

doi: 10.13241/j.cnki.pmb.2015.06.050

S-腺苷蛋氨酸在肝病患者中抗抑郁作用的研究进展*

张巍巍¹ 刘云顺² 王颖¹ 王青^{1△}

(1 青岛市市立医院东院消化内科 山东 青岛 266071; 2 青岛市市立医院东院干保科 山东 青岛 266071)

摘要: S-腺苷蛋氨酸(S-adenosyl-L-methionine, SAMe)是一种天然分子存在于人体所有细胞中,在肝脏、肾上腺以及松果体中具有较高浓度,在大脑中亦均匀分布。S-腺苷蛋氨酸通过抗氧化自由基及促进肝细胞再生等机制对肝细胞具有多重保护作用长久以来被广泛应用于肝病所致的肝内胆汁淤积、抗肝纤维化等治疗。近年来,研究亦发现 S-腺苷蛋氨酸可增加患者脑中神经元膜的流动性及促进兴奋性神经递质的产生等对改善肝病患者情绪、治疗肝病患者抑郁症等方面具有重要的双重作用。通过静脉或口服用药,均可提高患者脑脊液中 SAMe 浓度,对于轻、中度抑郁患者的辅助治疗,更具安全性、有效性,这为人类的"生理-心理"疾病的治疗带来更广阔的应用前景。现将其对肝病患者抗抑郁的作用机制及临床应用综述如下。

关键词: 胆汁淤积;焦虑;抑郁;S-腺苷蛋氨酸

中图分类号: R575; R74 **文献标识码:** A **文章编号:** 1673-6273(2015)06-1196-02

Research on Antidepressant Effects of S-adenosylmethionine in Patients with Liver Diseases *

ZHANG Wei-wei¹, LIU Yun-shun², WANG Ying¹, WANG Qing^{1△}

(1 Department of Gastroenterology, Qingdao Municipal Hospital, Qingdao, Shandong, 266071, China;

2 Department of cadre health care, Qingdao Municipal Hospital, Qingdao, Shandong, 266071, China)

ABSTRACT: S-adenosylmethionine (S-adenosyl-L-methionine, SAMe) is a natural molecule existing in all human cells, expressing a higher concentration in the liver, adrenal gland as well as in the pineal gland, and also uniformly distributed in the brain. S-adenosylmethionine has long been widely used in most of intrahepatic cholestasis and liver fibrosis diseases because of its multiple protection mechanisms of liver cells by anti-oxidant free radicals and promoting the regeneration of liver cells. Moreover, in recent years, literature illustrates that it has a vital dual role in improving the mood and treating depression of patients with liver diseases by increasing the neurons membrane fluidity in patients' brains and promoting the generation of excitatory neurotransmitter. The cerebrospinal concentration of SAMe can be improved by either intravenous or oral intake. SAMe safely and efficiently serves as an adjuvant medication for patients with mild to moderate depression, which will bring broad application prospects for the treatment of human physiological - psychological diseases. Therefore, its antidepressant mechanisms and clinical applications in patients with liver diseases are summarized below.

Key words: Cholestasis; Anxiety; Depression; S-adenosylmethionine

Chinese Library Classification(CLC): R575; R74 **Doctmlent code:** A

Article ID: 1673-6273(2015)06-1196-02

S-腺苷蛋氨酸(S-adenosyl-L-methionine, SAMe)因其对肝细胞具有多重保护机制长久以来被广泛应用于肝病所致的肝内胆汁淤积、抗肝纤维化等治疗。近年来,研究发现其对改善肝病患者情绪、治疗肝病患者抑郁症等方面^[1,2]具有重要的作用并逐渐引起人们的重视^[3-5],现对 S-腺苷蛋氨酸抗抑郁作用机制及临床研究综述如下。

