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5-HT受体乙酰化修饰在阿尔茨海默病患者精神行为症状发生发展中的作用研究

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摘　要：痴呆合并精神行为症状 (behavioral and psychological symptoms of dementia, BPSD) 包括精神运动性兴奋、心境障碍 (焦虑、抑郁和淡漠) 和精神症状 (妄想和幻觉) 等，是阿尔茨海默病 (Alzheimer's disease, AD) 患者的主要并发症，伴随着 90% 的 AD 患者。随着病程进展和认知功能下降，BPSD 症状的严重程度加深，成为 AD 患者住院的首位原因。然而，AD 患者并发 BPSD 的机制还不清楚，也缺乏有效的治疗。最近的研究推测，5- 羟色胺 (5-hydroxytryptamine, 5-HT) 系统可能参与 BPSD 的发生和发展。现对 5-HT 系统在 BPSD 发病和症状恶化过程中的作用进行综述，重点探讨了 5-HT 受体乙酰化修饰在其中的可能作用以及去乙酰化酶抑制剂的治疗潜力，以期深入理解 AD 患者并发 BPSD 的机制。

关键词：5-HT 受体；组蛋白乙酰化；阿尔茨海默病；精神行为症状；去乙酰化酶抑制剂
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Research progress in roles of 5-hydroxytryptamine receptor histone acetylation in regulation of behavioral and psychological symptoms of Alzheimer's disease

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Abstract: Behavioral and psychological symptoms of dementia (BPSD), including psychomotor excitement, mood disturbances (e.g. anxiety, depression, and the loss of motivation), and psychosis (e.g. delusion and hallucination) are common complications that occur in more than 90% of Alzheimer's disease (AD) patients. Increased severity of BPSD is significantly accelerated with disease progression and remains the main reason for hospitalization, significantly affecting the quality life of both patients and caregivers. However, the mechanisms underlying BPSD are not known, and there is no targeted or widely effective treatment strategy available. Recent studies suggest that the 5-hydroxytryptamine (5-HT) may be involved in the initiation and progression of BPSD. In order to further understand the mechanism of AD in patients with BPSD, this article reviews the role of 5-HT in the pathogenesis of BPSD and the deterioration of symptoms. A particular focus is placed on the implication of 5-HT receptors histone modifications in BPSD pathogenesis and antipsychotic efficacy.

Key words: 5-HT receptor; histone acetylation; AD; BPSD; deacetylase inhibitor

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阿尔茨海默病 (Alzheimer's disease, AD) 是最常见的神经退行性疾病，影响约 11% 的 65 岁以上老人和将近 50% 的 85 岁以上老人 [1]。而超过 90% 的 AD 患者合并不同程度的精神行为症状 (behavioral and psychological symptoms of dementia, BPSD)[2]，其临床表现包括精神运动性兴奋、心境障碍 (如焦虑、抑郁和淡漠) 和精神症状 (如妄想和幻觉) 等 [2]。一个持续 5 年的流行病学研究表明，AD 患者最频繁出现的 BPSD 症状是淡漠、抑郁和妄想，持续最久的症状是进攻性 [3-5]。AD 患者合并 BPSD (AD+BPSD) 会加快其疾病进程，快速降低其认知功能 [6-7]，恶化其全面健康状况 [6]，增加死亡率，给照护者带来较大的精神压力和身体疲劳 [6]，是 AD 患者住院的首位原因 [6-7]。另外，研究发现 BPSD 症状在轻度认知功能障碍 (mild cognitive impairment, MCI) 患者的发生率也高达 35%~85%，某些 BPSD 症状的发生可能早于 MCI 诊断之前 [7]；但是，与单纯 AD 的发病机制和治疗研究开展得如火如荼相比，无论是临床研究，还是基础研究都较少涉及 AD 患者的 BPSD 症状 [8]。尽管确有几项研究调查了 AD+BPSD 的易感基因变异情况 [9-11]，国际 AD 研究者学会 (The Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment, ISTAART) 也成立了专业兴趣小组，但在 BPSD 发生机制方面的研究仍是相当缺乏。2001 年以来，在体和离体证据均表明，5- 羟色胺 (5-hydroxytry-ptamine, 5-HT) 神经递质系统紊乱与部分 BPSD 症状的发生和发展有关 [12-15]。本文综述了 5-HT 系统在 AD 患者精神行为症状发生发展中过程中的作用，重点分析了 5-HT 受体乙酰化修饰在其中的可能作用。

