· 双相情感障碍专题 ·

# 青少年双相情感障碍与超重/肥胖脑–代谢神经生理及治疗研究进展

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【摘要】 青少年双相情感障碍（BD）与超重/肥胖在脑–代谢形成复杂的病理关联，涉及母体妊娠、大脑结构、脑血流、血脂、食欲激素等方面。现对青少年 BD 与超重/肥胖在脑–代谢及治疗进行综述，并探讨潜在的研究方向。

【关键词】 双相情感障碍；　青少年；　超重/肥胖；　脑生化代谢；　神经生理；　治疗；　综述

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**Research progress on brain-metabolism neurophysiology and treatment in adolescent bipolar disorder and overweight/obesity**

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【**Abstract**】 Adolescent bipolar disorder (BD) exhibits complex pathophysiological associations with overweight/obesity in brain-metabolism, involving maternal pregnancy, brain structure, cerebral blood flow, blood lipids, and appetite hormones. This paper reviews the relationship between adolescent BD and overweight/obesity in terms of brain-metabolism and treatment, and explores potential research directions.

【**Key words**】 Bipolar disorder;　Adolescent;　Overweight/obesity;　Brain biochemical metabolism;　Neurophysiology;　Therapy;　Review

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双相情感障碍（bipolar disorder，BD）的特征是交替发作的抑郁和躁狂（BD-Ⅰ型）或轻躁狂（BD-Ⅱ型）。1990—2019 年，BD 患病、发病人数分别增加 59.3%、51.1%，伤残损失寿命年（years lived with disability，YLD）增加 59.0%[1]。目前，BD 影响了全球约 4 000 万人[2]，全球患病率约为 2.4%[3]。BD 患者 15%～20% 死于自杀[4]，预期寿命较一般人群减少 12～14 年[5]。WHO 将青少年年龄划分为 10～19 岁，而 BD 发病的高峰年龄为 15～19 岁[6]。BD 对青少年的伤残调整寿命年（disability adjusted life years，DALYs）和 YLD 有显著影响，且这一影响在全球范围内呈上升趋势[7]。青少年 BD 患者具有发病年龄早、临床症状不典型、易复发、社会功能损害严重、自杀和共病率高、预后不良以及诊断治疗更困难等特点[8]。

2022 年，全球有 1.59 亿的儿童和青少年面临超重/肥胖问题[9]。我国 6～17 岁儿童青少年超重、肥胖率分别为 11.1% 和 7.9%[10]。一方面，肥胖者的 BD 患病风险显著增加[11]；另一方面，BD 患者超重/肥胖患病率为 32.2% 和 21.0%，显著高于健康人群[12]。在青少年 BD 患者中，超重/肥胖已被证明与身体虐待、自杀企图、自残行为、精神药物治疗和精神住

院有关[13]，提示BD不仅仅是肥胖的风险因素，同时也是多项BD伴随特征的相关因素。母亲妊娠早期体重指数(body mass index, BMI)≥25 kg/m$^2$与子代发生BD的风险存在剂量-反应关系[14]；同时，Ratanatharathorn等[15]也发现子代发生BD的风险与母亲妊娠前超重/肥胖有关，提示母亲孕前、孕早期的超重/肥胖是青少年阶段发生BD的风险因素。本文旨在对超重/肥胖青少年BD患者的中枢神经-代谢调节、治疗进行综述，并对未来研究方向进行展望。

