·综述·

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重复经颅磁刺激干预中枢神经系统疾病的生物标志物研究进展

杨娅婕[1,2,3],赵 宁[1,2*],曹玉婷[1,2],王桂喜[1,2]

(1.深圳大学第六附属医院康复医学科,广东 深圳 518052;2.华中科技大学协和深圳医院康复医学科,广东 深圳 518052;3.湖南中医药大学,湖南 长沙 410208)

〔摘要〕生物标志物对于医学的合理发展至关重要,在科学研究与临床实践中具有重要意义。本文就近年来重复经颅磁刺激治疗中枢神经系统疾病研究中基于生物标志物分析的文献进行总结,发现治疗后中枢神经系统疾病患者的行为学改变与生物标志物的改变呈特定相关性,这些研究的报道可能为经颅磁治疗中枢神经系统疾病提供了更客观的代谢组学证据。

〔关键词〕重复经颅磁刺激;生物标记物;神经系统;可塑性;神经递质;氨基酸;炎症;细胞凋亡

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Progress on Biomarkers of Repetitive Transcranial Magnetic Stimulation Intervention for Central Nervous System Diseases

YANG Yajie[1,2,3], ZHAO Ning[1,2], CAO Yuting[1,2], WANG Guixi[1,2]*

(1. Department of Rehabilitation Medicine, Sixth Affiliated Hospital of Shenzhen University, Shenzhen, Guangdong 518052, China; 2. Department of Rehabilitation Medicine, Huazhong University of Science and Technology Union Shenzhen Hospital, Shenzhen, Guangdong 518052, China; 3. Hunan University of Chinese Medicine, Changsha, Hunan 410208, China)

〔**Abstract**〕Biomarkers are very important for the rational development of medicine, and have wide significance in scientific research and clinical practice. We summarized the literatures based on biomarker analysis in the study of repetitive transcranial magnetic stimulation in the treatment of central nervous system diseases in recent years, and found that the behavioral changes of patients with central nervous system diseases after treatment were specifically related to the changes of biomarkers. The reports of these studies may provide more objective metabonomics evidence for transcranial magnetic therapy of central nervous system diseases.

〔**Keywords**〕repetitive transcranial magnetic stimulation; biomarkers; nervous system; plasticity; neurotransmitters; amino acids; inflammation; cell apoptosis

生物标志物是一种特征,可作为正常生物过程、致病过程和对暴露或干预(包括治疗干预)的反应的指标[1-2]。生物标志物检测在循证医学中发挥着核心作用,能够促进临床结果的改善,减轻经济负担[3]。代谢组学是近年出现的具有生命科学整体观念的研究方法,与经颅磁刺激整体调节的特点相契合[4-6]。代谢组学是一种系统生物学方法,它从整体的角度,通过对特定组织代谢物的定量分析,研究内源性代谢物质的代谢途径及其所受内在环境因素影响及动态变化规律[7-8]。蛋白组学与代谢组学作为生物标志

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〔作者简介〕杨娅婕,女,在读硕士研究生,研究方向:神经康复。

