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肝性脑病发病机制新进展

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摘要：肝性脑病是急性肝功能衰竭和肝硬化患者常见的并发症，表现为从轻微认知障碍到昏迷等一系列神经症状。根据临床表现可分为轻微肝性脑病、明显肝性脑病和昏迷；依据基础肝病的类型，HE分为A、B、C 3型。10%～50%接受门体静脉分流术的患者1年内可发生明显的B型肝性脑病。肝性脑病是影响预后的不利因素，1年内病死率为54%～85%。肝性脑病的发病机制尚未明确，本文通过对肝性脑病发病机制的阐述，以期对临床诊断及治疗提供帮助。

关键词：肝性脑病；发病机制；高氨血症；氧化应激；脑能量代谢

Recent advances on the pathogenesis of hepatic encephalopathy

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Abstract: Hepatic encephalopathy (HE) is a common complication of acute liver failure and liver cirrhosis. HE presents as a spectrum of neuropsychiatric symptoms ranging from subtle fluctuating cognitive impairment to coma. HE can be divided into minimal HE (MHE), overt HE (OHE) and coma. According to the type of basic liver diseases, HE is divided into A, B and C types. The 1-year incidence of patients with type B OHE who underwent transjugular intrahepatic portosystemic shunt (TIPS) is estimated to be 10%～50%. HE is a very poor prognostic factor with a 1-year mortality of 54%～85%. The pathogenesis of HE is not clear. This review explains the pathogenesis of HE, which is helpful for clinical diagnosis and treatment.

Key words: Hepatic encephalopathy; Pathogenesis; Hyperammonemia; Oxidative stress; Brain energy metabolism

肝性脑病（hepatic encephalopathy，HE）或门体静脉肝性脑病（portosystemic encephalopathy，PSE）是在晚期肝功能衰竭患者中发生的一种可逆转的脑功能受损综合征，表现为可逆的代谢脑病、脑萎缩及脑水肿等[1]。根据临床表现，HE可分为轻微肝性脑病（minimal hepatic encephalopathy，MHE）、明显肝性脑病（overt hepatic encephalopathy，OHE）和昏迷。依据基础肝病的类型，HE分为A、B、C 3型。OHE在慢性肝病中占10%～14%，5年内首次发作的可能性＞25%，近40%慢性肝病患者至少经历1次HE发作，20%～80%肝硬化患者可出现MHE[2-4]。肝功能衰竭导致脑功能障碍的病理生理机制复杂，涉及高氨血症、氧化应激、脑能量代谢、神经递质功能障碍、胆汁酸盐和神经炎性反应等，肝性脑病的发病机制尚未明确，但各种假说并不相互排斥，可能共同作用，最终导致肝性脑病的发生[5]。目前关于肝性脑病发病机制的研究数据多来自实验模型而非体内研究，具有一定的局限性。本文通过对肝性脑病发病机制的新进展进行阐述，以期为临床诊断及治疗提供参考。

1 高氨血症

血氨的积累是导致HE发展的主要因素，肝脏中特异性谷氨酰胺合成酶（氨代谢中的关键酶）的缺失会导致高氨血症、大脑氧化应激和认知变化[6]。出现高氨血症时大脑中星形胶质细胞迅速将血氨转化为谷氨酰胺，谷氨酰胺水平随之升高[7]。发生HE时高氨血症对星形胶质细胞功能的影响仍未明确，传统观点认为大脑内血氨的作用是增加氧化应激、渗透压以及随后的星形胶质细胞肿胀，然而最近研究表明，血氨也对许多信号转导通路、基因表达和转录后蛋白修饰有影响[8-12]，共同导致星形胶质细胞功能受损，表现为异常增殖[13,14]、神经递质释放[11]甚至是细胞凋亡[13]。高氨血症也与星形胶质细胞内钙释放的短暂增加有关，可能的作用机制是激活N-甲基-D-天冬氨酸（N-Methyl-D-aspartic acid，NMDA）受体、瞬时

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受体电位通道1或Cav1.2-L型钙通道，或更有可能是上述因素的结合[8-10]。

血氨影响基因表达的可能机制之一是改变微小RNA（micro RNA）的表达。micro RNA是小的非编码RNA序列，可在基因转录和翻译水平使基因沉默并通过氧化应激来调节基因的表达。高氨血症时，星形胶质细胞中micro RNA结构发生改变，从而导致靶基因（如血红素氧合酶1）的改变[14]。血氨已被证实可改变参与调控星形胶质细胞摄取和神经递质释放基因（如血小板反应蛋白1）的表达。降低血氨治疗可降低星形胶质细胞中血小板反应蛋白1的表达，从而降低神经元中突触蛋白的表达[15]。发生HE时血氨也可能导致细胞间串扰，但对细胞间的相互作用、相互影响以及氨在肝性脑病中作用的研究仍十分有限，特别是在星形胶质细胞中阻断细胞间相互作用可显著减弱血氨诱导的神经毒性，包括膜完整性、氧化应激和促炎性细胞因子释放[16]方面，仍需进一步研究。