1 五羟色胺受体亚型功能异常可能参与AD+BPSD的发生发展

五羟色胺 (5-HT) 广泛存在于大脑皮层，参与调节情绪、精力、睡眠和心理应激的反应水平，也调节自我控制和认知功能 [16]。病理学研究揭示 5-HT 系统异常 (包括递质异常、受体异常、5-HT 能神经元和突触退化) 与 AD 病理改变联系紧密 [13,17-18]。影像学研究表明，AD 患者脑内早期即有 5-HT 显著减少 [13]，也有代谢产物 5- 羟吲哚乙酸 (5-hydroxyindoleacetic acid, 5-HIAA) 和 5-HT 受体 (5-HTRs) 减少 [13-14]，可能与 AD 患者的病情进展有关 [2,13,16]。行为学研究表明，5-HTRs 水平降低增加 AD 患者抑郁和精神症状 [19-20]，增强动物攻击性和焦虑 [21-22]。在临床研究中，靶向多型单胺类受体的抗精神病药是目前治疗 BPSD 的常用处方药 [2,15]，如非典型抗精神病药利培酮 (Risperidone) 常被用来改善 AD+BPSD 患者的情感症状，如焦虑和抑郁，它既能高亲和力结合 5-HT2AR 和多巴胺 D2 受体 (D2R)，也能作用于去甲肾上腺素受体 (α1-AR)[23]，在老年患者清除速度较慢，常见不良反应为与剂量相关的锥体外系症状。综上所述，病理学、影像学、行为学和临床多方面研究结果都表明，5-HTRs 异常很有可能与 BPSD 的发生发展有关。

然而，5-HTRs 包括 7 个家族 (5-HT1~7)，每个家族又有多个亚型，目前已经鉴别出来的 5-HTRs 亚型达 20 余种 [2]。大量研究也探讨了这些受体亚型与 BPSD 的相关性，但结果相互冲突 [24-25]。总结起来，5-HT1AR、5-HT2AR、5-HT2CR、5-HT6R 和 5-HT7R 可能与各种 BPSD 样症状和感知功能的发生发展有关 (表 1)，比较一致的是认为 5-HT1A 受体在 AD+BPSD 患者多个脑区减少 [26-27]，并且，5-HT2A 受体和 5-HT2C 受体的减少可能与 AD 患者的 BPSD 症状的发生有关 [28]。另外，5-HTRs 亚型也是某些抗精神疾病药物 (antipsychotic drugs, APDs) 在体内的主要作用靶点，但是目前临床上使用的一些 5-HTRs 激动剂或拮抗剂对某类或某种亚型的针对性不强 [2,29]，治疗精神疾病时导致严重的副作用 [2]。因此，弄清 5-HTRs 不同亚型与 AD+BPSD 发生发展之间的对应关系在开发安全有效的药物方面就特别重要。

2 5-HTRs亚型基因启动子组蛋白乙酰化水平降低可能与AD+BPSD发生发展有关

组蛋白乙酰化修饰是基因调控的重要方式。组蛋白乙酰化修饰广泛参与衰老过程 [30-33]。与年龄依赖的认知功能下降和 AD 患者记忆加速恶化明显相关。董红心实验室在 AD+BPSD 患者尸检脑组织中发现，相比于单纯 AD 患者，AD+BPSD 患者脑中 *5-Ht2a* 基因启动子乙酰化水平显著降低，与 5-HT2AR 表达减少有关 [34]。他们评估了 *5-Ht2a* 基因启动子中组蛋白修饰的水平，检测了 H3 Lysine9 (H3K9ac)、H3 Lysine27 (H3K27ac) 和 H4 Lysine12 (H4K12ac) 残基，发现老年小鼠纹状体中 *Htr2a* 基因启动子中 H3K27ac、H4K12ac 和 H3K9ac 残基乙酰化水平降低。同时，他们在老年小鼠中进一步研究发现，*5-Ht2a* 基因启动子的组蛋白乙酰化水平减弱与抗精神病药副作用的产生和程度加重有关，而