〔通讯作者〕* 赵 宁,女,副主任医师,硕士研究生导师,E-mail:zhaoning2018@email.szu.edu.cn。

物的检测手段，能够提高对疾病的诊断与预测，因此，被广泛应用于医学科学等领域[1]。

重复经颅磁刺激(repetitive transcranial magnetic stimulation, rTMS)作为一项非侵入性的神经电生理刺激技术，具有无痛无创、操作简便等优点[4]，在脑卒中[9-11]、帕金森病[12-15]、情感障碍[16-19]、认知障碍[20-23]及神经科疾病[22,24-25]中广泛应用。rTMS 能够促进神经发生与修复，提高大脑突触可塑性[26]。rTMS 也可影响神经递质释放、蛋白质表达和基因活性的短暂与长久变化，达到治疗神经精神疾病的目的[5]。众所周知，rTMS 通过引发长期增强(long-term potentiation, LTP)作用和长期抑制(long-term depression, LTD)作用来影响大脑的神经元可塑性。低频率 rTMS 主要刺激低阈值抑制神经元，而高频率 rTMS 激发投射神经元[5-6,26]。目前，关于 rTMS 作用机制的研究，多源于临床行为学评定，应用脑电、核磁等技术揭示其临床疗效及影像学机制，代谢组学与蛋白组学的机制研究主要集中在某些特定通路、常见代谢产物的改变等方面。目前，利用生物标志物分析的方法研究 rTMS 治疗神经精神疾病方面已有诸多报道，本文对近 5年来 rTMS 治疗神经精神疾病研究中基于生物标志物分析的文献进行总结。

1 rTMS 对脑卒中及其生物标志物的影响

rTMS 作为一种无创性脑刺激技术，在脑卒中后运动功能障碍、认知/言语/偏侧忽略及相关并发症的临床康复中发挥着重要的作用。

Boonzaier 等[27]在运用 rTMS 对脑卒中动物模型作用机制研究中发现，rTMS 的效应可能与缺血耐受、神经保护、抗凋亡、神经发生、血管生成或神经可塑性相关。Baek 等[28]探讨 rTMS 在体外神经元缺血/再灌注(ischemia/reperfution, I/R)损伤模型中的差异效应，用维甲酸诱导小鼠脑神经瘤细胞分化，建立体外缺氧缺糖/复氧(oxygen glucose deprivation/reperfusion, OGD/R)条件下 I/R 损伤模型，结果发现 10 Hz rTMS 通过激活细胞外信号调节激酶和蛋白激酶 B(protein kinase B, PKB)信号通路促进细胞增殖、抑制 OGD/R 损伤细胞凋亡。此外，10 Hz rTMS 增加 Ca^{2+}-CaMKⅡ-CREB 信号通路，进一步导致 OGD/R 损伤细胞脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)表达和突触可塑性的改变。Luo 等[29]用 20 Hz rTMS 干预大脑中动脉闭塞大鼠，发现高频 rTMS 显著促进了梗死周围纹状体的神经发生，并伴随着 BDNF 和磷酸化和酪氨酸激酶受体 B(tyrosine kinase receptor B, TrkB)蛋白水平的升高。NⅡmi 等[30]对脑卒中后上肢偏瘫患者行康复加 rTMS 联合治疗，结果发现联合治疗可使 BDNF、基质金属蛋白酶 9(matrix metalloprotein-9, MMP-9)水平升高，而对 BDNF 的前体无明显影响，但血清 BDNF 和 MMP-9 水平与运动功能改善无关。研究结果发现，BDNF 及其前体也极有可能是脑卒中后运动恢复的潜在生物标志物，这些结果提示 BDNF/TrkB 信号通路与神经功能恢复的相关性。

脑卒中后大脑启动内源性修复，细胞凋亡是其重要途径之一。Caglayan 等[9]研究发现高频 rTMS 可以通过诱导脑的内源性修复和恢复机制来促进脑卒中患者的功能恢复。在脑卒中发病后 3 d 开始应用 rTMS，持续 28 d，发现实验动物的 DNA 碎片减少、梗死体积和脑血流量改善，这与 B 细胞淋巴瘤/白血病-xL(B cell lymphoma/leukemia-xL, BCL-xL)基因活性增加及 B 细胞淋巴瘤相关 X 蛋白(BCL2-associated X, BAX)、天冬氨酸特异性半胱氨酸蛋白酶 1(cysteinyl aspartate specific proteinase-1, Caspase-1)和 Caspase-3 活性降低有关。Zong 等[10]探讨 rTMS 对大鼠光血栓性脑卒中模型行为缺陷的影响及其潜在机制，研究表明 rTMS 能显著减少梗死周围皮质区的突触丢失和神经元变性，梗死周围区域抗炎细胞因子和线粒体超氧化物歧化酶 (superoxide dismutase, SOD)的释放增加，有效地保护了梗死周围皮质线粒体膜的完整性，抑制了线粒体 Caspase-9/3 凋亡途径。Guo 等[31]评估了 rTMS 对脑卒中后认知障碍的治疗效果，并探讨了其在大脑中动脉阻塞大鼠模型中的作用机制，结果表明 rTMS 增加同侧海马神经发生和减少凋亡的机制显著改善认知功能。Sasso 等[32]研究 rTMS 对局灶性脑损伤模型的远侧退行性变、炎症及功能恢复的影响，采用 rTMS 方案治疗大鼠半小脑切除术 7 d，结果显示 rTMS 能显著降低远端神经元死亡和胶质细胞活化，促进功能恢复。

