中国细胞生物学学报 Chinese Journal of Cell Biology 2026, 48(7): 1931–1943
DOI: 10.11844/cjcb.2026.07.0015
CSTR: 32200.14.cjcb.2026.07.0015

胆汁酸及其受体在肠–肝–脑轴调控肝性脑病中的作用

陈军庭　胡雪峰　吕翼*
(福建师范大学生命科学学院/福建省发育与神经生物学重点实验室, 福州 350117)

摘要　肝性脑病(hepatic encephalopathy, HE)是由肝衰竭或门体分流引起的严重神经精神并发症, 其发病机制由肠–肝–脑轴紊乱、炎症反应、氧化应激及血脑屏障损伤等多因素共同介导。目前临床针对HE的基础治疗原则涵盖营养支持、原发病治疗及纠正诱因、药物治疗(包括中医药治疗)等方面, 但迄今仍缺乏特异性的治疗手段。胆汁酸受体作为机体代谢调节与稳态维持的核心分子, 通过调控肠–肝–脑轴功能, 与肝脏疾病及HE的发生发展密切相关。该文系统总结胆汁酸受体在HE发病机制中的研究现状, 以期为HE治疗策略的探索提供新的思路与方向。

关键词　肝性脑病; 胆汁酸; 胆汁酸受体; 肠–肝–脑轴

The Role of Bile Acids and Their Receptors in Regulating Hepatic Encephalopathy via the Gut-Liver-Brain Axis

CHEN Junting, HU Xuefeng, LÜ Yi*
(*Fujian Key Laboratory of Developmental and Neurobiology, College of Life Sciences, Fujian Normal University, Fuzhou 350117, China*)

Abstract　HE (hepatic encephalopathy) is a severe neuropsychiatric complication caused by liver failure or portosystemic shunting. Its pathogenesis is jointly mediated by multiple factors such as disruption of the gut-liver-brain axis, inflammatory responses, oxidative stress, and blood-brain barrier damage. Currently, the fundamental treatment principles for HE in clinical practice include nutritional support, treatment of the underlying disease and correction of precipitating factors, pharmacological therapy including traditional Chinese medicine interventions. However, specific treatment methods are still lacking. Bile acid receptors, as key molecules in the regulation of metabolism and maintenance of homeostasis, are closely related to the development and progression of liver diseases and HE by modulating the function of the gut-liver-brain axis. This article systematically summarizes the current research status of bile acid receptors in the pathogenesis of HE, aiming to provide new ideas and directions for exploring HE treatment strategies.

Keywords　hepatic encephalopathy; bile acids; bile acid receptors; gut-liver-brain axis

肝性脑病(hepatic encephalopathy, HE)是一种由肝功能衰竭或门体分流引起的脑功能障碍, 表现为一系列神经或精神异常, 涵盖从亚临床状态改变到昏迷[1]。该病常见于肝硬化、急慢性肝衰竭及其他肝病的终末期阶段, 其中肝硬化是HE最主要的基础疾病。在我国及其他亚洲国家, 乙肝肝硬

收稿日期: 2026-04-08　　接受日期: 2026-05-19
福建省自然科学基金(批准号: 2025J01637)资助的课题
*通信作者。Tel: 0591-22868201, E-mail: lvyi@fjnu.edu.cn
Received: April 8, 2026　　Accepted: May 19, 2026
This work was supported by the Fujian Province Natural Science Foundation (Grant No.2025J01637)
*Corresponding author. Tel: 86-591-22868201, E-mail: lvyi@fjnu.edu.cn

化作为肝硬化的首要病因，在HE的疾病构成中占据重要地位[2]。研究显示，肝硬化患者HE发生率为30%~45%[3]，急性肝衰竭患者中HE发生率可高达80%[4]。HE不仅严重降低患者生活质量，还显著增加死亡风险，是肝病病程中危及生命的严重并发症。

HE分类方式多样，根据病因可主要分为三种类型：A型由急性肝衰竭(acute liver failure, ALF)引起，表现为在无慢性肝病基础情况下，以肝细胞大量坏死、肝功能急剧恶化诱发脑功能障碍，发病急促、病情危重，进展迅速且预后较差；B型由门体分流引起，无实质性肝损伤，因门静脉与体循环间异常分流导致未经肝脏解毒的血液直接进入体循环而诱发，临床相对罕见；C型由肝硬化引起，为临床最常见类型，因肝脏结构与功能严重损害、代谢紊乱及毒性物质蓄积引发脑功能障碍，病程较长且症状反复发作[5]。当前对HE发病机制的认知，仍以ALF阶段血清及脑皮质氨的蓄积为核心；此类氨蓄积可与外周及中枢炎症反应产生协同效应，进而诱发HE特征性的神经系统症状[6-7]。然而，近年来研究发现胆汁酸可能在此过程中扮演独立且关键的角色。基于啮齿动物模型的研究证实，无论是在急性还是慢性肝损伤背景下，脑组织中总胆汁酸水平均显著升高，且其在慢性模型中的累积被视为HE发生前的早期事件[8-10]。由肝衰竭介导的循环胆汁酸蓄积，已被明确列为HE复杂病因学机制中的另一潜在致病因素。肠道屏障功能与门静脉压力可被胆汁酸受体调控，而肠–肝轴紊乱引发的肠道细菌移位及炎症激活，被证实是HE发生发展的核心环节[11]。因此，作为机体代谢调节核心分子的胆汁酸受体，可能通过维持肠–肝轴稳态、干预胆汁酸代谢及中枢神经炎症等途径，在HE的发病进程中发挥潜在调控作用。

1 胆汁酸循环稳态

胆汁酸是胆固醇代谢产生的两亲性终末产物，在生理状态下，其经肝脏分泌进入肠道发挥生理作用，其中约95%的胆汁酸通过肠–肝循环被重吸收回肝脏，具体是通过回肠上皮细胞的主动运输途径重吸收，再经门静脉回流至肝脏重新分泌到胆汁中[12-13]。仅有5%的胆汁酸通过体循环经粪便排泄[14]。逸出肠–肝循环的胆汁酸可穿过血脑屏障，通过被动扩散或胆汁酸转运蛋白转运进入中枢神经系统(central nervous system, CNS)[13]。机体可通过调控相关通路快速合成与分解胆汁酸，维持胆汁酸池稳定，表明肠–肝循环对胆汁酸代谢平衡至关重要(图1)。

胆汁酸作为调控脂质与能量代谢核受体的内源性配体，可有效促进营养物质的吸收；肠–肝–脑轴则在维持机体血糖稳态、胆汁酸代谢平衡及免疫稳态中发挥关键调控作用[15]。肠–肝循环通过肠道重吸收实现胆汁酸的高效回收，同时借助负反馈机制调控肝脏胆汁酸的合成速率，这是维持机体胆汁酸

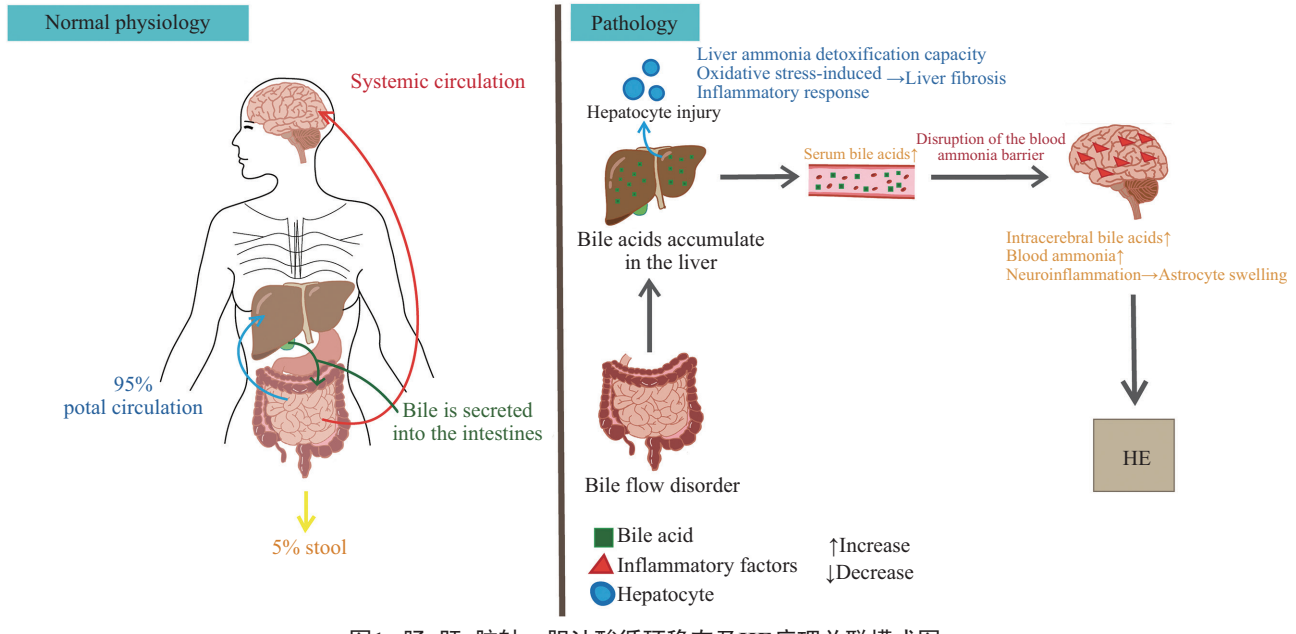


图1 肠–肝–脑轴、胆汁酸循环稳态及HE病理关联模式图

Fig.1 Schematic diagram of the gut-liver-brain axis, bile acid homeostasis, and their pathological associations in HE

