加 BCAAs 合成,也会导致母体血浆 BCAAs 水平的升高^[35-36]。

2.2 母体支链氨基酸水平对胎儿的影响 母体

BCAAs 的水平对胎儿的宫内发育有显著影响,如影响胎儿神经系统功能、身体发育以及出生体重等^[32,37-38]。研究发现,母体的 BCAAs 水平与胎儿体重增加有关^[37-38]。例如,有研究显示母体内 BCAAs 水平增加 50%,胎儿出生时体重将增加 1%~2.4% ($P < 0.005$)^[37]。另有研究显示,母血和脐带血 BCAAs 水平之间存在显著正相关(r 约为 0.20~0.44, $P < 0.001$)^[38];同时,脐血中的 BCAAs 与出生体重呈正相关(β 约为 0.42~1.54, $P < 0.001$)^[38]。此外,孕期体重增加与子代婴儿期(0~12 月)血浆中 BCAAs 水平有关,母亲孕期体重增加较多的婴儿 BCAAs 水平更高^[39]。这些研究表明,母体 BCAAs 水平不仅是胎儿发育的关键物质,也与胎儿的出生体重和 BCAAs 代谢水平有关,为探究母体 BCAAs 水平与后代肥胖风险的提供了直接证据。

3 母体与子代间支链氨基酸传递的作用机制

通常情况下,BCAAs 经胎盘转运至宫内,对胎儿组织、器官和骨骼等生长发育至关重要^[40]。例如,亮氨酸能够刺激肌肉蛋白合成,影响胎儿肌肉生长^[41]。在能量代谢中,BCAAs 可通过转氨作用和线粒体生物合成等途径转化为能量,以满足胎儿的生长发育需求^[42]。此外,BCAAs 还参与构成神经递质及神经传导过程,促进胎儿的智力和神经行为发育^[32]。但过高的 BCAAs 水平或致胎儿胰岛素抵抗、代谢紊乱等问题^[42-43]。研究发现,母体血浆高 BCAAs 水平与胎盘 BCAAs 水平升高以及相应氨基酸转运蛋白表达升高有关^[31,44-45]。胎盘是胎儿获取营养的重要途径,胎盘氨基酸转运蛋白表达升高,即胎儿可通过胎盘获取更多 BCAAs,而这可能导致子代过度生长、肥胖风险增加^[31,43-44]。

3.1 mTOR 信号通路在肥胖母体中激活 mTOR 是一种非典型的丝氨酸/苏氨酸激酶,参与机体的生长和代谢调节^[46]。mTOR 通过调控多种下游因子(如 p70S6K1、4E-BP1 和 Srebp1)影响蛋白质合成、脂质代谢和细胞增殖等过程^[46-47]。mTOR 有两种复合物,mTOR 复合物 1(mTORC1)和 mTOR 复合物 2(mTORC2)^[46-47]。mTORC1 主要负责调控细胞生长、蛋白质合成和糖脂代谢等;而 mTORC2 则与细胞存活、迁移和细胞骨架组织有关^[46]。在妊娠中,mTOR 调控母体-胎盘-胎儿的通路,促进胎盘滋养层分化、代谢及营养转运,以维持胎盘及胎儿的正常发育^[48]。BCAAs 通常与蛋白质合成(即 mTORC1 的功能)相关,因此 BCAAs 的代谢转运主要与 mTORC1 的调控有关^[46,48-49]。肥胖孕妇中,高 BCAAs 水平可通过过度激活 mTORC1,干扰胰岛

素信号,导致胰岛素抵抗^[48]。总之,mTOR 信号通路在妊娠中扮演着关键角色,而肥胖孕妇中 BCAAs 水平的异常升高可通过过度激活 mTORC1,从而影响母体、胎盘和胎儿的健康。

3.2 mTOR 信号通路在胎盘转运 BCAAs 中的作用 胎儿在宫内的发育依赖胎盘氨基酸营养,其中 mTOR 作为关键营养传感器,能够感知母体营养状况并相应地调节胎盘的 BCAAs 通量^[50-51]。参与 BCAAs 胎盘转运的蛋白分子,主要包括系统 A 的 SNAT1、SNAT2 和 SNAT4 以及系统 L 的 LAT1、LAT2 等蛋白分子,其主要通过与 Na^+ 耦合的方式主动转运 BCAAs^[51]。mTORC1 在胎盘中高度表达,并通过调节氨基酸转运体(如系统 A 和系统 L)来影响胎盘的转运能力^[51-52]。在小鼠模型中,mTORC1 通过 Nedd4-2 介导的泛素化过程直接调节 SNAT2 和 LAT1 的运输,特异性降低 SNAT2 的表达可导致胎儿生长受限,而胎盘 LAT1 的特异性过表达则与胎儿过度生长有关^[51-53]。此外,在肥胖小鼠的胎盘中观察到 mTORC1 信号通路的关键效应分子—核糖体蛋白 S6(RPS6)和 4E-BP1 的磷酸化水平增加,同样支持了 mTORC1 信号通路的激活^[54]。人群研究也发现,肥胖孕妇胎盘中 mTORC1 活性增强可上调氨基酸转运蛋白的表达和活性,增加 BCAAs 从母体向胎儿的转运^[47,55]。以上结果不仅表明 mTORC1 在肥胖母体胎盘中的活跃状态^[47,55],也暗示了 BCAAs 转运通量的改变可能影响子代的生长发育和代谢状态^[51-53]。也就是说,肥胖母体环境下,mTORC1 介导的 BCAAs 转运增强可能是子代肥胖风险的一个重要机制。

4 调控体内支链氨基酸水平的干预措施

现有研究显示,机体内 BCAAs 水平可以通过药物或手术干预进行调节^[10,18,56]。例如,在肥胖小鼠模型中,脂肪组织中 BCAAs 分解代谢减少,而通过药物干预恢复 BCAAs 代谢后,血浆 BCAAs 水平降低,葡萄糖耐受性和胰岛素敏感性也有所改善^[56]。人群研究的结果显示,肥胖患者接受减重手术后,随着体重的减轻,体内的 BCAAs 水平也显著降低^[10,18]。

尽管已有研究表明某些干预措施可以调节体内的 BCAAs 水平,但在孕期的特殊条件下,无论是在人群层面还是动物实验,均尚无通过调控母体 BCAAs 摄入或者代谢等以影响子代体内 BCAAs 水平的探讨,也未见评估母体 BCAAs 的干预是否能降低子代超重肥胖风险的研究。未来研究需进一步探究 BCAAs 在母婴肥胖防控中的潜在应用价

值,以优化针对母子健康的干预策略。

总之,BCAAs 在母体超重肥胖与子代发育中起关键作用。肥胖孕妇的 BCAAs 水平高于正常体重者,并可通过胎盘经 mTOR 信号通路调节氨基酸转运蛋白活性,将 BCAAs 运送至胎儿体内,促进胎儿的生长发育,但高水平的 BCAAs 可能增加子代未来肥胖和代谢紊乱的风险。目前研究虽已认识到 BCAAs 与肥胖及代际传递的相关性,但在基于 BCAAs 调控的干预措施方面仍存在空白。未来研究应深入探讨 BCAAs 在超重肥胖代际传递中的干预机制,并制定有效的干预措施,为预防和干预儿童肥胖提供科学依据和实践指导。

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收稿日期: 2024-10-31 修回日期: 2025-02-19 本文编辑: 李少闻

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收稿日期: 2024-08-09 修回日期: 2025-01-21 本文编辑: 李少闻