·综述·

# 双相情感障碍认知功能损害与脑源性神经营养因子基因遗传学研究的进展

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【摘要】 双相情感障碍(BD)患者存在持续的认知功能损害,这种损害可对患者的病程以及预后产生不利影响。脑源性神经营养因子(BDNF)是神经生长因子家族的一种神经营养因子,参与神经元的发生、存活以及突触可塑性,与BD患者认知功能损害密切相关。本文综述了BDNF表达水平、基因多态性与BD认知功能损害的关系,BDNF表观遗传学与BD及认知功能损害的研究,为早期识别及治疗BD患者认知功能损害提供理论依据。

【关键词】 双相情感障碍; 脑源性神经营养因子; 认知功能; 基因遗传; 综述
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**Research progress on cognitive impairment in bipolar disorder and genetic inheritance of brain-derived neurotrophic factor**

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【Abstract】 Patients with bipolar disorder (BD) exhibit persistent cognitive impairment, which has adverse effects on the course and prognosis of the disease. Brain-derived neurotrophic factor (BDNF) is a type of neurotrophic factor in the family of nerve growth factors, which is involved in the genesis, survival, and synaptic plasticity of neurons, and is closely related to cognitive impairment in BD patients. This paper reviews the relationship between BDNF expression levels, gene polymorphisms, and cognitive impairment in BD, as well as the study of BDNF epigenetics, BD and cognitive impairment, aiming to provide a theoretical basis for early identification and treatment of cognitive impairment in BD patients.

【Key words】 Bipolar disorder; Brain-derived neurotrophic factor; Cognition; Genetic inheritance; Review
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双相情感障碍(bipolar disorder, BD)是一种慢性复发性疾病,是轻躁狂/躁狂发作、抑郁发作、交替发生或者混合发作为主要特征的一种心境障碍。据WHO统计,全球BD的终生患病率为2.4%[1],在致残性疾病中排名第6位[2]。认知功能损害不仅持续存在于BD疾病发作期,也存在于缓解期,且涵盖大部分认知领域,包括注意力和处理速度、记忆力以及执行功能[3-5]。认知功能损害会导致BD患者不良情绪的频繁发作[6],影响疾病康复,消耗更多的医疗资源[7]。此外,及时评估和治疗认知功能损害是BD标准管理方案的重要部分[8]。部分BD患者一级亲属也表现出一定程度的神经认知功能损害[9-10],这种损害被认为是具有高遗传性BD的内在表型[11]。

BDNF是神经发育的一种重要生物因子,其参与了BD发病并介导了BD的认知功能损害,受到国内外学者密切关注。但有文献分析了精神分裂症-BD谱系血液中BDNF水平与认知功能损害的关系,发现血液BDNF水平似乎并不是精神分裂症-BD谱系患者认知功能损害的有效生物标志物[12];尽管BD患者BDNF水平较健康对照组低,但BDNF与BD

认知功能之间的相关性较弱。这也提示虽然既往证据表明BDNF可能是BD的生物标志物[13]，但BDNF作为BD认知功能损害生物标志物的证据仍不够明确。因此，本文进一步探讨BD认知功能损害与BDNF表达、基因多态性的关系，阐述BDNF表观遗传学在BD认知功能损害的可能机制，旨在为BD认知功能损害的诊疗提供理论依据。

一、BDNF表达与BD认知功能损害的关系

BDNF由位于11号染色体的基因所编码，参与脑内突触的可塑性以及神经元的发生、成熟和维持，介导神经元的存活，在与记忆和学习功能相关的大脑皮层及边缘区域高度表达。动物实验表明，注射钠钾泵抑制剂所致躁狂症小鼠模型出现了类似于BD患者的认知灵活性欠佳和工作记忆缺陷，并与小鼠额叶皮层中的BDNF mRNA和蛋白质水平表达下调相关[14]。另一项由D-苯丙胺诱导伴有认知障碍的躁狂小鼠模型中，利拉鲁肽逆转了D-苯丙胺诱导下小鼠前额叶皮层和海马体中BDNF水平降低，并增强锂盐的抗氧化作用，防止小鼠行为和认知功能的进一步恶化[15]。