池稳态的关键通路。近二十年来的研究表明, 胆汁酸兼具消化功能与信号分子功能, 其中作为信号分子时, 可特异性结合并激活多种受体, 进而参与调控肝脏、肠道等器官的生理功能[16]。胆汁酸稳态的精准维持, 有赖于肝肠组织中特异性受体与转运体对其合成、吸收及排泄过程的严密调控[15]。一旦胆汁酸代谢稳态失衡, 则可引发肝脏、肠道功能异常及全身性代谢紊乱[12]。而在肝功能严重受损的条件下, 这一失衡将进一步加剧, 异常蓄积的胆汁酸可经肠–肝–脑轴介导, 过度激活CNS相关信号通路, 诱发神经炎症、突触功能障碍等病理改变, 从而诱发并加重HE。

2 肠–肝–脑轴介导的胆汁酸紊乱与HE

肠–肝–脑轴的病理生理改变, 是介导HE发生发展的核心机制基础[17]。在病理状态下, 受损的肝细胞会释放大量胆汁酸至外周血, 同时肝脏对血中胆汁酸的再摄取能力显著下降, 双重因素促使血清胆汁酸水平异常升高, 且该变化可见于不同类型的急慢性肝病[18]。Horvatits等[19]临床研究证实, 血清胆汁酸水平的升高程度可有效预测肝硬化患者急性失代偿与慢加ALF的发生风险, 而这两类肝脏重症正是HE发生的重要诱因, 提示血清胆汁酸异常升高可能通过介导重症肝病进展, 间接参与HE的发病过程。尤其在ALF及慢性肝病状态下, 胆汁酸从肝窦向肝细胞的摄取转运功能受损, 会进一步造成血清胆汁酸浓度的升高[20]。

胆汁酸的异常蓄积会产生多重毒性作用, 在肝细胞内蓄积时, 可通过诱导线粒体功能障碍和活性氧(reactive oxygen species, ROS)的形成导致细胞毒性, 最终引发细胞凋亡或坏死[21]。肝损伤后血清胆汁酸水平的升高, 还可能破坏血脑屏障并导致脑损伤[22]。暴发性肝衰竭患者的血清、脑脊液和脑组织中胆汁酸水平均升高, 且HE发生时脑内胆汁酸含量进一步增加[23]。相较于无HE的肝硬化患者及健康人群, 肝硬化合并HE患者的血清总胆汁酸水平显著升高, 其中结合型胆汁酸亚型, 包括甘氨胆酸(glycocholic acid, GCA)、甘氨鹅脱氧胆酸(glycochenodeoxycholic acid, GCDCA)、牛磺胆酸(taurocholic acid, TCA)及牛磺鹅脱氧胆酸(taurochenodeoxycholic acid, TCDCA)的水平升高尤为明显, 且血清胆汁酸水平与氨水平呈显著正相关。

Chan等[24]研究进一步验证了胆汁酸与HE的关联。胆管结扎(bile duct ligation, BDL)是构建大鼠C型HE模型的常用手段, 该模型可诱导慢性胆汁淤积性肝损伤, 仅当肝损伤进展至肝硬化阶段时, 大鼠才会出现明显的认知功能障碍, 而胆汁淤积引发的胆汁酸蓄积是串联肝损伤与HE的关键病理环节。BDL会导致胆汁酸积聚, 进而诱发氧化应激和炎症反应, 引发胆汁淤积性肝纤维化, 同时胆汁酸会破坏血脑屏障通透性, 加剧神经炎症[25]。在非酒精性脂肪性肝炎合并肝细胞癌模型中, CNS内结合胆汁酸的蓄积早于高氨血症发生, 且与星形胶质细胞及神经元的缺失密切相关, 提示胆汁酸在CNS中具有独立于氨的致病作用[26]。此外, 牛磺结合胆汁酸的蓄积现象, 已在HE患者与实验动物中被证实并报道, 这一发现同样值得未来研究重点关注[27-28]。

已有研究证实, 在ALF所致HE患者及ALF小鼠模型中, 脑内胆汁酸水平显著升高, 且该变化与神经功能衰退密切相关, 可诱发或加重神经功能损伤[8]。在急性HE模型中, 胆汁酸还被发现可影响神经炎症信号转导[29]。

综上, 胆汁淤积是HE的主要诱因之一, 其会扰乱胆汁流动并导致有害胆汁酸在肝脏内积聚, 同时削弱肝脏对氨的解毒能力, 使肝脏和血液中氨含量升高。胆汁酸与氨的共同积累会进一步损伤肝细胞, 引发氧化应激和炎症反应, 推动肝纤维化进展; 这些相互关联的过程通过多种途径诱发神经炎症、星形胶质细胞肿胀, 最终介导HE的发生发展(图1)[30]。

3 胆汁酸受体的空间特异性及其对HE核心机制的交叉调控

动物模型研究证实, 胆汁酸在HE干预中具有潜在治疗优势。法尼醇X受体(farnesoid X receptor, FXR)信号受损是肝内胆汁淤积的关键驱动因素, 靶向纠正FXR信号紊乱可显著逆转小鼠HE的病理表型, 提示在CNS中调控特定胆汁酸受体(尤其是脑内FXR)是HE的潜在干预策略[31]。然而, 胆汁酸受体家族庞大, 循环胆汁酸池由初级胆汁酸与次级胆汁酸共同构成。不同胆汁酸亚型对核受体及膜受体的激活具有高度组织特异性与配体选择性, 这构成了其在HE中发挥复杂调控功能的分子基础。初级胆汁酸主要在肝脏内合成, 是肝脏内FXR的高效内源性配体; 次级胆汁酸由肠道菌群代谢生成, 主要

在肠道内发挥作用，如牛磺石胆酸(taurolithocholic acid, TLCA)与石胆酸(lithocholic acid, LCA)可激活胃肠道G蛋白偶联受体5(takeda G protein-coupled receptor 5, TGR5)、孕烷X受体(pregnane X receptor, PXR)与维生素D受体(vitamin D receptor, VDR)。这种肝脏–初级胆汁酸/肠道–次级胆汁酸的配体–受体对应关系，为胆汁酸信号在空间上调控肠–肝对话提供了重要基础。

胆汁酸受体的功能并非局限于其所在组织，而是通过肠–肝–脑轴相互关联，共同构成调控HE病理进程的分子网络。一方面，肠道内胆汁酸受体的激活可直接调节肠道屏障功能与炎症反应。例如，肠道特异性*VDR*敲除会导致肝脏胆汁酸过度积聚，加重LCA诱导的肝内胆汁淤积；而将人源细胞色素P450 3A4(cytochrome P450 3A4, CYP3A4)转入肠道特异性*VDR*基因敲除小鼠则可显著增强LCA的肠道代谢与解毒，缓解其诱导的肝毒性[32]。另一方面，源自肠道的信号可经循环系统或迷走神经通路传递至CNS，影响神经炎症与认知功能。因此，不同胆汁酸受体在肠–肝–脑轴上的空间特异性激活作用，决定了其在HE发生发展过程中的多重调控效应。经肠–肝轴转导的信号，最终通过CNS发挥调控作用，系统性干预HE病理进展；而胆汁酸受体在脑组织中的直接表达，为胆汁酸直接参与中枢调控提供了关键分子基础。McMillin等[33]研究采用偶氮甲烷(azoxymethane, AOM)诱导的HE小鼠模型，证实TGR5在皮层神经元及小胶质细胞中均有表达，且在经AOM处理的小鼠中表达水平显著上调；进一步研究表明，TGR5激活后可通过环磷酸腺苷/蛋白激酶A(cyclic adenosine monophosphate/protein kinase A, cAMP/PKA)信号通路抑制NOD样受体家族含pyrin结构域蛋白3炎症小体[NLRP3 (NLR family pyrin domain containing 3) inflammasome)活化[34-36]，同时通过腺苷酸活化蛋白激酶/哺乳动物雷帕霉素靶蛋白(adenosine monophosphate-activated protein kinase/mammalian target of rapamycin, AMPK/mTOR)通路诱导保护性自噬[37]，二者协同减轻神经炎症、促进抗炎信号转导，从而延缓神经功能恶化。此外，FXR及鞘氨醇-1-磷酸受体2(sphingosine-1-phosphate receptor 2, S1PR2)亦在神经元中表达，参与突触可塑性调节与神经甾体信号转导[38]。这些发现表明，胆汁酸不仅通过肠–肝轴间接影响CNS功能，还能作为信号分子直接进入大脑，通过激活特定受体调控神经炎症与突触功能，最终在HE认知障碍的发生发展中发挥关键作用。

胆汁酸受体与HE核心病理机制存在密切交叉调控关系。在氨代谢层面，肝脏FXR激活可通过上调谷氨酰胺合成酶及尿素循环相关酶系增强氨解毒能力、降低血氨水平并减轻CNS功能损伤[39]；而调控胆汁酸的肠–肝循环，可能通过调节肠道菌群间接抑制肠源性氨的产生，从源头降低血氨负荷[26]。FXR作用具有显著组织特异性，外周激活多发挥保护效应，但脑内异常激活可能加剧神经元损伤。在氧化应激方面，FXR异常活化会加剧肝细胞与神经元的氧化损伤，而甘氨熊去氧胆酸(glycoursodeoxycholic acid, GUDCA)可通过自身抗氧化特性及对FXR信号通路的调节，有效拮抗胆红素诱导的神经元氧化损伤[40]。FXR在中枢自噬调控中的作用尚不明确，现有证据提示其过度激活可能参与神经炎症，具体机制仍待进一步验证。此外，VDR与PXR主要参与胆汁酸代谢调节和抗氧化防御，可能间接影响氨稳态，与FXR、TGR5共同构成胆汁酸受体在肠–肝–脑轴水平调控HE核心病理环节的网络。