1 S-腺苷蛋氨酸的抗抑郁的作用机制

SAMe 是一种天然分子存在于人体所有细胞中,在肝脏、肾上腺以及松果体中具有较高浓度,在大脑中亦均匀分布。

SAMe、叶酸、维生素 B12、同型半胱氨酸共同参与"一碳循环",即叶酸在亚甲基四氢叶酸还原酶(MTHFR)作用下生成 5-亚甲基四氢叶酸(5-MTHF),5-MTHF 与同型半胱氨酸在蛋氨酸酶作用下形成蛋氨酸,后者在蛋氨酸腺苷酶作用下与维生素 B12 形成 SAMe。SAMe 抗抑郁作用机制尚未完全明确^[6,7]。但目前研究多认为 SAMe 作为膜磷脂,髓磷脂,胆碱,儿茶酚胺和其他分子的甲基供体对脑功能具有重要作用,影响受体的功能、膜的流动性及神经递质的产生^[8],具有抗抑郁作用。内源性的 SAMe 可促进神经元膜流动性,脑脊液中低叶酸、低 SAMe 水平均可致神经元膜的流动性的降低^[9],导致在膜结合的底物受

* 基金项目:青岛市科技发展计划项目(11-2-3-2-c81-nsh)

作者简介:张巍巍(1979-),女,博士,主治医师,研究方向:胰腺癌转移机制及肿瘤微环境,

电话:15092100035, E-mail: Apfelzhangweiwei@hotmail.com

△通讯作者:王青, E-mail: apple19790117@yahoo.cn

(收稿日期:2013-08-21 接受日期:2013-09-19)

体亲合性和转运的中断,从而引发神经系统疾患,尤其是抑郁症状。S-腺苷蛋氨酸(SAMe)可以加强大脑多巴胺和5-羟色胺神经递质代谢和信息传递功能,在精神分裂症和情感障碍患者中发现SAMe的代谢异常,无法合成人正常所需的SAMe量,因此必须从外源补充^[10]。Pan等^[11]对台湾地区1371名中老年人营养状况调查表明老年人存在S-腺苷甲硫氨酸和血红蛋白生成不足的隐患,更容易体验到的抑郁情绪。Bjelland等^[12]对生活在挪威的6000名中老年人研究发现,MTHFR酶活性异常、基因突变以及基因多态性与抑郁症状密切相关。

2 S-腺苷蛋氨酸的抗抑郁的作用的临床应用

国外研究表明,SAMe具有明确的抗抑郁作用。腺苷蛋氨酸制剂是一种兼顾护肝及抗抑郁并且安全的用药选择,它在合成神经介质、褪黑激素以及在表观遗传调控机制中起着重要的作用,于20世纪70年代末应用于抑郁症的治疗,在欧洲是一种重要的治疗抑郁症的处方药,在俄罗斯广泛用于有抑郁症状的肝病患者,在美国用于抑郁症的营养补充剂^[13]。SAMe可治疗多种中枢神经系统疾病,如抑郁症、老年痴呆症、精神分裂症等,其可改善抑郁状态或抑郁症状、减少患者的侵略性,用于轻度认知功能障碍和轻度痴呆症的治疗和预防^[14]。临床上应用SAM治疗抑郁症,无依赖性,毒副作用轻微^[15],尤其适合于伴有慢性肝脏疾病或身体状况不佳的患者及老年人,对产后抑郁症的患者疗效更好^[5]。Y. Levkovitz等^[16]研究表明,将46名对SRI无应答的重度抑郁症患者进行6周随机、对照、双盲试验,通过口服SAMe治疗,患者记忆相关的认知症状得到明显改善。抑郁症患者血清和脑脊髓液中有低水平的SAMe,因此补充SAMe、多巴胺以及其他神经递质具有很好的抗抑郁作用^[17]。SAMe静脉用药和肌肉注射可有效改善患者的抑郁症状,口服用药也可提高患者脑脊液中SAMe浓度,表明其可通过血脑屏障而发挥作用。Caruso及Delle R等^[18,19]研究发现在抑郁症患者中静脉注射SAMe(200 mg/天)较安慰剂组具有显著疗效,肌肉注射SAMe(400 mg/天)4周与口服丙咪嗪(150 mg/天)6周抗抑郁作用相当,口服SAMe(1600 mg/天)与服用三环类抗抑郁药疗效相当。三环类抗抑郁药治疗重度抑郁症有多种副作用,对于此类患者给予静脉或口服SAMe作为药物的辅助治疗,更具有安全性、有效性,SAMe对于轻、中度抑郁症状短期的治疗有效,但并不能取代中、重度抑郁症患者传统的抗抑郁药物^[8],表明SAMe可作为抗抑郁治疗的一种辅助治疗^[20]。近来亦有个例报道^[21]SAMe增加了抑郁患者自杀的高风险,提示我们需要对其用量、疗程的安全性予进一步研究。