临床试验中，较多学者研究了血清BDNF表达与BD认知功能损害的关系。Zhang等[16]比较了单双相抑郁患者的认知功能以及血清BDNF水平，发现双相抑郁患者认知功能更差，BDNF水平更低。Teng等[17]比较了BD Ⅱ型患者、重度抑郁症患者和健康人群血清BDNF水平以及认知功能，发现BD Ⅱ型患者的血清BDNF水平最低，表现为注意力、延迟记忆、视觉空间/结构学习和执行功能受损。也有研究发现，血清BDNF、细胞因子和氧化应激等周围神经生物学因素中，BDNF是唯一与BD患者认知功能障碍存在相关性的因素，高BDNF血清水平与良好的认知功能相关[18]。伴有认知功能损害的缓解期成年男性BD患者的血清BDNF水平与健康对照人群也有差异[19]。

部分学者研究了血浆BDNF表达与BD认知功能损害的关系。一项有关青少年BD患者执行功能与血浆BDNF水平的研究显示，较低的血浆BNDF水平与执行功能受损呈正相关[20]。Liou等[21]通过比较伴有认知功能损害的BD患者以及共病酒精使用障碍(alcohol use disorder, AUD)的BD患者的血浆BDNF水平发现，两组患者的血浆BDNF水平与健康人群比较差异有统计学意义，且BD和AUD会加快认知功能损害过程。另一项研究显示，BD患者血浆BDNF mRNA与其认知功能呈正相关[22]。

在药物治疗和新药开发方面，就BD认知功能损害与BDNF表达关系也有相应研究。锂作为BD治疗的一线药物，可以改善BD认知症状[23]。作为锂作用机制的锂分子效应改变了中脑边缘和中皮层通路中的多巴胺能信号传导，且BDNF参与锂的分子效应以及锂的治疗反应[24-25]。Matosin等[26]在BD患者尸检中发现，致病基因糖皮质激素受体变构热休克蛋白伴侣基因(FKBP51)，通过BA11(新皮质分区之一)中浅层神经元中的蘑菇状树突棘密度和该分区内BDNF水平影响认知功能。

以上研究显示，BD认知功能损害与海马体以及前额叶等大脑相关皮层内BDNF mRNA和蛋白水平下降有关，表现为血浆或血清BDNF mRNA和蛋白水平降低，导致注意力、记忆力、学习能力以及执行功能等认知领域受损。虽然中枢和外周BDNF水平高度相关[27]，但血清和血浆BDNF水平有200倍差异，这是由于外周BDNF几乎都储存在血小板中(接近100%)，导致血浆中游离BDNF水平较低，而在制备血清样本测量BDNF水平的过程中，凝血和离心过程会导致血小板释放BDNF，升高BDNF水平[28]。由此可见，血清更值得推荐作为BDNF的样本来源。此外，BDNF表达水平介导锂的多巴胺系统反应从而治疗BD患者的认知功能，并参与FKBP51基因所致的认知功能损害，成为BD认知功能损害的重要中介物质之一。因此，BDNF表达有潜力成为BD认知功能损害的外周生物标志物。

二、BDNF基因多态性与BD认知功能损害的关系

BDNF基因多态性研究中研究最广泛的是负责BDNF表达变化的SNP rs6265，这是BDNF前体(pro-BDNF)密码子66上的一个缬氨酸(Val)被一个蛋氨酸(Met)取代，导致单个核苷酸发生突变，产生Val/Val、Val/Met、Met/Met共3种基因型。BDNF基因多态性影响着BDNF和BDNF前肽的细胞活性，BDNF前肽在折叠和分泌成熟的BDNF中发挥着重要作用，最终导致BDNF水平下降[29]。动物实验表明，与BDNF Val/Val小鼠相比，BDNF Met/Met小鼠在认知任务方面的正确反应较少。与雄性小鼠相比，雌性BDNF Val/Val小鼠的认知灵活性更好[30]。

BDNF基因多态性对BD认知功能影响与外周BDNF水平相关。在一项有关BD患者治疗12周后血浆BDNF水平基线变化的研究中，血浆BDNF水平与BD患者的执行功能呈正相关，受到BDNF Val66Met基因多态性的调节，而外周BDNF水平更好