4 菌群源性胆汁酸——肠–肝–脑轴的关键信使

肠道菌群作为胆汁酸代谢的重要调控者，可通过代谢初级胆汁酸生成多样化的菌源胆汁酸[如LCA、脱氧胆酸(deoxycholic acid, DCA)、熊去氧胆酸(ursodeoxycholic acid, UDCA)等]，显著扩展胆汁酸受体配体的种类与功能谱[34,41]。近年来，菌源胆汁酸已从代谢辅助因子，转变为关键信号分子，成为连接肠道微生态与宿主多器官系统、介导肠–肝–脑轴调控的核心信使[41]。这些菌源胆汁酸对FXR、TGR5、PXR、VDR等受体具有差异化的亲和力与激活效应[42]。其中，LCA不仅是PXR与VDR的高效激动剂，还可通过诱导解毒酶CYP3A4促进毒性胆汁酸的清除，并借助VDR/PXR双通路参与肠–肝–脑轴中的免疫交互调控。研究表明，由LCA衍生的某些次级胆汁酸(如3-oxoLCA和isoalloLCA)能够通过VDR等受体，一方面促进$FOXP3^+$调节性T细胞(regulatory T cell, Treg)分化，另一方面抑制促炎性Th17细胞分化，从而在肠道建立耐受性免疫基调，进而影响CNS的自身免疫反应[43]。在肠–肝–脑轴中，LCA可通过激活VDR直接调控$CD4^+$ T细胞的功能，

显著抑制IFNγ的产生[44]。VDR需与视黄醇X受体(retinoid X receptor, RXR)结合形成异二聚体, VDR与视黄酸受体等核受体对RXR的竞争性结合, 可能构成更复杂的调控网络[45]; PXR的激活则可通过上调P-糖蛋白等外排泵增强血脑屏障的屏障功能, 限制有害物质入脑, 同时参与调控炎症小体信号, 构成一条从肠道菌群到大脑免疫稳态的重要信号轴[46]。而UDCA的甘氨酸结合物GUDCA则主要通过拮抗肠道FXR, 同时可轻度激活TGR5, 在肠–肝–脑轴中发挥潜在保护作用[34]。此外, 肠道菌群的组成与功能变化直接影响菌源胆汁酸的生成谱, 进而调控胆汁酸受体的激活状态[41]。在HE病理背景下, 肠道菌群失调可导致毒性菌源胆汁酸(如LCA)蓄积, 毒性胆汁酸蓄积可过度激活S1PR2或抑制TGR5, 加剧神经炎症与血脑屏障损伤[34]; 反之, 部分胆汁酸衍生物则可通过拮抗FXR、选择性激活TGR5发挥保护效应[41]。

最新研究进一步揭示, 菌源胆汁酸还作为内源性再生介质调控肝脏再生[47], 并可通过色氨酸结合型胆汁酸(tryptophan-conjugated cholic acid, Trp-CA)等新配体激活孤儿受体Mas-related G蛋白偶联受体成员E(Mas-related G protein-coupled receptor member E, MRGPRE)参与葡萄糖代谢调控[48]。因此, 肠道菌群–菌源胆汁酸–胆汁酸受体轴构成了肠–肝–脑轴中连接微生态失衡与HE进展的关键环节[49-50], 靶向调控菌源胆汁酸代谢或可成为打破病理恶性循环的新策略。

5 胆汁酸受体介导肠–肝–脑轴对HE的调控作用

胆汁酸所激活的受体主要分为两大类, 具体如下(表1和图2)。

一类为核受体, 包括FXR、VDR、PXR和组成型雄甾烷受体(constitutive androstane receptor, CAR); 另一类为G蛋白偶联受体, 包括TGR5和S1PR2。

5.1 法尼醇X受体(FXR)

FXR作为核受体超家族成员, 是肝脏胆汁酸代谢领域研究最广泛的核心感知受体, 在维持胆汁酸合成、转运及代谢稳态中发挥关键调控作用, 可特异性靶向调控细胞色素P450 7A1(cytochrome P450 7A1, *CYP7A1*)、小异二聚体伴侣(small heterodimer partner, *SHP*)等多种参与胆汁酸稳态维持的靶基因, 通过负反馈调节精准控制胆汁酸水平, 避免其过量蓄积引发的脏器毒性[51-52]。FXR对胆汁酸平衡的精准调节是其发挥生理及病理调控作用的核心机制, 其核心功能为抑制胆汁酸的生成与异常蓄积, 维持肠–肝–脑轴的稳态。

FXR在肝损伤进程中具有明确的抗炎特性[53], 活化FXR不仅能显著提高肝损伤小鼠的氨代谢能力、发挥强效肝保护作用, 还可有效减轻HE的神经功能紊乱症状[54]。McMillin等[8]研究发现, 在AOM诱导的ALF小鼠模型中, 额叶皮层中的*FXR*及其共调节因子*SHP*的mRNA表达水平显著上调。与此同时, 该模型小鼠肠道内结合型胆汁酸[TCA、TCDCA、牛磺脱氧胆酸(taurodeoxycholic acid, TDCA)]比例显著升高, 导致肠道FXR活性不足, 进而上调顶膜钠依赖性胆汁酸转运体(apical sodium-dependent bile acid transporter, ASBT)表达; FXR激动剂可抑制ASBT, 拮抗剂则相反。AOM联合布地奈德(budesonide, BUD)引发组织特异性FXR表达异常, 扰乱FXR-ASBT调控轴与胆汁酸代谢稳态, 表明FXR与ASBT存在紧密调控关联, 同时提示FXR在肝衰竭相关病理进程中具备潜在调控作用[26]。Verbeke等[55]研究发现, FXR激动剂奥贝胆酸(obeticholic acid, OCA)对回肠屏障功能的改善效应依赖于肠道炎症的缓解, 最终可有效降低肠道胆汁酸转运效率, 这一结果明确揭示了FXR通过调控肠–肝轴稳态发挥脏器保护作用的重要分子路径。研究证实, 肝纤维化患者体内狄氏副拟杆菌(*Parabacteroides distasonis*, *P. distasonis*)丰度显著降低; 向雄性小鼠补充该菌可有效逆转硫代乙酰胺(thioacetamide, TAA)及蛋氨酸–胆碱缺乏(methionine-choline deficient, MCD)饮食诱导的肝纤维化。同时, 补充*P. distasonis*能显著增强小鼠肠道胆汁盐水解酶(bile salt hydrolase, BSH)活性, 抑制肠道FXR信号通路的转导, 同时降低肝脏中TCDCA的水平, 从而逆转胆汁酸代谢紊乱, 减轻肝纤维化[56]。由此可见, FXR并非一个“激活即有益”的单向靶点, 在肝纤维化等慢性肝病中呈现出复杂的双向调控特征, 激动剂(如OCA)与间接抑制剂(如*P. distasonis*介导的肠道FXR抑制)均可能产生治疗效应, 其具体方向取决于疾病阶段、靶组织(肝脏或肠道)以及胆汁酸代谢网络的具体状态。这一双向性为开发基于FXR的精准治疗策略提供理论依据, 也提示在干预FXR通路时必须谨慎评估病理背景。FXR激动剂

表1 胆汁酸受体在肝性脑病中的功能

Table 1 The role of bile acid receptors in hepatic encephalopathy

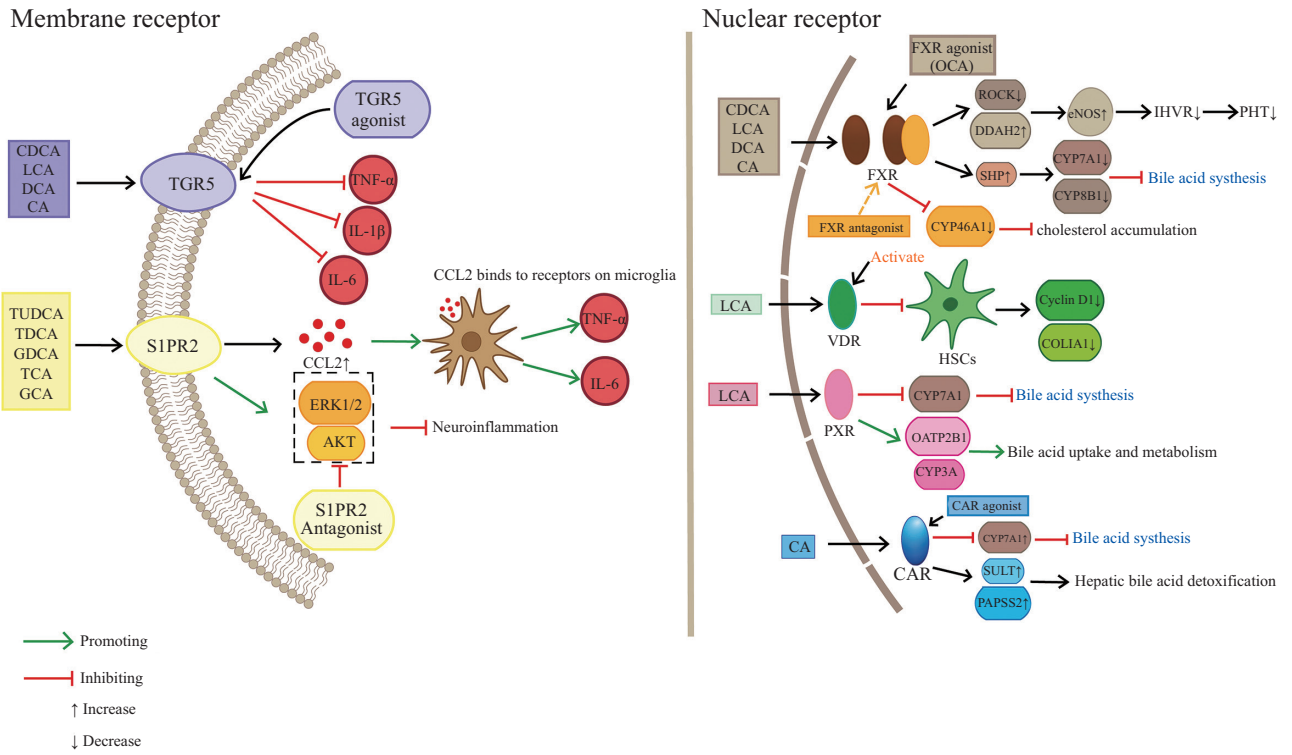
胆汁酸受体 Bile acid receptors	胆汁酸配体 Bile acid ligand	功能 Function	参考文献 References
FXR	CDCA, LCA, DCA, CA	Inhibit the production and abnormal accumulation of bile acids, anti-inflammatory, and maintain the homeostasis of the gut-liver-brain axis	[8,39,54]
VDR	LCA	Activation of VDR can inhibit the activation and proliferation of HSCs, downregulate the expression of pro-fibrotic markers such as Cyclin D1 and COL1A1, and reduce collagen deposition in liver tissue	[63,66]
PXR	LCA	Liver injury can be alleviated by regulating liver detoxification and the metabolic clearance of toxic bile acids, indirectly intervening in the pathological process of hepatic encephalopathy	[77]
CAR	CA	Regulate bile acid synthesis, antagonize bile acid toxicity, and alleviate liver injury	[79,84]
TGR5	LCA, DCA, CDCA, CA	Activation of TGR5 alleviates neuroinflammation and exerts neuroprotective effects, making its agonists potential intervention targets	[33,89-91]
S1PR2	TCA, GCA, TDCA, GDCA, UDCA	It exerts pro-inflammatory and pro-fibrotic effects, aggravating liver injury and promoting the progression of HE; its antagonists/inhibitors can suppress related abnormal signals, alleviate liver damage and portal hypertension, providing potential directions for HE intervention	[9,94]