表1 5-HT受体亚型功能

受体亚型	K1 (nmol/L)	受体功能
5-HT1A	3.17	
5-HT1B	4.32	记忆力(激动剂↓)、学习(激动剂↓)、焦虑(激动剂↓)、抑郁(激动剂↓)、精神分裂症的阳性阴性以及中性症状表现(不完全激动剂↓)、痛觉缺失(激动剂↑)、攻击性(激动剂↓)、大脑皮层前叶多巴胺分泌(激动剂↑)、5-羟色胺释放以及合成(激动剂↓)
5-HT1D	5.03	血管收缩(激动剂↑)、攻击性(激动剂↓)、骨密度(↓)、5-羟色胺自受体
5-HT1E	7.53	
5-HT1F	10.00	
5-HT2A	11.55	迷幻剂(激动剂↑，拮抗剂↑)、抑郁(激动剂↑，拮抗剂↓)；焦虑(拮抗剂↓)、精神分裂症的阳性阴性以及中性症状表现(拮抗剂↓)、蓝斑核释放去甲肾上腺素(拮抗剂↑)、谷氨酸钠在大脑皮层前叶分泌
5-HT2B	8.71	心血管功能(激动剂增加肺动脉高血压症的风险)、精神共鸣(通过梭形神经细胞或冯埃科诺莫神经细胞)
5-HT2C	5.02	多巴胺分泌到中脑边缘通路多巴胺系统(激动剂↓)、大脑皮层前叶乙酰胆碱分泌(激动剂↑)、食欲(激动剂↓)、安定药药效(激动剂↑)、抗抑郁药物药效(激动剂&拮抗剂↑)
5-HT3		呕吐(激动剂↑)、抗焦虑(拮抗剂↓)
5-HT4	125.89	食物通过G1通道移动(激动剂↑)、记忆力&学习(激动剂↑)、抗抑郁药物药效(激动剂↑)、通过Gas激活腺苷酸环化酶发送信号
5-HT5A	251.2	记忆抑制巩固、信号通过Gi/o腺苷酸环化酶
5-HT6	98.41	认知(激动剂↑)、抗抑郁药物药效(激动剂&拮抗剂↑)、Gs通过活化的腺苷酸环化酶发送信号
5-HT7	8.11	认知(激动剂↑)、抗抑郁药物药效(拮抗剂↑)、因Gs通过活化的腺苷酸环化酶发送信号起作用

注：(1) 5-HT1受体家族通过$G_{i/o}$发出信号减弱腺苷酸环化酶功能；(2) 5-HT2受体家族通过Gq发出信号增强磷脂酶C功能。

去乙酰化酶抑制剂 (HDACis) 能够逆转这一副作用[35]。这些研究结果进一步表明，老年小鼠5-HT2AR功能障碍与 *5-Ht2a* 基因启动子的某些位点组蛋白乙酰化水平降低有关。根据这些前期工作，他们推测组蛋白去乙酰化程度影响5-HTRs亚型基因表达和功能，5-HTRs亚型的表达和功能异常直接与AD+BPSD相应症状的发生和发展直接相关。

3　去乙酰化酶抑制剂(HDACi)可能具有治疗AD+BPSD潜力

目前还没有被正式批准的用来治疗AD+BPSD的药物[2]。临床上用来治疗AD的胆碱酯酶抑制剂和NMDA受体阻断剂只能非常有限地稳定或者改善患者认知功能，极少数情况下改善患者的BPSD样行为表现[36]。当面临AD患者BPSD样症状加重时，临床上往往选用几种APDs来对症治疗，这不符合药品使用说明书上指定的用药范围[2]，副作用大，治疗效果在不同的患者间差别很大，而且有增加患者死亡率的危险[37-42]。APDs往往作用于体内多类受体靶点，患者服用APDs后，引发多种类型的副作用[39-41,43-44]，除了认知功能下降更加明显以外[13-14]，还并发锥体外系症状[43-44]、代谢综合征[14]以及突发心血管意外[40-41]。从前面的分析发现，5-HTRs亚型基因启动子的组蛋白乙酰化水平降低在BPSD发生发展具有重要的地位，那么，是否可以直接用HDACis来防治BPSD呢？