上述研究发现，rTMS 能够干预 BDNF/TrkB、Ca^{2+}-CaMKⅡ-CREB 等神经保护的信号通路以及线粒体 Caspase 凋亡途径，因此，rTMS 有可能在多通道、多靶点改善了相应代谢物的表达，从而促进脑卒中模型动物神经功能的恢复。

2 rTMS 对抑郁症及其生物标志物的影响

目前，rTMS 已经被美国 FDA 确认为治疗抑郁症安全有效的措施[33]。rTMS 能调节氨基酸类与单胺类神经递质，其中对 DA(dopamine, DA)能系统、γ-

氨基丁酸(γ-aminobutyric acid, GABA)能系统与谷氨酸(glutamic acid, Glu)能系统的影响更大。GABA能系统和 Glu 能神经递质系统是抑郁症病理生理学的核心,是 rTMS 的潜在靶点[34]。

Kim 等[35]对慢性不可预测轻度应激(chronic unpredictable mild stress, CUMS)大鼠抑郁模型采用 10 Hz rTMS 治疗后,磁共振波谱显示其前额叶和海马 GABA 水平显著降低, 结果表明 rTMS 治疗可逆转行为并带来神经化学改变。Tan 等[36]用 1 Hz rTMS 治疗 2 周有效地缓解了年轻成年大鼠的抑郁样行为,表明 rTMS 可通过调节突触 GABA 的传递,促进兴奋性和抑制性(excitability/inhibition, E/I)活性之间的平衡的恢复。Levitt 等[19]用 10 Hz rTMS 治疗难治性抑郁症患者,使用磁共振波谱来评估左前额叶背外侧皮质(dorsolateral prefrontal cortex, DLPFC) GABA 水平的变化,结果表明 rTMS 治疗与左侧 DLPFC 刺激部位 GABA 水平升高有关,GABA 变化程度与临床改善有关,同时接受 GABA 激动剂治疗的受试者对 rTMS 的反应较小。抑郁症的病理生理涉及重要的边缘结构(如脑岛),Guo 等[31]研究 rTMS 诱导的 E/I 传递改变是否与额叶边缘连接改变有关,通过前额叶 rTMS 间歇性 θ 刺激模式对健康对照组的岛叶进行神经调节,结果发现间歇性 θ 刺激模式能显著抑制了两种体素的前岛连接和 GABA/Glu。Dubin 等[34]用磁共振波谱评价了 10 Hz rTMS 对抑郁症患者左侧 DLPFC 内侧前额叶皮质 GABA 和 Glu 联合共振的影响,发现抑郁症患者内侧前额叶皮质中 GABA 增加 13.8%,rTMS 对 Glu 无明显影响,GABA 和 Glu 在重度抑郁症患者在基线水平中呈正相关,与中度抑郁症患者无相关性, 在 rTMS 后也无显著性差异。Erbay 等[18]评估 rTMS 对抑郁症患者的临床疗效,并研究了rTMS 对 N-乙酰天冬氨酸(N acetyl aspartate, NAA)、胆碱(choline, Cho)、肌酸(creatine, Cr)、乳酸(lactate, Lac)、肌醇(myo-inositol, mIns)、Glu、谷胱甘肽(glutathione, GSH)的影响,结果发现 rTMS 前后汉密尔顿抑郁量表评分差异有统计学意义,发现 rTMS 后 NAA/Cr、GSH/Cr 和 Glu/Cr 的峰值代谢率明显高于 rTMS 前。