FXR: 法尼醇X受体; CDCA: 鹅脱氧胆酸; LCA: 石胆酸; DCA: 脱氧胆酸; CA: 胆酸; VDR: 维生素D受体; PXR: 孕烷X受体; CAR: 组成型雄甾烷受体; TGR5: G蛋白偶联受体5; S1PR2: 鞘氨醇-1-磷酸受体2; TLCA: 牛磺石胆酸; TCA: 牛磺胆酸; GCA: 甘氨胆酸; TDCA: 牛磺脱氧胆酸; GDCA: 甘氨脱氧胆酸; UDCA: 熊去氧胆酸; GCDCA: 甘氨鹅脱氧胆酸; HE: 肝性脑病。

FXR: farnesoid X receptor; CDCA: chenodeoxycholic acid; LCA: lithocholic acid; DCA: deoxycholic acid; CA: cholic acid; VDR: vitamin D receptor; PXR: pregnane X receptor; CAR: constitutive androstane receptor; TGR5: takeda G protein-coupled receptor 5; S1PR2: sphingosine-1-phosphate receptor 2; TLCA: taurolithocholic acid; TCA: taurocholic acid; GCA: glycocholic acid; TDCA: taurodeoxycholic acid; GDCA: glycodeoxycholic acid; UDCA: ursodeoxycholic acid; GCDCA: glycochenodeoxycholic acid; HE: hepatic encephalopathy.

OCA作为胆汁酸核受体靶向调节剂, 在多种肝脏疾病中展现出多效性治疗潜力。在TAA中毒大鼠模型和BDL肝损伤模型中均观察到, OCA可通过重激活FXR下游信号通路, 下调肝内血管阻力(intrahepatic vascular resistance, IHVR)以减轻门静脉高压(portal hypertension, PHT), 同时规避全身性低血压这一潜在不良反应, 为PHT的治疗提供新路径[57-58]。此外, OCA还能有效抑制肝脏胆汁酸蓄积, 直接调控胆汁酸代谢过程, 间接抑制纤维化信号通路的活化, 从而减轻肝细胞损伤、缓解炎症反应、阻断肝纤维化进程[59]。

FXR的调控作用不仅局限于肠–肝轴, 还延伸至神经系统, 参与神经功能稳态的调控。*FXR*基因敲除小鼠的研究证实, FXR对维持脑内不同区域多种神经递质系统的稳态及调控神经行为具有重要意义, 且该调控效应至少部分由胆汁酸介导。已知胆汁酸可通过血脑屏障中的有机阴离子转运体穿透屏障进入大脑, 进而诱导神经细胞毒性损伤[60]。血清中的胆汁酸也可以通过该途径进入大脑, 并通过涉及FXR激活的机制, 加剧与HE相关的神经功能衰退[8]。因此, 降低血清胆汁酸水平或特异性抑制脑内FXR信号通路的活化, 可有效减轻神经细胞损伤, 为急性肝衰竭相关神经功能衰退及HE的临床干预提供重要方向。尤为关键的是, FXR在肝脏、肠道与脑组织中呈现出截然不同的调控效应。在肝脏和肠道中激活FXR可增强氨代谢、维护屏障功能、减轻炎症, 从而间接抑制HE的发生发展; 而在脑内, FXR信号异常激活反而通过下调细胞色素P450 46A1(cytochrome P450 46A1, CYP46A1)表达、抑制胆固醇代谢清除, 诱发胆固醇蓄积, 直接加剧神经损伤。这种组织特异性的双向作用提示, 理想的HE治疗策略应区分靶组织, 在外周(肝脏/肠道)倾向于激活FXR, 在中枢(脑)则需要抑制FXR的异常信号转导。在HE动物模型中, 激活FXR可上调肝脏内氨代谢通路相关关键酶的表达, 增强尿素循环功能以降低血氨水平, 同时减轻肝脏损伤与脑部炎症, 逆转小鼠的异常行为活动; 体外细胞实验也显示, 激活FXR可以增强C3A肝细胞的氨代谢能力和氨耐受性[39]。而在ALF病程中, 脑内FXR信号转导异常会导致CYP46A1表达下调, 抑制脑内胆固醇的代谢清除, 进而引发胆固醇蓄积及相关神经系统症状。



TUDCA: 牛磺熊去氧胆酸; TNF-α: 肿瘤坏死因子-α; IL-1β/6: 白介素-1β/6; CCL2: C-C基序趋化因子配体2; ERK1/2: 细胞外信号调节激酶1/2; AKT: 蛋白激酶B, 即PKB; SHP: 小异二聚体伴侣; CYP7A1: 细胞色素P450 7A1; CYP8B1: 细胞色素P450 8B1; CYP46A1: 细胞色素P450 46A1; ROCK1: Rho相关卷曲螺旋蛋白激酶 1; DDAH2: 二甲基精氨酸二甲胺水解酶 2; eNOS: 内皮型一氧化氮合酶; IHVR: 肝内血管阻力; PHT: 门静脉高压; HSCs: 肝星状细胞; COL1A1: I型胶原α1链; OATP2B1: 有机阴离子转运多肽2B1; CYP3A: 细胞色素P450 3A; SULT: 磺基转移酶; PAPSS2: 3′-磷酸腺苷-5′-磷酰硫酸合成酶2。其他同表1。

TUDCA: tauroursodeoxycholic acid; TNF-α: tumor necrosis factor-α; IL-1β/6: interleukin-1β/6; CCL2: C-C motif chemokine ligand 2; ERK1/2: extracellular signal-regulated protein kinases 1/2; AKT: protein kinase B, PKB; SHP: small heterodimer partner; CYP7A1: cytochrome P450 7A1; CYP8B1: cytochrome P450 8B1; CYP46A1: cytochrome P450 46A1; ROCK1: Rho-associated coiled-coil containing protein kinase 1; DDAH2: dimethylarginine dimethylaminohydrolase 2; eNOS: endothelial nitric oxide synthase; IHVR: intrahepatic vascular resistance; PHT: portal hypertension; HSCs: hepatic stellate cells; COL1A1: collagen type I α1 chain; OATP2B1: organic anion transporting polypeptide 2B1; CYP3A: cytochrome P450 3A; SULT: sulfotransferase; PAPSS2: 3′-phosphoadenosine 5′-phosphosulfate synthase 2. Others are the same as table 1.

图2 不同胆汁酸受体在HE中的核心信号通路与相互作用网络图

Fig.2 Core signaling pathways and interaction network of different bile acid receptors in HE

针对这一病理机制, 阻断脑内异常胆汁酸信号转导(如施用胆汁酸螯合剂考来烯胺、脑室内灌注FXR拮抗剂)或抑制脑内胆固醇异常积聚(如脑室内灌注胆固醇螯合剂), 均可有效逆转上述病理改变, 从而防止神经症状发生, 提示靶向脑内胆固醇积聚可能成为HE的潜在治疗方向[61]。

5.2 维生素D受体(VDR)

VDR是一种介导活性维生素D(1,25-二羟基维生素D_3)发挥作用的配体依赖性核转录因子, 在肝星状细胞(hepatic stellate cells, HSCs)和肠道组织中均有表达[62]。研究证实, HSCs中存在VDR的高表达, VDR被激活后可特异性抑制HSCs的活化, 并抑制肝组织胶原沉积, 从而对肝纤维化发挥显著的保护作用, 这一特征提示VDR可能是调控肝纤维化发生发展的潜在关键调节因子[63-64]。作为肝纤维化进程中的核心效应细胞, HSCs的静息状态被打破后, HSCs会大量增殖并分泌细胞外基质, 最终推动肝组织纤维化重构[65]。而VDR作为重要的核受体, 可对HSCs的促纤维化效应发挥负向调控作用。HSCs是肝纤维化发展过程中的关键参与者, VDR抑制HSCs增殖, 并下调细胞周期蛋白D1(cyclin D1)、I型胶原蛋白α1链(collagen type I α1 chain, COL1A1)等关键促纤维化标志物的表达。在动物实验中, VDR激活还能有效减轻TAA诱导的大鼠肝纤维化, 进而减轻肝组织病理损伤[66]。肝纤维化与肝硬化是HE的关键病理诱因, VDR通过上述机制在肝轴上发挥抗纤维化、