一、青少年BD与超重/肥胖中枢神经-代谢调节

1.BMI与BD大脑结构的关联：特定的大脑变化与发生BD的风险和早期症状表现有关[16]。腹内侧前额叶皮层(ventromedial prefrontal cortex, vmPFC)编码食物奖赏信号，背外侧前额叶皮层(dorsolateral prefrontal cortex, DLPFC)涉及自我控制[17]。BD患者死后脑组织分析显示，DLPFC神经元密度和细胞大小显著降低[18]，可能是该区域突触密度减少的结构基础。在应激状态下，BD患者的BMI与DLPFC、眶额叶皮层(orbitofrontal cortex, OFC)、vmPFC、杏仁核、海马和小脑的突触密度呈负相关[19]。突触连接减少可能促进BD青少年患者冲动性进食与自我调节能力下降，从而加剧BD青少年的超重/肥胖风险。BD遗传度为60%～85%[20]，在14～19岁具有BD家族史的高危青少年中，肥胖伴随额叶-纹状体回路体积的代偿性增大[21]，提示在疾病临床前期，大脑试图通过结构重塑应对肥胖相关的代谢挑战。然而，在确诊BD后，肥胖与脑结构的关联特征发生显著逆转，在青少年BD患者中，BMI升高与OFC和前扣带回皮层(anterior cingulate cortex, ACC)体积减小呈显著负相关[22]。OFC和ACC是情绪调节与决策的核心脑区，其体积缩小可能提示BD的疾病负担加重。大规模研究(如ENIGMA)证实，相较于健康对照组，BD患者出现更显著的杏仁核、海马体、苍白球等边缘系统萎缩及侧脑室扩张。BMI在BD与脑室容量之间的正向关联中起中介作用，其贡献的中介效应占比为18.41%[23]，提示肥胖可能通过扩大脑室体积和加速边缘系统退化，进而加速神经退行性进程。在成人BD患者中，肥胖(BMI≥30 kg/m$^2$)BD患者的前额叶和颞叶皮层更薄，这与青少年BD患者中观察到的额叶变薄方向一致，且范围更广，46.8%的低厚度亚组与高BMI、年龄相关[24]，提示肥胖与衰老在损害脑结构方面存在协同作用。弥散张量成像显示BD合并肥胖患者的胼胝体与丘脑放射冠白质纤维束各向异性分数显著降低，提示白质微结构受损[25]。鉴于该研究中BD患者的平均发病年龄为25.52岁，平均病程长达15.63年，且白质发育持续至青年期，BD相关的白质微结构损伤可能起始于青少年后期并在肥胖影响下持续进展恶化。神经进展是指神经生物学疾病进展，12个月内体重增加(clinically significant weight gain, CSWG)≥基线7%的15～35岁的BD患者出现显著左侧眶额皮质、扣带回体积损失，且左侧中颞回体积损失与抑郁天数增加相关[26]。CSWG达到基线7%可预测青少年及年轻成人BD患者神经进展，其通过驱动左侧眶额皮质-扣带回-中颞回体积萎缩，直接关联脑结构退行与抑郁症状恶化。因此，在具有BD家族史的高危青少年中，肥胖伴随额叶-纹状体系统代偿性体积增大；而确诊BD后，则成为加速边缘-前额叶-颞叶萎缩及白质损伤的关键共病因素。青少年期是大脑发育的关键窗口期，因此对确诊BD青少年实施积极的体重管理策略对保护脑结构至关重要。

2.超重/肥胖对青少年BD脑血流的影响：脑血流反映神经活动能量供应，青少年BD研究显示，ACC及全脑血流降低与抑郁核心症状(抑郁情绪、快感缺失)呈显著负相关，且BD组的平均BMI更高[27]。BD与肥胖可能均与奖赏回路的功能异常相关，针对13～20岁青少年及年轻成人群体的全脑血流研究发现，青少年BD超重/肥胖组在奖赏相关脑区(如基底节、伏隔核和前额叶皮层)的全脑血流显著低于BD非超重/肥胖组，但与健康对照组差异无统计学意义[28]。表明BD本身可能伴随ACC及全脑血流异常；超重/肥胖可能通过影响神经代偿机制削弱BD患者的奖励回路血流调节能力。

3.血脂、食欲激素与BD及肥胖的交互网络：BD患者中，升高的甘油三酯、低密度脂蛋白(low-density lipoprotein, LDL)与BMI呈正相关，而高密度脂蛋白(high-density lipoprotein, HDL)与BMI呈负相关[29]。青少年BD患者更高的致动脉粥样硬化血脂与躁狂状态相关[30]，在BD组中，LDL、HDL升高分别与海马体积减小与增大相关，排除使用二代抗精神病药物的BD患者后结果未改变，血脂升高与BD患者脑结构减小程度显著大于健康对照组[31]，提示BD本身可能增强血脂对神经退化的敏感性。青少年BD患者食欲激素(如胰岛素、瘦素、胃饥饿素和脂联素)水平失调与代谢障碍(如肥胖)相关[32]。BD患者胰岛素水平较高，可能通过损害葡萄糖代谢降低认知功能和情绪调节能力。BD患者瘦素较低，可能减弱