2 氧化应激

在大脑中，氧化应激、活性氧的生成和氮的种类均与HE有关。线粒体功能受损和关键抗氧化酶的表达下调均会增加细胞膜脂质、蛋白质和DNA的氧化损伤[17]。最近的研究强调了氧化损伤在肝性脑病发病机制中的重要性，各种试验性治疗手段均着重降低活性氧/氮的种类或恢复抗氧化酶（如过氧化氢酶、超氧化物歧化酶、硫氧多辛或谷胱甘肽过氧化物酶等）的活性[18-21]。尤其值得注意的是，Bosoi等对高氨血症啮齿动物模型进行谷胱甘肽抑制剂治疗后发现，氧化应激与高氨血症间的协同作用是导致HE发生脑水肿的必要条件[22]。

3 脑能量代谢

HE发病机制与脑能量代谢障碍（包括葡萄糖的利用、糖酵解和线粒体功能障碍）的改变有关，尤其与HE期间脑内乳酸水平变化有关，在猪和啮齿动物HE模型以及急性高氨血症患者中均已证实血和脑内乳酸水平增加[23-26]。然而，在C型HE模型中，脑内乳酸含量增加并不明显。与年龄和性别匹配的对照组相比，肝硬化患者血浆中乳酸水平升高[27]。然而有研究表明，有明显肝性脑病症状与无明显肝性脑病症状肝硬化患者间血浆乳酸水平无显著差异，但不能排除后者存在MHE的可能性[28]。最近研究表明，C型HE大鼠的脑皮质中，星形胶质细胞内的含乳酸转运蛋白功能受损在一定程度上是由高氨血症引起的[28]。乳酸穿梭机制（the astrocyte-neuron lactate shuttle）假说认为，星形胶质细胞中乳酸的产生能够促进和调节神经元的活动[29]，因此可推测转运乳酸的连接蛋白半通道损伤可能是HE发病原因之一[28]。

4 神经炎症

神经炎症是所有类型HE的共同特征，主要由大脑中类似巨噬细胞的小神经胶质细胞调控[30]。一项基因表达分析谱显示，在肝硬化所致的HE患者中，促炎性M1和抗炎M2小神经胶质细胞表型标志物有所增加[31]。小神经胶质细胞的激活是促炎和抗炎信号间的动态平衡，在生理条件下有利于抑制小神经胶质细胞的激活[32]，这些信号可能来自小神经胶质细胞本身，也可能是神经元或星形胶质细胞间信号转导的结果[32]。在高氨血症大鼠模型中，小神经胶质细胞和星形胶质细胞在促炎性细胞因子白细胞介素-1β（interleukin 1β，IL-1β）和IL-6的表达中被激活，虽无法单独证实神经炎症的调节是高氨血症的结果，但仍提示血氨在HE中可诱发神经炎症[33]。有证据表明，发生HE时，神经炎症与认知和运动功能损伤间存在因果关系，抑制神经炎症信号的疗法也可使认知障碍和运动缺陷得到纠正[34,35]。

5 神经递质功能障碍

HE期间观察到的认知障碍和神经肌肉运动受损，无论其机制如何，最终结果主要是神经转导改变，在慢性肝病期间可观察到谷氨酸神经转导功能障碍[36]。A型和C型HE均与γ-氨基丁酸（gama-amnio-butyric acid，GABA）有关，由多因素所致，如GABA浓度升高、GABA受体表达增加。增加的神经类固醇（如四氢孕酮）为可调节GABA的神经递质[37,38]。神经类固醇是在大脑中产生的类固醇激素，其生成机制和具体功能尚未明确[39]。有研究观察到通过抑制神经类固醇合成或抑制GABA受体的激活，在HE中表现的运动协调、空间记忆和昼夜节律等功能障碍有所减弱[40,41]，该研究还表明另一种神经递质抑制剂——多巴胺，在MHE中处于失调状态，肝硬化患者中有大量多巴胺分泌至血液中。抑制海马体中谷氨酸-一氧化氮-环单磷酸鸟苷通路（glutamate-nitric oxide-cyclic GMP pathway）有助于减少HE导致的脑功能损伤，从而改变患者学习和记忆能力[42-44]。

6 胆汁酸

早在1977年，已有研究发现HE患者脑内胆汁酸水平升高。在啮齿动物模型、A型和C型HE患者脑脊液和脑组织中均发现总胆汁酸水平升高[45-47]。然而，胆汁酸在HE中的确切作用仍存在争议，血清胆汁酸增加与大鼠慢性肝病模型血脑屏障的渗透性有关，导致胆汁酸和其他信号分子作用于大脑[47]。