保肝作用, 或为HE的防治提供新策略。

与此同时, VDR可通过调控肠–肝–脑轴介导间接神经保护效应, 在肠道层面, VDR激活能够上调紧密连接蛋白的表达, 维护肠道屏障完整性, 抑制脂多糖、氨、苯乙胺等肠源性毒素向门静脉系统易位[67-69]; 此外, VDR参与胆汁酸代谢调控, 其活性改变可影响FXR等信号通路, 进而调节肠道菌群稳态与肠屏障功能。在肝功能失代偿状态下, 肝细胞对门静脉血中神经毒素的清除能力显著下降, 这些毒素可通过结构和功能受损的血脑屏障进入CNS, 诱发星形胶质细胞改变与神经炎症, 最终导致HE相关的认知及运动功能障碍[70]。因此, VDR不仅在肝轴层面发挥抗纤维化作用, 还可通过强化肠道屏障从源头降低肠源性神经毒素负荷, 在肠–脑轴上游实现间接神经保护。这种多靶点调控模式为HE的治疗提供了超越传统降氨策略的新思路。

5.3 孕烷X受体(PXR)

在小鼠TAA模型、缺血诱导大鼠ALF模型、大鼠门腔静脉吻合模型及啮齿类动物高氨血症模型等多种ALF实验模型中, 均证实脑内异孕烯醇酮与孕烯醇酮水平呈显著升高趋势[71-74]。孕烯醇酮及其衍生物均为内源性PXR的配体, 而PXR广泛参与神经甾体的合成与代谢调控, 提示该受体可能在ALF脑内神经甾体异常升高中发挥关键调控作用, 进而通过肠–肝–脑轴参与HE的发病过程。PXR作为机体重要的外源性物质传感器, 可调控多种细胞色素P450酶家族成员的表达, 进而参与体内内外源性物质的识别、代谢与清除过程, 发挥肝脏解毒功能[75]。已有研究表明, 物种间PXR的激活特性存在显著差异, 这种差异与人、大鼠原代肝细胞实验中得到的细胞色素P450 3A(cytochrome P450 3A, CYP3A)诱导数据高度吻合; 因此, 外源性物质诱导CYP3A表达的物种特异性, 可能由PXR激活水平的不同所导致; 而CYP3A作为PXR下游关键代谢酶, 其表达差异会进一步影响肠–肝–脑轴中有害物质的代谢效率, 间接调控HE的发病进程[76]。研究证实, 毒性次级胆汁酸LCA及其3-酮代谢产物可特异性激活PXR[77]; 此外, PXR还可调控CYP7A1、钠离子非依赖性有机阴离子转运体2(organic anion-transporting polypeptide 2B1, OATP2B1)等胆汁酸生物合成、转运及代谢相关基因的表达, 且其激活能够拮抗LCA诱导的重度肝损伤, 发挥肝脏保护作用。由此可知, PXR可作为LCA的生理传感器, 通过协调下游代谢、转运相关基因的表达, 降低该毒性胆汁酸的体内蓄积浓度; 当LCA水平升高至病理生理阈值时, PXR可能与FXR协同介导其清除作用。而毒性胆汁酸蓄积是肠–肝–脑轴紊乱的重要诱因, 其可通过肠道黏膜损伤、肝脏代谢异常, 进一步加剧CNS功能障碍, 因此PXR对LCA的调控作用, 可通过调节肠–肝–脑轴的胆汁酸代谢平衡, 减轻HE相关病理损伤, 这些结果表明, PXR激动剂在人类胆汁淤积性肝病合并HE中具有潜在应用价值[77]。HE临床常采用乳果糖联合利福昔明治疗, 利福昔明为PXR激动剂, PXR是其明确的作用靶点之一, 但其促进肠上皮细胞氨清除、增强HE的药理效应, 主要通过不依赖PXR的通路介导[78]。进一步说明PXR在肠–肝–脑轴调控HE的过程中存在多通路、多靶点的复杂作用模式, 既可以通过调控肝脏解毒、胆汁酸代谢参与HE发病, 也可与其他通路协同维持肠–肝–脑轴稳态, 为HE的治疗提供新的靶点方向。

5.4 组成型雄甾烷受体(CAR)

CAR在肝、肺、肾、心脏及大脑中低水平表达。Litwa等[79]研究证实, RXRα/PXR/CAR信号通路在壬基酚诱导的细胞促凋亡效应及神经毒性过程中发挥关键作用; CAR作为调控肝脏解毒与炎症的重要核受体, 其介导的神经损伤调控通路与HE核心病理机制存在潜在交互关联。Stedman等[80]研究发现, *CAR*敲除小鼠对胆汁酸(含CA)的毒性更敏感, 肝损伤程度更严重, 这表明CAR是胆汁酸(含CA)的重要感知受体, 可介导胆汁酸解毒与肝保护。CA可激活CAR, 通过降低肝脏胆汁酸含量、增加胆汁流量、抑制毒性胆汁酸蓄积, 维持胆汁酸代谢稳态并发挥肝保护作用, 提示CA-CAR信号轴是肝脏抵御胆汁酸毒性损伤的重要代偿通路[81-82]。CAR激动剂可显著抑制肝细胞中胆汁酸从头合成关键限速酶CYP7A1的表达, 进而调控机体胆汁酸合成水平[83]。在小鼠胆汁淤积模型中, CAR激活可有效拮抗胆汁酸毒性; 而*CAR*敲除小鼠经LCA处理或BDL诱导胆汁淤积后, 肝损伤显著加剧[84]。此外, Saini等[85]基于转基因小鼠模型证实, CAR可诱导磺基转移酶(sulfotransferase, SULT)与3′-磷酸腺苷-5′-磷酸硫酸合成酶2(3′-phosphoadenosine 5′-phosphosulfate synthase 2, PAPSS2)表达上调, 增强机体对LCA介导肝毒性的耐受能力, 通过维持肠–肝轴胆汁酸代谢稳

态, 间接减轻CNS的毒性应激, 进而参与HE的病理生理调控。

Sepehrinezhad等[86]基于多组学整合分析揭示, 次级胆汁酸等肠道菌群代谢物可通过影响CNS的线粒体功能、神经炎症及谷氨酸能信号通路参与HE病理进程, 首次从系统生物学层面构建肠道代谢物与HE中枢基因网络的联系框架, 提示CAR介导的胆汁酸解毒可能通过改变外周代谢物谱远程调控上述中枢基因表达。同时, 肠–脑轴神经免疫通信机制表明, 肠道来源的炎症信号可通过体液、细胞免疫及神经元途径传递至中枢[87], 而CAR在肝脏中的抗炎效应有助于降低全身炎症负荷, 间接抑制中枢小胶质细胞活化和神经炎症反应。综上, CAR通过肝内胆汁酸解毒、肠–肝轴稳态维持、外周代谢物谱改变与中枢转录调控这一级联效应, 在HE的病理生理调控中发挥多层次的间接保护作用。

5.5 G蛋白偶联受体5(TGR5)

Kawamata等[88]研究首次证实, TGR5可将胆汁酸作为内源性激动剂并产生特异性响应; 同时也是首个被鉴定的胆汁酸响应性G蛋白偶联受体(G protein-coupled receptor, GPCR)。进一步研究发现, TGR5的一级结构及其胆汁酸响应特性在人、牛、兔、大鼠及小鼠中高度保守, 提示该受体在跨物种的生理调控中具有关键作用, 为其参与肠–肝–脑轴的协同调控奠定了基础。作为肠–肝–脑轴调控中的关键分子, TGR5兼具神经甾体与胆汁酸受体双重属性, 其调控作用贯穿脑、肝两大核心器官, 并与肠道信号转导密切相关。在脑层面, TGR5在HE患者脑组织中的表达水平降低[89], 且被明确赋予神经保护功能; 在动物实验中, C57BL/6小鼠大脑皮层中存在TGR5受体, 且该受体在HE病程进展中表达显著上调。以桦木酸作为TGR5激动剂实施干预后, 被激活的TGR5可通过介导神经元与小胶质细胞之间的旁分泌信号转导, 有效减轻神经炎症反应, 并改善AOM处理小鼠的疾病预后, 直接发挥脑内神经保护作用, 抑制HE相关神经功能衰退[33]。然而, 目前尚无临床研究将TGR5表达水平与患者生存或显性肝性脑病(overt hepatic encephalopathy, OHE)发生风险进行关联分析。在肠–肝交互层面, TGR5与TUDCA存在明确功能关联, 二者相互作用可介导TUDCA的抗炎效应, 推动小胶质细胞表型在体内外环境中均向抗炎方向偏移, 该效应已在急性神经炎症小鼠模型中得到证实[90], 而小胶质细胞的抗炎表型调控可进一步通过肠–肝–脑轴的信号转导, 间接影响脑内神经炎症状态, 形成轴性调控闭环。

除此之外, TGR5还可介导抗炎、抗胆汁淤积、抗纤维化三重生物学效应, 既能直接缓解肝损伤、发挥肝脏保护作用, 还能针对性调节胆汁淤积、肝纤维化/肝硬化等HE发生发展的核心肝脏病理基础。在啮齿动物模型中, TGR5激动剂可显著减轻胆汁淤积性、非酒精性脂肪性肝炎及肝纤维化/肝硬化相关肝损伤。其通过逆转肝脏病理损伤、恢复肝脏正常生理功能, 打通肠–肝–脑轴的转导通路, 提示TGR5可成为靶向干预HE肠–肝–脑轴调控环节的重要潜在靶点[91]。