Leblhuber 等[16]研究了老年抑郁症患者在前额叶皮层刺激后神经递质前体氨基酸利用率的变化,结果发现血清苯丙氨酸显著下降,表明 rTMS 对抑郁评分有显著影响,还表明其对苯丙氨酸羟化酶(phenylalanine hydroxylase, PAH)可能有影响,PAH 在老年抑郁症相关神经递质前体的生物合成中起着关键作用。Zheng 等[37]用磁共振波谱观察了对年轻抑郁症患者 15 Hz rTMS 前后前扣带回皮质的代谢,发现与健康对照组相比,干预前患者左前扣带回皮质中 NAA 和 Cho 含量显著降低,治疗后受试者左侧前扣带回皮质的 NAA 水平显著升高。有研究尝试通过体液的代谢组分分析来检测新生物标志物。Alesha 等[38]发现 α-氨基-正丁酸和 3-甲基组氨酸可作为生物标记物,客观监测 rTMS 治疗抑郁症的疗效,用中等强度 rTMS 和盐酸氟西汀治疗嗅球切除小鼠模型,目前的研究结果表明高强度 rTMS 标准化了血浆 α-氨基-正丁酸和 3-甲基组氨酸的浓度,显示嗅球切除小鼠模型和中高等强度的 rTMS 治疗后,谷氨酰胺和谷氨酸信号传导发生了显著变化。还有研究发现,rTMS 可以逆转海马神经元的凋亡,恢复下丘脑-垂体-肾上腺(hypothalamic-pituitary-adrenal, HPA) 轴在治疗抑郁症中的平衡。Zhao 等[39]对 CUMS 模型大鼠进行连续 15 d 的 rTMS,CUMS 组大鼠脑内 BAX、促肾上腺皮质激素(adrenocorti cotropic hormone, ACTH)和皮质醇(corticosteroid, CORT)水平升高,海马神经元形态异常、数量减少。rTMS 逆转了这些变化,改善了抑郁样行为。Khodaie 等[40]研究 rTMS 对海马和皮层扩散性抑郁的影响,发现长期应用 rTMS 能显著减少大鼠暗神经元的产生,增加正常神经元的平均体积,减少皮质区凋亡神经元的数量,提示 rTMS 对皮层扩散性抑郁所致大鼠大脑皮层和海马区损伤具有明显的预防和保护作用。

rTMS 对血清中 BDNF 的影响存在争议。Lu 等[41]研究发现双侧低频 rTMS 减轻广泛性焦虑症可能与脑内 BDNF 水平升高和 5-羟色胺(5-hydroxytryptamine, 5-HT)释放有关,分析显示血清 5-HT 水平的升高与血清 BDNF 水平的升高呈正相关,焦虑评分的变化与血清 BDNF、5-HT 水平的变化呈负相关。与此同时,Jiang 等[24]进行了一项荟萃分析,推测 BDNF 介导rTMS 的治疗效果,但与以往的结果是矛盾的。rTMS 治疗效应或许存在,但并不能提高血清 BDNF 水平。

上述研究提示 rTMS 干预抑郁,可能是与调控 GABA 水平、逆转海马神经元的凋亡、恢复 HPA 轴在治疗抑郁症中的平衡有关,但是与脑卒中的代谢组学机制不一样的是,与 BDNF 的相关性尚不明确。