地描述了Val/Met基因型BD Ⅰ型患者的认知表现[31]。也有研究表明，基因型为Val纯合子的BD Ⅱ型患者在即时视觉记忆方面优于携带Met等位基因患者，但较健康对照组差；不同基因型患者BDNF血浆浓度相似，但较健康对照组低；患者BDNF水平与BDNF多态性之间可能没有显著关联[32]。

BDNF基因多态性对BD认知功能的影响可能独立于外周BDNF水平。Cao等[33]的研究发现，与重度抑郁症患者和健康人群相比，携带BDNF Met等位基因的BD患者的海马体积更小，在言语学习以及记忆方面表现更差。也有学者通过影像学检查了BD等精神疾病患者的脑容量，发现在选定BDNF-rs6265的情况下，海马、海马旁回、双侧背外侧前额叶、扣带皮层体积减小[34]。BDNF rs6265影响BD患者前扣带回中N-乙酰天冬氨酸、总肌酸等神经代谢物[35]，这些物质的减少与处于缓解期BD患者记忆力以及执行功能受损相关[36]。然而，Hørlyck等[37]发现，基因型为Val纯合子的BD患者和携带Met等位基因的BD患者在参与假设的记忆编码区域(即海马体和背侧前额叶皮层)方面并没有差异，但携带Met等位基因的BD患者表现出更好的图片记忆功能。

综上所述，有关BDNF基因多态性对BD认知功能影响的研究结果不尽相同，甚至相互矛盾，提示BDNF Val66 Met多态性可能通过复杂的基因-环境相互作用和大脑结构变化调节BD患者的认知功能。BDNF基因多态性对BD认知功能的影响可能独立于外周BDNF水平，通过影响海马、前额叶和扣带回等脑区体积以及扣带回内的生化代谢物实现；但外周BDNF水平与BD认知功能损害受到BDNF基因多态性的调节，主要在记忆力和执行功能等认知领域受损。携带Val等位基因的BD患者较携带Met等位基因的BD患者有着更好的认知功能。另有研究认为，携带Met等位基因患者有着更好的图片记忆能力。两项研究结果不完全一致，可能原因是缺乏健康人群作为对照且BD残留的情绪症状会削弱BDNF基因型引起的潜在差异。总之，BDNF基因多态性对于BD认知功能损害具有一定的指导意义。

三、BDNF表观遗传学与BD及认知功能损害的关系

表观遗传学是研究在不改变基因核苷酸序列的情况下，基因表达变化可遗传的一门遗传学分支学科，主要包括DNA甲基化、组蛋白修饰、非编码RNA等[38]。DNA甲基化是由DNA甲基转移酶催化S腺苷甲硫氨酸作为甲基供体，将胞嘧啶转化为5-甲基胞嘧啶的反应；组蛋白修饰是指组蛋白在相关酶作用下发生甲基化、乙酰化、磷酸化、腺苷酸化等修饰的过程；MicroRNA(miRNA)在脊椎动物和无脊椎动物的突触可塑性和记忆中起着重要的作用[39]。

1. BDNF表观遗传学与BD的研究：目前，BDNF表观遗传学与BD的研究集中在DNA甲基化。Duffy等[40]学者将BD患者后代定义为高风险后代，通过有无情绪障碍分为受影响和未受影响高风险后代；与对照组比较，受影响和未受影响高风险后代的BDNF甲基化率增高，且受影响高风险后代最高。不管是BD Ⅰ型还是Ⅱ型患者，BDNF启动子区的DNA甲基化水平较健康对照组均升高[41]。Redlich等[42]发现，BD患者高BDNF甲基化可能会降低BDNF mRNA表达并上调杏仁核反应性。在早发BD患者的BDNF启动子Ⅸ/CPG-2的甲基化水平显著增高[43]；而且BD患者血清BDNF mRNA及蛋白水平与CpG位点甲基化水平相关，血清BDNF蛋白水平与CpG位点177的甲基化程度呈负相关，BDNF mRNA水平与CpG位点217的甲基化程度呈负相关[44]。