5.6 鞘氨醇-1-磷酸受体2(S1PR2)

脑内胆汁酸通过调控S1PR2信号通路, 介导HE的神经炎症反应, 诱导小胶质细胞激活与趋化因子C-C基序趋化因子配体2([chemokine (C-C motif) ligand 2, CCL2, 又称单核细胞趋化蛋白-1(monocyte chemoattractant protein-1, MCP-1)]表达上调, 进而间接调控血脑屏障的通透性, 参与HE的病理进程[9]。其中, TCA激活的S1PR2信号转导是HE中炎症反应的重要诱因, 也是胆汁酸参与HE病理过程的重要机制之一。TCA已被证实可通过S1PR2诱导神经元MCP-1信号转导[9,92]。Arenas等[93]研究证实, 在高氨血症大鼠的小脑中, S1PR2的膜表达显著上调, 其介导的S1PR2-CCL2-脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)-原肌球蛋白受体激酶B(tropomyosin receptor kinase B, TrkB)通路激活是高氨血症诱导的神经炎症与运动协调障碍的关键中介机制。S1PR2被胆汁酸激活后, 可通过启动细胞外信号调节激酶1/2(extracellular signal-regulated protein kinases 1/2, ERK1/2)及蛋白激酶B(protein kinase B, PKB, 又称AKT)依赖性信号通路介导神经炎症反应; 而S1PR2拮抗剂JTE-013能抑制该效应, 阻断脑内炎症进一步发展。同时研究表明, JTE-013还可抑制*SHP*的表达, 提示S1PR2介导的信号转导可能影响FXR信号通路[94], 间接参与肠–肝–脑轴的功能调节。在BDL诱导的胆汁酸淤积大鼠模型中, S1PR2拮抗剂可有效缓解实验动物的PHT症状[95], 为S1PR2作为HE干预靶点提供了可靠的动物实验依据。

除了介导脑内神经炎症外, S1PR2还具有明确的促炎、促纤维化作用, 直接加重肝损伤, 加速胆汁

淤积、肝纤维化/肝硬化的进展。S1PR2信号抑制剂可减轻啮齿动物模型中胆汁淤积性、非酒精性脂肪性肝炎及肝纤维化/肝硬化相关肝损伤，通过逆转肝脏病理状态、修复肝组织功能，稳定肠–肝–脑轴稳态，为HE的肝脏病理环节干预提供潜在靶点[91]。

6 小结与展望

胆汁酸在HE进展中具有双重调控作用[96]。作为肠–肝–脑轴的关键信号分子，胆汁酸稳态失衡及其受体(如FXR、TGR5、S1PR2等)的调控异常共同构成HE的核心发病机制。FXR是胆汁酸稳态的核心调控因子，在肠–肝轴中参与缓解肠道炎症、调节胆汁酸转运，并在肠–肝–脑轴间接调控脑内神经递质与胆固醇代谢，其在外周激活可减轻HE相关神经损伤，而脑内FXR的异常激活则相反，会加剧神经损伤。TGR5在肝脏、肠道及CNS中具有多重调节功能，部分研究提示其激活可通过抑制神经炎症发挥保护效应，但其在HE中的具体作用仍需进一步验证。S1PR2则介导胆汁酸诱导的神经炎症与血脑屏障损伤，在HE中发挥致病作用。此外，PXR与CAR参与毒性胆汁酸的代谢解毒，VDR通过抑制HSCs活化减轻肝纤维化，三者均间接影响HE进展。在病理状态下，胆汁酸可穿透血脑屏障，通过受体信号异常引发脑内炎症与神经毒性，形成肠–肝–脑轴的病理性循环。

然而，将上述肠–肝–脑轴机制转化为临床HE治疗策略，仍面临显著的动物模型差异与临床转化挑战。当前常用的HE动物模型(如BDL、TAA、AOM模型)虽能模拟部分病理特征，但与人类HE存在显著差异。BDL模型缺乏肝硬化典型的结节性再生，神经表型以运动障碍为主[92]；慢性TAA模型所诱导的门体分流程度有限[97]，难以完全复现临床病理特征；AOM模型则存在致癌性且对血脑屏障的破坏程度个体差异较大、稳定性不足[98]。这些局限导致部分基于受体靶点的临床前研究结论在向临床外推时受到明显制约。现阶段，直接以HE为适应证且进入临床试验阶段的胆汁酸受体靶向药物相对有限，但FXR激动剂(如OCA)、TGR5激动剂及S1PR2拮抗剂等靶向制剂的临床转化潜力已逐步明确，部分候选药物正在或已完成针对HE的早期临床试验验证。未来应进一步推动现有FXR激动剂、S1PR2拮抗剂等靶向药物的临床转化验证，同时研发组织选择性更强、不良反应更低的新型靶向制剂。

目前多种胆汁酸受体与HE的关联已初步明确，但受体间协同或拮抗的分子机制及其组织特异性调控仍待深入解析。未来研究应聚焦于肠–肝–脑轴中胆汁酸受体的交叉调控网络，明确不同受体的特异性靶点；同时，应进一步探讨肠道菌群与胆汁酸代谢互作在HE中的作用，构建多靶点协同干预策略，从而为HE的精准防治提供新方向。基于该思路形成的干预手段有望打破胆汁酸稳态失衡与肠–肝–脑轴紊乱的恶性循环，改善HE患者的临床预后。

参考文献 (References)

[[1] Higuera-de-la-Tijera F, Velarde-Ruiz Velasco J A, Raña-Garibay R H, et al. Current vision on diagnosis and comprehensive care in hepatic encephalopathy [J]. Revista de Gastroenterologia de Mexico, 2023, 88(2): 155-174.

[2] Huang D Q, Terrault N A, Tacke F, et al. Global epidemiology of cirrhosis-aetiology, trends and predictions [J]. Nature Reviews Gastroenterology & Hepatology, 2023, 20(6): 388-398.

[3] 徐小元, 丁惠国, 李文刚, 等. 肝硬化肝性脑病诊疗指南[J]. 临床肝胆病杂志, 2018, 34(10): 2076-2089.
Xu X Y, Ding H G, Li W G, et al. Guidelines for diagnosis and treatment of hepatic encephalopathy in liver cirrhosis [J]. Journal of Clinical Hepatology, 2018, 34(10): 2076-2089.

[4] 王玉洁. 肝性脑病: 肝脏与大脑的“致命对话”[J]. 肝博士, 2025(5): 25-27.
Wang Y J. Hepatic encephalopathy: the fatal dialogue between liver and brain [J]. Liver Doctor, 2025(5): 25-27.

[5] Rivera Ramos J F, Rodríguez Leal C. Review of the final report of the 1998 Working Party on definition, nomenclature and diagnosis of hepatic encephalopathy [J]. Annals of Hepatology, 2011, 10: S36-S39.

[6] Bémeur C, Butterworth R F. Liver-brain proinflammatory signalling in acute liver failure: role in the pathogenesis of hepatic encephalopathy and brain edema [J]. Metabolic Brain Disease, 2013, 28(2): 145-150.

[7] Butterworth R F. Pathogenesis of hepatic encephalopathy in cirrhosis: the concept of synergism revisited [J]. Metabolic Brain Disease, 2016, 31(6): 1211-1215.

[8] McMillin M, Frampton G, Quinn M, et al. Bile acid signaling is involved in the neurological decline in a murine model of acute liver failure [J]. The American Journal of Pathology, 2016, 186(2): 312-323.

[9] McMillin M, Frampton G, Grant S, et al. Bile acid-mediated sphingosine-1-phosphate receptor 2 signaling promotes neuroinflammation during hepatic encephalopathy in mice [J]. Frontiers in Cellular Neuroscience, 2017, 11: 191.

[10] McMillin M, Frampton G, Quinn M, et al. Suppression of the HPA axis during cholestasis can be attributed to hypothalamic bile acid signaling [J]. Molecular Endocrinology, 2015, 29(12): 1720-1730.

[11] Arab J P, Martin-Mateos R M, Shah V H. Gut-liver axis, cirrhosis and portal hypertension: the chicken and the egg [J]. Hepatology