3 rTMS 对帕金森病及其生物标志物的影响

帕金森病是一种神经退行性疾病,其病理生理基础是纹状体 DA 的严重缺乏。

Dong 等[42]探讨低频 rTMS 对帕金森病模型小鼠

的神经保护作用，结果显示低频rTMS 能显著改善黑质 DA 能神经元的变性和酪氨酸羟化酶的表达；低频 rTMS 还可促进 BDNF 和胶质细胞源性神经营养因子的表达。纹状体 DA 水平的波动和酪氨酸磷酸化的上调与左旋多巴诱导的帕金森病运动障碍有关。Ba 等[43]制备左旋多巴诱发异动症大鼠模型，评估 rTMS 对异常非自愿运动的影响，结果表明 rTMS 能减少黑质 DA 能神经元的丢失和纹状体 DA 水平的波动，同时，rTMS 可显著增加胶质细胞源性神经营养因子的表达，从而恢复 DA 能神经元的损伤。此外，rTMS 还降低了左旋多巴诱发异动症大鼠模型纹状体损伤后酪氨酸磷酸化水平及其与酪氨酸激酶的相互作用。而在延迟折扣中，内侧前额叶皮质和纹状体 DA 神经传递均起重要作用。Cho 等[44]用 rTMS 短暂激活前额叶皮质，测量其对纹状体 DA 的影响，发现前额叶皮质兴奋性的调节干扰纹状体的突触 DA 水平。

泛素-蛋白酶体系统功能异常是帕金森病的又一重要发病机制。Ba 等[45]探讨 rTMS 对泛素-蛋白酶体系统损伤所致帕金森病大鼠模型是否具有神经保护作用，采用蛋白酶体抑制剂、乳酸菌素诱发帕金森病大鼠模型，结果显示 rTMS 能明显减轻乳酸菌素损伤的黑质酪氨酸羟化酶阳性 DA 能神经元的丢失，防止纹状体 DA 水平的丢失。此外，rTMS 还降低了受损黑质中凋亡蛋白 Caspase-3、炎症因子环氧化酶-2(cyclooxygenase-2, COX-2)和肿瘤坏死因子 α 的水平，提示 rTMS 可保护黑质 DA 能神经元免受泛素-蛋白酶体系统损伤所致的凋亡和抗炎分子机制的影响。

rTMS 治疗可以对神经元基质产生长期的影响。Etiévant 等[46]发现应用于觉醒小鼠额叶皮层的 rTMS 诱导了 DA 受体依赖的周期素依赖性蛋白激酶 5 和突触后致密蛋白 95 蛋白水平的持续变化，特别是在受刺激的脑区。重要的是，这些修饰与这些基因启动子组蛋白乙酰化的变化相关，并且通过给药组蛋白去乙酰化酶抑制剂来预防。rTMS 还显示出调节局部脑活动的潜力。Pettorruso 等[47]在左 DLPFC 区rTMS 治疗两周后，发现纹状体区域的 DA 转运体有效性降低。Malik 等[48]用 1 Hz rTMS 以岛叶皮层为靶点，可显著降低黑质、感觉运动纹状体和联合纹状体中的 DA 水平。还有研究者对帕金森病治疗的氨基酸代谢途径做了相关研究。Flamez 等[12]研究 1 Hz rTMS 对晚期帕金森病患者脑代谢产物的影响，磁共振波谱检测体内代谢物，发现晚期帕金森病患者在 SMA 前右室低强度 rTMS 不改变 NAA/Cr，但影响 tCho/tCr 比值，尤其是病程较短的患者。而多种炎症因子对 rTMS 有调节作用，Aftanas 等[15]探讨了 rTMS 对帕金森病患者神经炎症相关细胞因子水平的可能作用机制，平行安慰剂对照研究观察了运动皮层(双侧)和左 DLPFC 的双靶点 rTMS 对血细胞自发合成促抗炎细胞因子和促有丝分裂原的治疗作用，结果显示 rTMS 组促炎细胞因子干扰素-γ 和白介素-17(Interleukin-17, IL-17)的自发产生显著下降，rTMS 对血清 BDNF 无显著影响。