2. BDNF表观遗传学与认知功能损害的研究：BDNF表观遗传学与认知功能损害的研究主要集中于组蛋白修饰且绝大部分为动物实验。早期缺铁幼鼠发生的认知障碍与抑制性组蛋白修饰有关，其海马中BDNF启动子组蛋白的乙酰化以及磷酸化富集较低[45]。另一项实验发现，孤立饲养会导致小鼠认知功能下降和神经系统发育迟缓，与小鼠内侧前额叶皮质中BDNF mRNA水平、BDNF基因H3乙酰化水平和BDNF蛋白表达水平升高以及在海马表达水平的降低相关[46]。运动降低了老年鼠BDNF启动子Ⅵ处的H3K9me3(一种抑制性的组蛋白修饰)，并改善了老年鼠因大脑衰老所致的认知功能损害[47]。此外，组蛋白修饰参与BDNF信号转导通路。由异氟醚诱导的大鼠认知功能障碍与染色质组蛋白乙酰化下降导致的BDNF-TrkB信号通路下调有关[48]。Ionescu-Tucker等[49]发现，衰老带来的认知能力下降与BDNF信号传导抑制有关，BDNF信号传导抑制后H3K9me3上调，并在体外培养的海马神经元的12个区域内升高，这种升高部分由氧化应激介导。纹状神经退行性疾病的认知缺陷伴随着BDNF相关标记的空间染色质重组和转录诱导减少，与H3K9乙酰化的记忆依赖性调节在控制细胞外基质和髓鞘形成的基因方面受损相关[50]。L-丝氨酸处理上调了生长激素释放激素敲除(GHRH-KO)小鼠H3K4me、H3K9ac、H3K14ac和H3K18ac以

及大脑皮层 H3K4me 的组蛋白表观遗传标记，增加 GHRH-KO 小鼠 BDNF mRNA 表达，缓解了实验小鼠短期物体识别记忆损害[51]。BDNF DNA 甲基化也与认知功能损害有关。动物实验表明，暴露于七氟醚大鼠锥体神经元中的 DNA 甲基转移酶表达增加，进而使 BDNF 高甲基化，导致大鼠海马锥体神经元中树突棘的减少并产生认知功能损害[52-53]。同样，处于应激状态小鼠发生的认知功能损害与其海马内的 BDNF 基因甲基化水平增高有关，伴随着低 BDNF mRNA 水平以及蛋白水平[54]。也有研究表明，小鼠海马体内微生物代谢物会导致 BNDF 发生 DNA 甲基化变化，并与认知建立了联系[55]。上述相关性在 miRNA 也有体现，具有下调 miRNA-206(抗 miRNA-206) 的人脐带间充质干细胞可缓解 D-半乳糖诱导的老年鼠认知能力下降，与 BDNF 过表达相关[56]。因此，BDNF 表观遗传学与 BD 及认知功能损害紧密联系。

BD 患者有着较高的 BDNF DNA 甲基化水平，主要分布于启动子区，伴随着血清 BDNF mRNA 水平和蛋白水平的降低。压力、衰老、氧化应激、物质暴露会改变 BDNF 表观遗传学机制，导致 DNA 甲基化、组蛋白修饰以及 miRNA 水平发生变化，直接或间接影响 BDNF 表达水平，进而导致认知功能损害。尽管目前关于 BDNF 表观遗传学与 BD 认知功能损害的直接相关证据较少，但 BDNF 表观遗传学仍有很大潜力成为 BD 认知损害的潜在机制。

四、总结与展望

综上所述，BDNF 表达水平、基因多态性与 BD 认知损害紧密联系，而 BDNF 表观遗传学与 BD 认知损害具有潜在联系。BDNF 表达在海马体以及前额叶等大脑相关皮层的下降会影响脑内突触可塑性及神经元发育，导致认知功能损害，这种作用受到 BDNF 基因多态性的调节。BDNF 基因多态性介导 BD 患者认知功能损害可能独立于 BDNF 表达水平，携带 Met 等位基因 BD 患者的海马、前额叶和扣带回等脑区体积缩小以及扣带回内的生化代谢物降低，进而导致认知功能损害。BDNF 表观遗传学通过直接或间接影响 BDNF 表达在 BD 发病和介导认知功能损害中发挥重要作用。但目前的研究多为关联性研究，而非因果验证。特别是 BDNF 表观遗传学与 BD 认知功能损害，没有直接关联证据。未来可以开展更多的因果验证以及临床试验研究，而 BDNF 表观遗传学在 BD 认知功能损害方面可能会成为研究热点。

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