International, 2018, 12(S1): 24-33.
[12] Dawson P A, Lan T, Rao A. Bile acid transporters [J]. Journal of Lipid Research, 2009, 50(12): 2340-2357.
[13] Hurley M J, Bates R, Macnaughtan J, et al. Bile acids and neurological disease [J]. Pharmacology & Therapeutics, 2022, 240: 108311.
[14] Perino A, Demagny H, Velazquez-Villegas L, et al. Molecular physiology of bile acid signaling in health, disease, and aging [J]. Physiological Reviews, 2021, 101(2): 683-731.
[15] Chiang J Y L, Ferrell J M. Bile acids as metabolic regulators and nutrient sensors [J]. Annual Review of Nutrition, 2019, 39: 175-200.
[16] Chiang J Y L, Ferrell J M. Bile acid metabolism in liver pathobiology [J]. Gene Expression, 2018, 18(2): 71-87.
[17] Bajaj J S, Salzman N, Acharya C, et al. Microbial functional change is linked with clinical outcomes after capsular fecal transplant in cirrhosis [J]. JCI Insight, 2019, 4(24): e133410.
[18] Alm R, Carlson J, Eriksson S. Fasting serum bile acids in liver disease. A comparison with histological features [J]. Scandinavian Journal of Gastroenterology, 1982, 17(2): 213-218.
[19] Horvatits T, Drolz A, Roedl K, et al. Serum bile acids as marker for acute decompensation and acute-on-chronic liver failure in patients with non-cholestatic cirrhosis [J]. Liver International, 2017, 37(2): 224-231.
[20] Pazzi P, Morsiani E, Vilei M T, et al. Serum bile acids in patients with liver failure supported with a bioartificial liver [J]. Alimentary Pharmacology & Therapeutics, 2002, 16(8): 1547-1554.
[21] Perez M J, Briz O. Bile-acid-induced cell injury and protection [J]. World Journal of Gastroenterology, 2009, 15(14): 1677-1689.
[22] Wang X N, Xie G X, Zhao A H, et al. Serum bile acids are associated with pathological progression of hepatitis B-induced cirrhosis [J]. Journal of Proteome Research, 2016, 15(4): 1126-1134.
[23] Bron B, Waldram R, Silk D B, et al. Serum, cerebrospinal fluid, and brain levels of bile acids in patients with fulminant hepatic failure [J]. Gut, 1977, 18(9): 692-696.
[24] Chan C Y, Huang S W, Wang T F, et al. Lack of detrimental effects of nitric oxide inhibition in bile duct-ligated rats with hepatic encephalopathy [J]. European Journal of Clinical Investigation, 2004, 34(2): 122-128.
[25] Quinn M, McMillin M, Galindo C, et al. Bile acids permeabilize the blood brain barrier after bile duct ligation in rats via Rac1-dependent mechanisms [J]. Digestive and Liver Disease, 2014, 46(6): 527-534.
[26] Xie G X, Wang X N, Jiang R Q, et al. Dysregulated bile acid signaling contributes to the neurological impairment in murine models of acute and chronic liver failure [J]. EBioMedicine, 2018, 37: 294-306.
[27] Hadjihambi A, Harrison I F, Costas-Rodríguez M, et al. Impaired brain glymphatic flow in experimental hepatic encephalopathy [J]. Journal of Hepatology, 2019, 70(1): 40-49.
[28] Weiss N, Barbier Saint Hilaire P, Colsch B, et al. Cerebrospinal fluid metabolomics highlights dysregulation of energy metabolism in overt hepatic encephalopathy [J]. Journal of Hepatology, 2016, 65(6): 1120-1130.
[29] DeMorrow S. Bile acids in hepatic encephalopathy [J]. Journal of Clinical and Experimental Hepatology, 2019, 9(1): 117-124.
[30] Simicic D, Cudalbu C, Pierzchala K. Overview of oxidative stress findings in hepatic encephalopathy: from cellular and ammonium-based animal models to human data [J]. Analytical Biochemistry, 2022, 654: 114795.
[31] Dantas Machado A C, Ramos S F, Gauglitz J M, et al. Portosystemic shunt placement reveals blood signatures for the development of hepatic encephalopathy through mass spectrometry [J]. Nature Communications, 2023, 14(1): 5303.
[32] Cheng J, Fang Z Z, Kim J H, et al. Intestinal CYP3A4 protects against lithocholic acid-induced hepatotoxicity in intestine-specific VDR-deficient mice [J]. Journal of Lipid Research, 2014, 55(3): 455-465.
[33] McMillin M, Frampton G, Tobin R, et al. TGR5 signaling reduces neuroinflammation during hepatic encephalopathy [J]. Journal of Neurochemistry, 2015, 135(3): 565-576.
[34] Butcher E L, Arthur S. Emerging roles of bile acids in neuroinflammation [J]. International Journal of Molecular Sciences, 2025, 26(23): 11301.
[35] Hu X, Yan J, Huang L, et al. INT-777 attenuates NLRP3-ASC inflammasome-mediated neuroinflammation via TGR5/cAMP/PKA signaling pathway after subarachnoid hemorrhage in rats [J]. Brain, Behavior, and Immunity, 2021, 91: 587-600.
[36] Guo C S, Xie S J, Chi Z X, et al. Bile acids control inflammation and metabolic disorder through inhibition of NLRP3 inflammasome [J]. Immunity, 2016, 45(4): 802-816.
[37] Ni C Y, Wang L P, Bai Y Y, et al. Taurochenodeoxycholic acid activates autophagy and suppresses inflammatory responses in microglia of MPTP-induced Parkinson's disease mice via AMPK/mTOR, AKT/NFκB and Pink1/Parkin signaling pathways mediated by Takeda G protein-coupled receptor 5 [J]. Free Radical Biology & Medicine, 2025, 235: 347-363.
[38] Williams E, Chu C, DeMorrow S. A critical review of bile acids and their receptors in hepatic encephalopathy [J]. Analytical Biochemistry, 2022, 643: 114436.
[39] Ye W L, Bai X J, Zhao Y, et al. Farnesoid X receptor activation alleviates hepatic encephalopathy by improving hepatic ammonia metabolism in murine models [J]. Biochimica et Biophysica Acta-Molecular Basis of Disease, 2025, 1871(5): 167750.
[40] Brito M A, Lima S, Fernandes A, et al. Bilirubin injury to neurons: contribution of oxidative stress and rescue by glycoursodeoxycholic acid [J]. Neurotoxicology, 2008, 29(2): 259-269.
[41] Stanimirov B, Đanić M, Pavlović N, et al. Gut-brain axis and bile acid signaling: linking microbial metabolism to brain function and metabolic regulation [J]. International Journal of Molecular Sciences, 2025, 26(24): 12167.
[42] Anis M A, Shahid Y, Majeed A A, et al. Microbiome and gut-liver interactions: from mechanisms to therapies [J]. World Journal of Gastroenterology, 2025, 31(40): 111409.
[43] Antonini Cencicchio M, Montini F, Palmieri V, et al. Microbiota-produced immune regulatory bile acid metabolites control central nervous system autoimmunity [J]. Cell Reports Medicine, 2025, 6(4): 102028.
[44] Nikolai A, Iwashima M. A microbial metabolite, lithocholic acid, suppresses IFN-γ and AhR expression by human cord blood $CD4^+$ T cells [PP/OL]. bioRxiv (2028-12-19) https://www.biorxiv.org/content/10.1101/491241v1.
[45] Stanisic T, Ewing E U, Lindell A, et al. Vitamin D3-VDR and vi-

tamin A-RAR affect IL-13 and IFNγ secretion from human CD4$^+$ T cells directly and indirectly via competition for their shared co-receptor RXR [J]. Scandinavian Journal of Immunology, 2025, 101(1): e13429.

[46] Chan G N Y, Hoque M T, Cummins C L, et al. Regulation of P-glycoprotein by orphan nuclear receptors in human brain microvessel endothelial cells [J]. Journal of Neurochemistry, 2011, 118(2): 163-175.

[47] Pandey S N, Goyal K, Rana M, et al. Microbiome-derived bile acids as endogenous regenerative mediators in liver repair [J]. Regenerative Therapy, 2025, 30: 681-690.

[48] Lin J, Nie Q X, Cheng J, et al. A microbial amino-acid-conjugated bile acid, tryptophan-cholic acid, improves glucose homeostasis via the orphan receptor MRGPRE [J]. Cell, 2025, 188(17): 4530-4548.e4525.

[49] Vargas-Beltran A M, Mialma-Omana S J, Vivanco-Tellez D O. Targeting gut microbiota in liver disease: a pharmacological approach for hepatic encephalopathy and beyond [J]. World Journal of Gastrointestinal Pharmacology and Therapeutics, 2025, 16(4): 110271.

[50] Aghara H, Patel M, Chadha P, et al. Unraveling the gut-liver-brain axis: microbiome, inflammation, and emerging therapeutic approaches [J]. Mediators of Inflammation, 2025, 2025: 6733477.

[51] Swann J R, Want E J, Geier F M, et al. Systemic gut microbial modulation of bile acid metabolism in host tissue compartments [J]. Proceedings of the National Academy of Sciences of the United States of America, 2011, 108(S1): 4523-4530.

[52] Ma K, Saha P K, Chan L, et al. Farnesoid X receptor is essential for normal glucose homeostasis [J]. The Journal of Clinical Investigation, 2006, 116(4): 1102-1109.

[53] Di Ciaula A, Bonfrate L, Baj J, et al. Recent advances in the digestive, metabolic and therapeutic effects of farnesoid X receptor and fibroblast growth factor 19: from cholesterol to bile acid signaling [J]. Nutrients, 2022, 14(23): 4950.

[54] 白校杰. 活化核受体FXR对生物人工肝种子细胞及肝性脑病的作用研究[D]. 开封: 河南大学, 2020.

[55] Verbeke L, Farre R, Verbinnen B, et al. The FXR agonist obeticholic acid prevents gut barrier dysfunction and bacterial translocation in cholestatic rats [J]. The American Journal of Pathology, 2015, 185(2): 409-419.

[56] Zhao Q, Dai M Y, Huang R Y, et al. Parabacteroides distasonis ameliorates hepatic fibrosis potentially via modulating intestinal bile acid metabolism and hepatocyte pyroptosis in male mice [J]. Nature Communications, 2023, 14(1): 1829.

[57] Verbeke L, Mannaerts I, Schierwagen R, et al. FXR agonist obeticholic acid reduces hepatic inflammation and fibrosis in a rat model of toxic cirrhosis [J]. Scientific Reports, 2016, 6: 33453.

[58] Verbeke L, Farre R, Trebicka J, et al. Obeticholic acid, a farnesoid X receptor agonist, improves portal hypertension by two distinct pathways in cirrhotic rats [J]. Hepatology, 2014, 59(6): 2286-2298.

[59] Azizsoltani A, Niknam B, Taghizadeh-Teymorloei M, et al. Therapeutic implications of obeticholic acid, a farnesoid X receptor agonist, in the treatment of liver fibrosis [J]. Biomedicine & Pharmacotherapy, 2025, 189: 118249.

[60] Huang F, Wang T T, Lan Y Y, et al. Deletion of mouse FXR gene disturbs multiple neurotransmitter systems and alters neurobehavior [J]. Frontiers in Behavioral Neuroscience, 2015, 9: 70.