下丘脑–垂体–肾上腺轴负反馈，引发应激反应亢进和情绪波动。在非肥胖的青少年BD患者中，BMI和胃饥饿素水平与情绪失调呈正相关[33]。综上所述，血脂、食欲激素通过调节能量代谢与BD及肥胖形成交互网络，即BD患者的血脂异常，胰岛素抵抗，瘦素、胃饥饿素失衡，协同加剧BD的情感波动与代谢紊乱(如肥胖)。

4.青少年BD与超重/肥胖的脑生化代谢：磁共振波谱成像技术(magnetic resonance spectroscopy imaging, MRS)能无创检测脑内代谢物。对11～18岁的超重/肥胖与非超重/肥胖青少年进行研究，发现超重/肥胖青少年的下丘脑N–乙酰天冬氨酸(N-acetylaspartate, NAA)/肌酸(creatine, Cr)值较正常体重青少年低，且NAA/Cr值与BMI呈负相关[34]。NAA是反映神经元健康与密度的标志物，表明高BMI与青少年下丘脑神经元代谢异常或完整性受损相关。CSWG是首发BD的15～35岁患者中左海马NAA减少的风险因素，提示体重增加可能导致脑生化代谢变化[35]，进一步支持体重状态对青少年BD患者关键脑区生化代谢的影响。BD躁狂状态可能与大脑能量代谢的增强有关，涉及过度的糖酵解和谷氨酰胺分解[36]。当氧化葡萄糖代谢受损时，神经元可能转而利用谷氨酸作为替代底物，通过氧化磷酸化产生能量。BD患者脑内总谷氨酸或谷氨酸(glutamic acid, Glu)+谷氨酰胺(glutamine, Gln)水平的升高可能与丙酮酸羧化酶(pyruvate carboxylase, PC)介导的异生作用增加有关[37]，PC将丙酮酸转化为草酰乙酸，进而参与三羧酸循环和脂质合成[38]；同时，肥胖可上调肝脏和脂肪组织的PC表达，其代谢产物通过血脑屏障同步激活中枢PC，促进谷氨酸生成。研究显示，首发BD躁狂患者的双侧海马Glu+Gln水平显著升高，且与BMI呈正相关[39]。推测在青少年BD患者中可能存在PC活性异常，驱动谷氨酸代谢紊乱与脂质合成，加剧脑能量代谢失调与超重/肥胖。

二、治疗策略

1.药物治疗：儿童青少年BD患者的超重/肥胖患病率显著高于同龄人群[13]，需给予针对性健康干预[40]。超重/肥胖可能是BD疾病进展的一个可改变或控制的危险因素[41]；精神药物作为独立危险因素也进一步增加BD患者超重/肥胖的风险[42]，并导致BD患者治疗依从性下降[43]。奥氮平等二代抗精神病药通过干扰FOXO、PI3K/AKT等通路诱导代谢紊乱[44]。研究发现，体重增加风险较高的抗精神药物与禁食时奖励–感觉运动区域之间有更大连通性[45]。因此，避免使用可能诱发体重增加的精神药物，如奥氮平、氯氮平、米氮平和三环类抗抑郁药[46]。此外，纳曲酮是一种内源性阿片受体拮抗剂，通过减少食物摄入，进而控制体重，目前还在探索其在减轻抗精神病药物所致体重增加方面的应用[47]。BD患者罹患2型糖尿病的风险增加，Kittel-Schneider等[48]的研究指出，超重/肥胖可能是BD与糖尿病之间关联的中介因素，会进一步加重超重/肥胖BD患者的医疗负担并降低生活质量[49]。改善儿童抗精神病药物代谢参数研究显示，添加二甲双胍或改用代谢风险较低的抗精神病药物可以降低儿童抗精神病药物相关的超重/肥胖[50]。为探究胰高血糖素样肽–1受体激动剂(glucagon-like peptide-1 receptor agonist, GLP-1 RA)，如利拉鲁肽在BD患者中是否改善代谢指标。McElroy等[51]选取60例BMI ≥ 27 kg/m$^2$ BD患者，29例接受利拉鲁肽3.0 mg/d治疗，31例接受安慰剂治疗，结果显示利拉鲁肽(3.0 mg/d)在成人BD患者中能够显著降低体重(–3.3%)、改善暴食行为，且安全性、耐受性良好。针对拒绝传统情绪稳定剂(锂盐/阿立哌唑)的肥胖(BMI=32 kg/m$^2$) BD-Ⅱ患者，利拉鲁肽可减轻体重、维持心境稳定且不诱发躁狂或自杀倾向[52]。但其在青少年BD人群中的有效性和安全性需严格设计的临床试验以确认。