研究发现，由氮氧化甲烷（azoxymethane，AOM）所致的小鼠急性肝衰竭模型中，小鼠额叶皮层总胆汁酸水平升高，降低循环胆汁酸水平（如胆汁胺喂养或使用胆汁酸合成受损的转基因小鼠）被证实有神经保护作用[46]。胆汁酸可通过不同受体发挥作用。法尼酯X受体（farnesoid X receptor，FXR）是一种核胆汁酸受体，在额叶皮质中抑制FXR的信号转导，对肝性脑病患者的认知功能有保护作用[46]。此外，大脑中异常的胆汁酸信号也会通过1-磷酸鞘氨醇受体2（sphingosine-1-phosphate receptor 2）信号转导机制增加促炎性因子CCL2（C-C motif ligand 2）表达而影响神经炎症，从而导致小胶质细胞激活和促炎性因子表达增加[48]。多种治疗肝性脑病的方法（如乳酸和甲硝唑以消除肠道微生物菌群）目的均为减少氨的生成，同时也影响次级胆汁酸的结合，通过改变胆汁酸信号转导而产生保护作用[46]。

7 血脑屏障通透性

血脑屏障通透性在HE中的作用尚存在争议，目前尚无可靠证据表明HE患者血脑屏障的通透性存在功能障碍，然而，胆汁酸和促炎细胞因子可能会影响血脑屏障的渗透性[47,49-51]。在AOM诱导的A型HE小鼠急性肝衰竭模型中，血脑屏障通透性的显著变化是HE发展至晚期的结果[50,51]。相反，若未同时给予微量脂多糖，另一组AOM诱导的小鼠急性肝衰竭模型的血脑屏障通透性无显著改变。炎症反应与其他HE相关因素对于血脑屏障通透性的变化有协同作用[52]。急性肝功能衰竭模型的转化增长因子-β（transforming growth factor-β）可能导致血脑屏障通透性增加[50]，在胆管结扎的肝性脑病模型中，血脑屏障通透性显著增加，在一定程度上可归因于血清胆汁酸分泌增加[47]，这可能与紧密结蛋白表达减少有关[49]。

8 肠道微环境

HE发病机制中涉及的其他因素包括肠道微生物群失调和小肠细菌过度生长（small intestinal bacterial overgrowth，SIBO）。在肝硬化患者中，SIBO是肠道蠕动减少、胃酸分泌减少及营养不良的结果，SIBO使肠道屏障完整性受损，从而促使细菌易位、释放氨和内毒素进入血液循环[53]。肝硬化患者和非肝硬化患者间肠道微生物群存在显著差异[54,55]。肝硬化患者肠道中占主导地位的为链球菌科、维龙科、阿尔卡根科和斑岩藻科细菌，与氨水平升高和认知功能降低显著相关，其他细菌也与肝性脑病患者炎症反应增多有协同作用[56]。Tsai等[57]研究发现，慢性肝硬化患者应用质子泵抑制剂也易发展为HE，其推测质子泵抑制剂可能使肠道菌群失调而导致HE，质子泵抑制剂的应用与小肠细菌过度生长间存在协同作用。因此，临床上应用微生态制剂不仅对肠道菌群平衡有较好的协调作用，还可有效降低肝病患者的血氨和内毒素水平，对HE有一定疗效[58]。李新立等[59]认为枯草杆菌二联活菌肠溶胶囊联合乳果糖对肝性脑病具有较好的疗效。综上，HE患者存在不同程度的肠道菌群失调，使用调节肠道菌群药物能有效改善HE进一步证实了该观点[60]。

9 骨骼肌减少

肝硬化患者若出现骨骼肌减少（肌肉体积消耗）也易发展成HE[61]。骨骼肌是氨分解代谢的另一场所，氨和谷氨酰胺的分解消耗骨骼肌中的支链氨基酸，从而导致血浆中支链氨基酸减少，易造成高氨血症。Hanai等研究发现，骨骼肌减少的患者和肝硬化HE患者血浆中支链氨基酸减少，而补充支链氨基酸可减少营养不良、促进骨骼肌细胞体积恢复并降低血氨[61,62]。肌肉体积增加可促进肝外氨的解毒，肌生成抑制蛋白（myostatin）可负向调节周围细胞的分化和增殖，为骨骼肌减少的驱动因素。肝硬化患者血浆和肌肉中肌生成抑制蛋白水平均较高，同时氨也可促进肌生成抑制蛋白的表达[63]。

10 其他因素

锰与HE发病也有一定关系，由于肝脏排泄能力下降，血浆锰水平升高，从而在基底神经节沉积，研究表明肝硬化患者磁共振成像中观察到的大脑苍白球区的超强度信号可能与锰沉积有关[64]。HE发病机制中其他与氨有协同作用的因素包括：①低钠血症，可使星形胶质细胞的渗透性发生改变，从而加重HE[65]；②全身炎症反应综合征，使患者易发生HE，患者血脑屏障通透性发生改变，可能增强大脑对炎症细胞因子的敏感度[66]。

肝硬化患者肝功能逐渐恶化是HE发病率增加的主要原因，本文总结了近年来HE研究进展，进一步加深了对HE发病机制、病理生理学和治疗方法的理解。HE最新研究进展主要集中在高氨血症、氧化应激、神经炎症、神经递质功能、胆汁酸和血脑屏障方面，但仍需进一步研究明确其在HE病理生理学中的作用。随着对HE发病机制的深入研究，目前越来越多的研究认识到肝性脑病是多种机制协同作用的结果，对今后早期预防、及时诊断和有效治疗具有重要意义。

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