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S- 腺苷蛋氨酸在肝病患者中抗抑郁作用的研究进展 *

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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

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

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ABSTRACT: S-adenosylmethionine (S-adenosyl-L-methionine, SAMe) is a natural molecule exsisting 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 mutiple 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

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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

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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。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,无法合成人体正常所需的 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 增加了抑郁症患者自杀的高风险,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症患者等。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膜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。

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