临床上已经用HDACis治疗心境障碍，如广谱抑制剂丙戊酸钠 (VPA) 被用来治疗双向情感障碍[45-46]。一些基础研究表明，I型和II型HDACi伏立诺他 (vorinostat) 和I型HDACi恩替诺特 (entinostat, MS-275) 具有神经保护作用[47-48]和抗抑郁功效[49-50]，VPA也有治疗神经退行性疾病的潜能[51]。VPA和MS-275是HDACi中的两个能够透过血脑屏障的化合物[52-53]，VPA作用弱，且选择性不强；而MS-275选择性地抑制HDAC1。董红心实验室研究表明，VPA和MS-275均在老龄小鼠伏隔核和前额叶皮质调控c-fos启动子的组蛋白乙酰化[35]，减轻APDs氟哌啶醇 (haloperidol, HAL) 引起的锥体外系运动障碍的严重程度，增强HAL在老年小鼠的治疗效能。2017年，他们研究表明，VPA和MS-275的改善作用与它能逆转衰老相关组蛋白多巴胺受体基因 (Drd2) 启动子组蛋白低乙酰化有关，并且VPA和MS-275还能改善一种非典型APD利培酮所引起的生物学和行为方面的副作用[54]。这些研究结果表明，HDACis可能通过调控由衰老或AD引起的组蛋白乙酰化修饰，改善精神行为症状，减轻APDs治疗相关的副作用，是一个有前景的治疗AD+BPSD选择，研究其治疗潜能具有较大的科学和应用意义。

4 结语和未来研究重点

根据前期从患者和动物模型得到的初步研究结果，本文归纳总结如下 (图 1) ：(1) AD+BPSD 症状产生与其大脑皮层5-HTRs亚型异常相关；(2) 5-HTRs亚型异常变化又与其基因启动子的组蛋白乙酰化修饰失调有关；(3) HDACis 可以纠正组蛋白乙酰化修饰异常，矫正 5-HTRs 亚型的基因转录，影响某些 AD+BPSD 症状，减少 APDs 治疗的副作用。未来研究将重点厘清：(1) 年龄依赖的 5-HT 系统的改变，以及这种改变与 AD 患者和动物模型精神行为症状严重程度之间的相关性；(2) 明确 5-HT 受体基因启动子的乙酰化修饰对 AD 患者和动物模型 BPSD 症状严重程度的影响；(3) 评估 HDAC 抑制剂对 AD 动物模型 BPSD 样行为的治疗潜力。

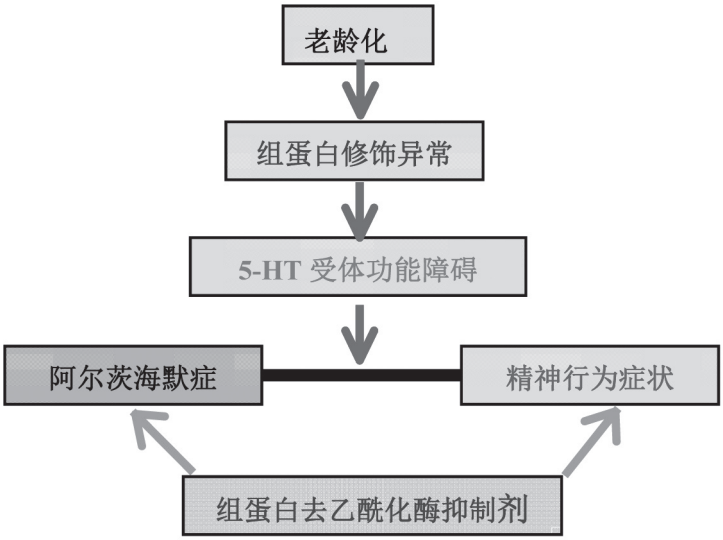

图1 5-HT受体乙酰化调节在阿尔茨海默病患者精神行为症状发生发展中的可能作用以及矫正手段

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