在我国,最早将SAMe应用于抑郁症的治疗开始于20世纪90年代。研究发现SAMe是一种安全有效的天然抗抑郁药物^[22],并认为其疗效肯定,不良反应轻,耐受性良好,可用于治疗对其它抗抑郁药物耐受性差的患者、老年患者、患有严重肝脏疾病者以及存在酒精中毒性肝脏损害的抑郁患者等。张海燕等^[1]将SAMe组与苦黄注射液组的肝内胆汁淤积患者的情志改变和临床疗效作对比,结果显示两组在改善肝功能、退黄疸方面均有效,但通过SAS和SDS量表对上述患者情志进行分析,SAMe组具有明显的抗抑郁、焦虑作用,两组间差异有显著性意义($P < 0.05$)。

3 展望

肝病合并抑郁症的原因很多,如长期疾病的痛苦、社会经济的压力、药物治疗引起的抑郁等,基于上述SAMe的研究,我们期待:通过抗氧化自由基及促进肝细胞再生等途径治疗肝内胆汁淤积的同时改善患者脑中神经元的流动性及促进兴奋性神经递质的产生,发挥SAMe护肝及抗抑郁的双重作用,将为人类的"生理-心理"疾病的治疗带来更广阔的应用前景。

参考文献(References)

- [1] 张海燕,王俐琼,邢练军,等. 思美泰对肝内胆汁淤积症患者情志的影响[J]. 中西医结合肝病杂志, 2010, 20(4): 218-220
Zhang Hai-yan, Wang Li-qiong, Xing Lian-jun, et al. Effects of transmetil on emotions in patients with intrahepatic cholestasis [J]. Chinese Journal of Integrated Traditonal and Western Medicine on Liver Diseases, 2010, 20(4): 218-220
- [2] Hardy ML, Coulter I, Morton SC, et al. S-adenosyl-L-methionine for treatment of depression, osteoarthritis, and liver disease [J]. Evid Rep Technol Assess (Summ), 2003, (64): 1-3
- [3] Sarris J. Clinical depression: an evidence-based integrative complementary medicine treatment model[J]. Altern Ther Health Med, 2011, 17(4): 26-37
- [4] Nahas R, Sheikh O. Complementary and alternative medicine for the treatment of major depressive disorder [J]. Can Fam Physician, 2011, 57(6): 659-663
- [5] Mischoulon D. Update and critique of natural remedies as antidepressant treatments [J]. Obstet Gynecol Clin North Am, 2009, 36(4): 789-807
- [6] Papakostas GI. Evidence for S-adenosyl-L-methionine (SAM-e) for the treatment of major depressive disorder[J]. J Clin Psychiatry, 2009, 70 (Suppl 5): 18-22
- [7] Bottiglieri T. Folate, vitamin B12, and s-adenosylmethionine [J]. Psychiatr Clin North Am, 2013, 36(1): 1-13
- [8] Carpenter DJ. St. John's wort and S-adenosyl methionine as "natural" alternatives to conventional antidepressants in the era of the suicidality boxed warning: what is the evidence for clinically relevant benefit? [J]. Altern Med Rev, 2011, 16 (1): 17-39
- [9] Papakostas GI, Cassiello CF, Iovieno N. Folate and S-adenosylmethionine for major depressive disorder [J]. Can J Psychiatry, 2012, 57 (7): 406-413
- [10] Salmaggi P, Bressa GM, Nicchia G, et al. Double-blind, placebo-controlled study of S-adenosyl-L-methionine in depressed postmenopausal women[J]. Psychother Psychosom, 1993, 59(1): 34-40
- [11] Pan WH, Chang YP, Yeh WT, et al. Co-occurrence of anemia, marginal vitamin B6, and folate status and depressive symptoms in older adults[J]. J Geriatr Psychiatry Neurol, 2012, 25(3): 170-178
- [12] Bjelland I, Tell GS, Vollset SE, et al. Folate, vitamin B12, homocysteine, and the MTHFR 677C->T polymorphism in anxiety and depression: the Hordaland Homocysteine Study [J]. Arch Gen Psychiatry, 2003, 60 (6): 618-626
- [13] Howland RH. Dietary supplement drug therapies for depression [J]. J Psychosoc Nurs Ment Health Serv, 2012, 50(6): 13-16