综上，rTMS 治疗帕金森病，机制可能与纠正纹状体 DA 的严重缺乏、调节泛素-蛋白酶体系统功能异常有关，rTMS 治疗还可以对神经元基质产生长期的影响。

4 中医对中枢神经系统疾病及相关生物标志物的影响

中医治疗中枢神经系统疾病已有诸多报道。近年来，受到各学科交叉渗透趋势的影响，越来越多的学者将中医学研究与生物标记物的研究相结合。

Luo 等[49]探讨针刺对慢性不可预测轻度应激大鼠抑郁行为的影响，发现增强海马和前额叶皮层中的胶质谷氨酸转运体是针刺抗抑郁作用的机制之一。Kim 等[50]观察针刺对慢性束缚应激(chronic restraint stress, CIS)所致抑郁小鼠的抗抑郁作用，结果显示针刺可增加海马和杏仁核 BDNF 的表达，并改善小鼠的抑郁行为。Han 等[51]发现电针可通过恢复海马 CA1 突触可塑性改善抑郁样行为，其机制主要是通过下调 5-HT 受体水平来实现的。Li 等[52]用艾灸治疗脂多糖诱导的抑郁样行为大鼠，发现艾灸对色氨酸(tryptophan, Trp)转运和 5-HT 生成有明显的促进作用，长期治疗可促进脑内 Trp 的摄取，使 Trp 代谢向 5-HT 转化，从而有利于抗抑郁作用的发挥。傅锦华等[53]研究发现舒肝解郁胶囊能增强抑郁模型大鼠中枢 5-HT 和 DA 系统的功能，改善抑郁症状。

He 等[54]用电针治疗缺血再灌注大鼠海马和前额叶皮层，发现可能通过提高 NAA 和 cho 的含量而改善学习记忆能力。Huang 等[55]电针治疗脑缺血再灌注损伤小鼠后，星形胶质细胞和小胶质细胞/巨噬细胞 P2 嘌呤受体介导的梗死周围海马 CA1 区和感觉运动皮层神经炎症和增生减弱，运动和记忆行为改善。Jittiwat[56]发现激光针刺治疗能显著提高海马

CA1 和 CA3 的记忆和神经元密度，结果显示海马神经功能评分改善，GSH-Px、SOD 活性提高，IL-6 与肌动蛋白密度比值降低，提示激光针刺通过抗氧化和抗炎作用减轻局灶性脑缺血大鼠的认知功能障碍和运动功能障碍。Zhang 等[57]发现电针对脑缺血再灌注后大鼠的认知修复有一定的作用，其作用机制可能是通过抑制 Glu 神经毒性和下调 Glu 受体的蛋白表达而减少 Ca^{2+}内流。Liu 等[58]针刺大脑中动脉闭塞大鼠，发现针刺可有效降低缺血所致 Glu 的过度释放，维持 GABA 的内源性抑制活性。这种现象在针灸治疗的整个过程中都会出现，在针灸治疗结束后还会持续一段时间。

上述研究结果表明，中医学方法治疗抑郁症主要通过调节 5-HT 水平来实现，而治疗脑卒中的机制则与氨基酸类和单胺类神经递质有关。而且针刺同样具有与 rTMS 相似的长期作用。

5 小结

迄今为止，已经有众多研究者试探性地提出了一些 rTMS 治疗疾病的生物机制，尽管尚未很好地描述详细的机制，但是已经提出了几种可能。rTMS 治疗脑卒中、抑郁症、帕金森等与神经递质、炎症因子、神经发生、细胞凋亡等改变呈相关性[4-6,59-63]。啮齿动物的实验证据表明，rTMS 产生复杂的神经生化作用。这些分子作用可能会改变神经元的电生理特性，并重新编程神经递质及其同源受体的表达，从而导致与突触可塑性相关的持久变化，例如长期增强和抑制[5]。临床上与病人相关的实验数据则更多侧重于代谢标志物的发现[38]，人们更倾向于找到一种标志物来指导临床治疗。同时也有代谢途径的探究，例如 GABA 能系统、Glu 能系统[34]、BDNF/CREB 通路[25]等。而在未来的研究中，生物标志物将不仅限于血液、尿液、脑脊液，脑-肠轴[64-66]及肠道微生物组学的发展，将与 rTMS 治疗神经精神系统疾病的发展密切关联。

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