[61] McMillin M, Grant S, Frampton G, et al. FXR-mediated cortical cholesterol accumulation contributes to the pathogenesis of type A hepatic encephalopathy [J]. Cellular and Molecular Gastroenterology and Hepatology, 2018, 6(1): 47-63.

[62] Haussler M R, Jurutka P W, Mizwicki M, et al. Vitamin D receptor (VDR)-mediated actions of 1α,25(OH)$_2$ vitamin D$_3$: genomic and non-genomic mechanisms [J]. Best Practice & Research Clinical Endocrinology & Metabolism, 2011, 25(4): 543-559.

[63] Ding N, Yu R T, Subramaniam N, et al. A vitamin D receptor/SMAD genomic circuit gates hepatic fibrotic response [J]. Cell, 2013, 153(3): 601-613.

[64] Gascon-Barré M, Demers C, Mirshahi A, et al. The normal liver harbors the vitamin D nuclear receptor in nonparenchymal and biliary epithelial cells [J]. Hepatology, 2003, 37(5): 1034-1042.

[65] Friedman S L. Hepatic stellate cells: protean, multifunctional, and enigmatic cells of the liver [J]. Physiological Reviews, 2008, 88(1): 125-172.

[66] Abramovitch S, Dahan-Bachar L, Sharvit E, et al. Vitamin D inhibits proliferation and profibrotic marker expression in hepatic stellate cells and decreases thioacetamide-induced liver fibrosis in rats [J]. Gut, 2011, 60(12): 1728-1737.

[67] 王征, 杨红, 金梦, 等. 维生素D受体对低氧下结肠细胞屏障蛋白的作用[J]. 中国医学科学院学报, 2019, 41(4): 506-511.
Wang Z, Yang H, Jin M, et al. Effects of vitamin D receptor on mucosal barrier proteins in colon cells under hypoxic environment [J]. Acta Academiae Medicinae Sinicae, 2019, 41(4): 506-511.

[68] Sun J, Zhang Y G. Vitamin D receptor influences intestinal barriers in health and disease [J]. Cells, 2022, 11(7): 1129.

[69] He X L, Hu M Y, Xu Y, et al. The gut-brain axis underlying hepatic encephalopathy in liver cirrhosis [J]. Nature Medicine, 2025, 31(2): 627-638.

[70] Morales-Galicia A E, Rincón-Sánchez M N, Ramírez-Mejía M M, et al. How the gut-liver axis shapes hepatic encephalopathy: mechanistic and therapeutic perspectives [J]. Exploration of Digestive Diseases, 2025, 4: 100597.

[71] Itzhak Y, Roig-Cantisano A, Dombro R S, et al. Acute liver failure and hyperammonemia increase peripheral-type benzodiazepine receptor binding and pregnenolone synthesis in mouse brain [J]. Brain Research, 1995, 705(1/2): 345-348.

[72] Bélanger M, Desjardins P, Chatauret N, et al. Mild hypothermia prevents brain edema and attenuates up-regulation of the astrocytic benzodiazepine receptor in experimental acute liver failure [J]. Journal of Hepatology, 2005, 42(5): 694-699.

[73] Ahboucha S, Jiang W, Chatauret N, et al. Indomethacin improves locomotor deficit and reduces brain concentrations of neuroinhibitory steroids in rats following portacaval anastomosis [J]. Neurogastroenterology and Motility, 2008, 20(8): 949-957.

[74] Cauli O, Mansouri M T, Agusti A, et al. Hyperammonemia increases GABAergic tone in the cerebellum but decreases it in the rat cortex [J]. Gastroenterology, 2009, 136(4): 1359-1367.e1-2.

[75] Sayaf K, Zanotto I, Russo F P, et al. The nuclear receptor PXR in chronic liver disease [J]. Cells, 2021, 11(1): 61.

[76] Lehmann J M, McKee D D, Watson M A, et al. The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions [J].

The Journal of Clinical Investigation, 1998, 102(5): 1016-1023.

[77] Staudinger J L, Goodwin B, Jones S A, et al. The nuclear receptor PXR is a lithocholic acid sensor that protects against liver toxicity [J]. Proceedings of the National Academy of Sciences of the United States of America, 2001, 98(6): 3369-3374.

[78] de Wit K, Beuers U, Mukha A, et al. Rifaximin stimulates nitrogen detoxification by PXR-independent mechanisms in human small intestinal organoids [J]. Liver International, 2023, 43(3): 649-659.

[79] Litwa E, Rzemieniec J, Wnuk A, et al. RXRα, PXR and CAR xenobiotic receptors mediate the apoptotic and neurotoxic actions of nonylphenol in mouse hippocampal cells [J]. The Journal of Steroid Biochemistry and Molecular Biology, 2016, 156: 43-52.

[80] Stedman C A, Liddle C, Coulter S A, et al. Nuclear receptors constitutive androstane receptor and pregnane X receptor ameliorate cholestatic liver injury [J]. Proceedings of the National Academy of Sciences of the United States of America, 2005, 102(6): 2063-2068.

[81] Lickteig A J, Csanaky I L, Pratt-Hyatt M, et al. Activation of constitutive androstane receptor (CAR) in mice results in maintained biliary excretion of bile acids despite a marked decrease of bile acids in liver [J]. Toxicological Sciences, 2016, 151(2): 403-418.

[82] Beilke L D, Aleksunes L M, Holland R D, et al. Constitutive androstane receptor-mediated changes in bile acid composition contributes to hepatoprotection from lithocholic acid-induced liver injury in mice [J]. Drug Metabolism and Disposition, 2009, 37(5): 1035-1045.

[83] Miao J, Fang S, Bae Y, et al. Functional inhibitory cross-talk between constitutive androstane receptor and hepatic nuclear factor-4 in hepatic lipid/glucose metabolism is mediated by competition for binding to the DR1 motif and to the common coactivators, GRIP-1 and PGC-1alpha [J]. The Journal of Biological Chemistry, 2006, 281(21): 14537-14546.

[84] Li T, Chiang J Y L. Bile acid signaling in metabolic disease and drug therapy [J]. Pharmacological Reviews, 2014, 66(4): 948-983.

[85] Saini S P S, Sonoda J, Xu L, et al. A novel constitutive androstane receptor-mediated and CYP3A-independent pathway of bile acid detoxification [J]. Molecular Pharmacology, 2004, 65(2): 292-300.

[86] Sepehrinezhad A, Shahbazi A. Linking brain and immune transcriptomes to gut-derived metabolites in hepatic encephalopathy: an explorative integrative multi-omics approach [J]. Hepatic Medicine: Evidence and Research, 2025, 17(1): 105-124.

[87] 林镛, 李炯汾, 李飞燕, 等. 肠–脑轴神经免疫通信在肝性脑病发病机制中的作用[J]. 临床肝胆病杂志, 2024, 40(12): 2518-2523.
Lin Y, Li J F, Li F Y, et al. Role of gut-brain axis neuroimmune communication in the pathogenesis of hepatic encephalopathy [J]. Journal of Clinical Hepatology, 2024, 40(12): 2518-2523.

[88] Kawamata Y, Fujii R, Hosoya M, et al. A G protein-coupled receptor responsive to bile acids [J]. The Journal of Biological Chemistry, 2003, 278(11): 9435-9440.

[89] Keitel V, Görg B, Bidmon H J, et al. The bile acid receptor TGR5 (Gpbar-1) acts as a neurosteroid receptor in brain [J]. Glia, 2010, 58(15): 1794-1805.

[90] Yanguas-Casás N, Barreda-Manso M A, Nieto-Sampedro M, et al. TUDCA: an agonist of the bile acid receptor GPBAR1/TGR5 with anti-inflammatory effects in microglial cells [J]. Journal of Cellular Physiology, 2017, 232(8): 2231-2245.

[91] Keitel V, Stindt J, Häussinger D. Bile acid-activated receptors: GPBAR1 (TGR5) and other G protein-coupled receptors [J]. Handbook of Experimental Pharmacology, 2019, 256: 19-49.

[92] Claeys W, van Hoecke L, Geerts A, et al. A mouse model of hepatic encephalopathy: bile duct ligation induces brain ammonia overload, glial cell activation and neuroinflammation [J]. Scientific Reports, 2022, 12(1): 17558.

[93] Arenas Y M, Balzano T, Ivaylova G, et al. The S1PR2-CCL2-BDNF-TrkB pathway mediates neuroinflammation and motor incoordination in hyperammonaemia [J]. Neuropathology and Applied Neurobiology, 2022, 48(4): e12799.

[94] Studer E, Zhou X Q, Zhao R P, et al. Conjugated bile acids activate the sphingosine-1-phosphate receptor 2 in primary rodent hepatocytes [J]. Hepatology, 2012, 55(1): 267-276.

[95] Kageyama Y, Ikeda H, Watanabe N, et al. Antagonism of sphingosine 1-phosphate receptor 2 causes a selective reduction of portal vein pressure in bile duct-ligated rodents [J]. Hepatology, 2012, 56(4): 1427-1438.

[96] Chen Z F, Ruan J S, Li D H, et al. The role of intestinal bacteria and gut-brain axis in hepatic encephalopathy [J]. Frontiers in Cellular and Infection Microbiology, 2020, 10: 595759.

[97] El-Mansoury B, Smimih K, El Khiat A, et al. Short working memory impairment associated with hippocampal microglia activation in chronic hepatic encephalopathy [J]. Metabolites, 2024, 14(4): 193.

[98] DeMorrow S, Cudalbu C, Davies N, et al. 2021 ISHEN guidelines on animal models of hepatic encephalopathy [J]. Liver International, 2021, 41(7): 1474-1488.