- Zheng Yi, Lu hui. Optimization of the Extraction Process of Saponins from *Panax ginseng* [J]. Journal of Jinling Institute of Technology, 2008, 24(2): 89-91
- [7] 胡晓红, 彭惠民, 刘昕, 等. PCR 及 Real-time PCR 评价细菌 DNA 提取方法[J]. 重庆医科大学学报, 2008, 33(2): 155-158
- Hu Xiao-hong, Peng hui-ming, Liu Xin, et al. Methods Of DNA extraction from bacteria for PCR and Real-time PCR [J]. Journal of Chongqing Medical University, 2008, 33(2): 155-158
- [8] Wu XK, Ma CF, Han L, et al. Molecule Characterization of the faecal microbiota in patients with type II diabetes [J]. Curr Microbiol, 2010, 61(1): 69-78
- [9] Muyzer G, Dewaal E C, Uitterlinden A G. Profiling of complex microbial populations by denaturing gradient gel electrophoresis analysis of polymerase chain reaction amplified genes coding for 16S rRNA[J]. Appl Environ Microbiol, 1993, 59(3): 695-700
- [10] Gavin PG, Victoria SL, Graham JR, et al. Statistical Analyses of Complex Denaturing Gradient Gel Electrophoresis Profiles [J]. Journal of Clinical Microbiology, 2005, 43(8): 3971-3978
- [11] Fromin N, Hamelin J, Tarnawski, et al. Statistical analysis of denaturing gel electrophoresis (DGE) fingerprinting patterns [J]. Environ Microbiol, 2002, 4(11): 634-643
- [12] Silva EP, Russo CAM. Techniques and statistical data analysis in molecular population genetics [J]. Hydrobiologia, 2000, 420 (1): 119-135
- [13] 周德庆. 微生物学教程(第三版)[M]. 北京: 高等教育出版社, 2011: 248-249
- Zhou De-qing. Essential Microbiology (Third edition) [M]. Beijing: Higher Education Press, 2011: 248-249
- [14] 张峻, 罗燕, 朱尤庆. 应用 16S rRNA 实验性结肠 PCR 技术评价益生菌 VSL#3 对肠炎大鼠肠道菌群的调节作用 [J]. 武汉大学学报, 2010, 31(6): 754-770
- Zhang Jun, Luo Yan, Zhu You-qing. Application of 16S rRNA-Based Polymerase Chain Reaction in the Evaluation of the Probiotics Treatment (VSL#3) on TNBS-Induced Colitis Through Modulation of Gut Flora in Rats [J]. Medical Journal of Wuhan University, 2010, 31 (6): 754-770
- [15] 李丽艳, 路新国. 人参皂甙的最新研究进展[J]. 四川省卫生管理干部学院学报, 2004, 23(4): 293-295
- Li Li-yan, Lu Xin-guo. Latest research progress of ginseng saponins [J]. Journal of Sichuan Continuing Education College of MS, 2004, 23(4): 293-295
- [16] 雷阳, 曾延松, 汪琳. 荧光假单胞菌的生物防治机理 [J]. 贵州农业科学, 2002, 30(5): 46-47
- Lei Yang, Zeng Yan-song, Wang Lin. Biological Control Mechanism of *Pseudomonas fluorescent* [J]. Guizhou Agricultural Sciences, 2002, 30(5): 46-47
- [17] 唐宝英, 朱晓慧, 刘佳. 酪酸菌对动物肠道致病菌体外拮抗作用的研究[J]. 生物技术, 2005, 15(1): 37-39
- Tang Bao-ying, Zhu Xiao-hui, Liu Jia. Studies on the Antagonism of *Clostridium butyricum* RH2 Strain against Three Animal Enteropathogens in Vitro [J]. Biotechnology, 2005, 15(1): 37-39
- [18] Takahashi M., Taguchi H., Yamaguchi H., et al. The effect of probiotic treatment with *Clostridium butyricum* on enterohemorrhagic *Escherichia coli* O157: H7 infection in mice [J]. FEMS Immunology and Medical Microbiology, 2004, 41 (3): 219-226
- [19] 朱晓慧, 唐宝英, 刘佳. 酪酸菌对肠道有益菌的增殖作用和共生关系研究[J]. 中国微生态杂志, 2004, 16(4): 193-196
- Zhu Xiao-hui, Tang Bao-ying, Liu Jia. Study on proliferation effect of *Clostridium butyrium* on intestinal available bacteria and symbiotic relation between them [J]. Chinese Journal of Microecology, 2004, 16 (4): 193-196