2.非药物治疗：与普通人群比较，BD患者参与体育活动的水平通常较低，且面临更高的慢性健康状况风险，如肥胖。McCartan等[53]的研究综合了定性证据，认为有规律的体育活动对青少年女性BD患者有益，包括步行、跑步/慢跑、游泳、骑自行车、团队运动、户外运动等。12周中等强度指导性运动(如步行、游泳)可改善肥胖BD患者的神经认知功能、降低炎症(IL-6)及氧化应激(mROS)[54]，并优化代谢指标(LDL、胰岛素)[55]。Vancampfort等[56]建议将体力活动生命体征纳入超重/肥胖BD患者的治疗计划中。成人BD合并肥胖的患者接受12周的生酮饮食(10%碳水化合物、30%蛋白质和60%脂肪)后实现体重减少10%，内脏脂肪减少27%，并缓解精神症状[57]。生酮饮食在青少年BD中的应用需极其谨慎，必须在专业医疗和营养团队严格监护下进行，确保不影响生长发育。严重精神疾病患者吸烟率较高，但戒烟后可能加剧超重/肥胖风险，在BD患者中，结合安非他酮和个体化行为支持可提升戒烟率，且无显著体重增加[58]。利拉鲁肽可通过调节

中脑-边缘多巴胺系统减少尼古丁渴求、戒断症状及自我给药行为，同时抑制戒烟后过度进食和体重增加[59]。肥胖与BD的关联被归类为提示性证据，需要早期治疗以最小化这些共病的风险[60]。因此，优先选择代谢风险较低的情绪稳定剂，利拉鲁肽既可辅助减重、稳定心境且不诱发躁狂；运动、生酮饮食则能降低体重、缓解精神症状；但应用生酮饮食需谨慎，确保不影响青少年生长发育。此外，个体行为干预与药物(安非他酮、利拉鲁肽)的戒烟策略可减少尼古丁依赖且避免体重反弹。减轻体重可作为一种新的情绪稳定治疗甚至疾病辅助治疗[61]，但仍需更多针对青少年群体的研究，验证体重管理策略的神经保护作用及长期效益。

三、总结与展望

BD的高患病率、高病死率已成为一个重大的公共卫生问题。母孕前、孕早期高BMI会增加子代患BD的风险。在具有BD家族风险的高危青少年中，肥胖与额叶-纹状体回路代偿性体积增大有关；确诊BD后，肥胖则加剧前额叶、颞叶皮层变薄，边缘系统萎缩，白质微结构损伤，奖赏回路脑血量下降及血脂-食欲激素失调；同时，BMI升高也是BD神经进展的重要预测因子。青少年BD躁狂状态与脑能量代谢亢进相关，肥胖通过上调PC加剧谷氨酸代谢紊乱。治疗策略需特别考虑青少年生长发育的特点，优先选择不易致胖的情绪稳定剂。利拉鲁肽可降低成人BD体重并稳定心境，其在青少年中的有效性和安全性有待进一步研究；运动能够改善BD神经认知功能及肥胖，生酮饮食可缓解BD超重/肥胖及精神症状，但青少年应用需极其谨慎。体重管理有望成为治疗青少年BD的重要辅助方法，但仍需更多长期研究验证其临床效果。

未来可进一步利用MRS技术纵向追踪青少年BD脑代谢物动态变化，明确PC介导的谷氨酸-脂质合成环路，研究优化血脂对BD患者脑结构、躁狂状态的影响，探索代谢-免疫-神经环路交互机制，验证利拉鲁肽等GLP-1 RA在青少年BD患者中的疗效及安全性，以及个体化体重管理方案的神经保护效应与长期预后价值。通过对这些领域的持续研究，有望更好地理解BD，并为患者提供更有效的治疗方法。

**利益冲突** 文章所有作者共同认可文章无相关利益冲突

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