(上接第 1197 页)

- [14] Krzystanek M, Pałasz A, Krzystanek E, et al. S-adenosyl L-methionine in CNS diseases [J]. Psychiatr Pol, 2011, 45(6): 923-931
- [15] Mischoulon D, Alpert JE, Arning E, et al. Bioavailability of S-adenosyl methionine and impact on response in a randomized, double-blind, placebo-controlled trial in major depressive disorder [J]. J Clin Psychiatry, 2012, 73(6): 843-848
- [16] Yechiel Levkovitz, Jonathan E Alpert, Carrie E. Brintz Yechiel Levkovitz, et al. Brintz Effects of S-adenosylmethionine augmentation of serotonin-reuptake inhibitor antidepressants on cognitive symptoms of major depressive disorder [J]. Journal of Affective Disorders, 2012, 136(3): 1174-1178
- [17] Nahas R, Sheikh O. Complementary and alternative medicine for the treatment of major depressive disorder [J]. Can Fam Physician, 2011, 57(6): 659-663
- [18] Caruso I, Pietrogrande V. Italian double-blind multicenter study comparing S-adenosylmethionine, naproxen, and placebo in the treatment of degenerative joint disease [J]. Am J Med, 1987, 83(5A): 66-71
- [19] Delle Chiaie R, Pancheri P, Scapicchio P. Efficacy and tolerability of oral and intramuscular S-adenosyl-L-methionine 1,4-butanedisulfonate (S-AMe) in the treatment of major depression: comparison with imipramine in 2 multicenter studies [J]. Am J Clin Nutr, 2002, 76(5): 1172S-1176S
- [20] Papakostas GI. Evidence for S-adenosyl-L-methionine (SAM-e) for the treatment of major depressive disorder [J]. J Clin Psychiatry, 2009, 70(Suppl 5): 18-22
- [21] Chitiva H, Audivert F, Alvarez C. Suicide attempt by self-burning associated with ingestion of S-adenosylmethionine: a review of the literature and case report [J]. J Nerv Ment Dis, 2012, 200(1): 99-101
- [22] 刘平, 顾牛范, 翁史旻, 等. S-腺苷蛋氨酸治疗抑郁症 [J]. 中国心理卫生杂志, 1998, 12 (2): 94
- Liu Ping, Gu Niu-fan, Weng Shi-yan, et al. Ademetionine in the Treatment of Depressive Disorders [J]. Chinese Mental Health Journal, 1998, 12(2): 94