

· 综述 ·

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基于中医阴阳学说探讨胆汁酸/短链脂肪酸代谢紊乱与肝性脑病的关系

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摘要: 肝性脑病是继发于严重肝脏疾病的神经精神综合征。近年研究表明, 肝性脑病的发生与胆汁酸/短链脂肪酸代谢紊乱密切相关。阴阳学说作为中医学理论的核心, 为阐释胆汁酸-短链脂肪酸与肝性脑病的关系提供了独特视角。胆汁酸功能类阳, 主疏泄、助代谢; 短链脂肪酸属阴, 安内守藏, 维系肠系屏障、抗御炎毒。二者在生理状态下相互制约、互根互用, 共同调控“肠-肝-脑轴”动态平衡。基于此, 通过调节胆汁酸与短链脂肪酸的代谢失衡, 有望从中西医协同角度恢复肝性脑病患者的阴阳动态平衡。

关键词: 肝性脑病; 阴阳学说; 胆汁酸类; 脂肪酸类

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Association between bile acid/short-chain fatty acid metabolic disorders and hepatic encephalopathy based on the traditional Chinese medicine theory of Yin and Yang

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Abstract: Hepatic encephalopathy is a neuropsychiatric syndrome secondary to severe liver disease. Recent studies have shown that the development of hepatic encephalopathy is closely associated with bile acid/short-chain fatty acid metabolic disorder. As the core theory of traditional Chinese medicine, the theory of Yin and Yang provides a unique perspective for analyzing the association between bile acids/short-chain fatty acids and hepatic encephalopathy. Bile acids function like Yang, governing the free flow of Qi and assisting in metabolic processes, while short-chain fatty acids belong to Yin, maintaining internal stability and conservation, preserving the intestinal barrier, and combating inflammation and toxins. Bile acids and short-chain fatty acids constrain each other and are interdependent to regulate the dynamic equilibrium of the gut-liver-brain axis. On this basis, by regulating the metabolic imbalance of bile acids and short-chain fatty acids, it is expected to restore the dynamic balance of Yin and Yang in patients with hepatic encephalopathy under the synergistic intervention of traditional Chinese medicine and Western medicine.

Key words: Hepatic Encephalopathy; Yin Yang Theory; Bile Acid; Fatty Acids

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肝性脑病是指由严重肝功能障碍或门静脉-体循环分流异常而引起的以代谢紊乱为基础的中枢神经系统功能紊乱综合征,临床可表现为行为异常、意识障碍甚至昏迷,严重威胁患者的生存质量^[1]。据报道,急性肝性脑病患者的1年生存率仅有42%^[2]。肝性脑病的发病机制尚未完全明确,近年来,“肠-肝-脑轴”作为肝性脑病致病机制研究的一个重要视域逐渐受到关注^[3]。中医学认为,阴阳失衡是疾病发生发展的核心病机。肠道菌群代谢物胆汁酸(bile acid, BA)与短链脂肪酸(short-chain fatty acid, SCFA)的代谢互作可类比为阴阳关系的微观体现,二者在“肠-肝-脑轴”中既相互制约又协同共生,其动态平衡的破坏可能是肝性脑病发生的关键病理环节^[4]。本研究聚焦“肠-肝-脑轴”,从理论层面系统阐释BA/SCFA在肝性脑病发病中的作用及其阴阳失衡机制,同时探讨恢复二者代谢平衡的中西医协同干预策略,为肝性脑病的发病机制研究和中西医协同防治提供新思路。

1 阴阳失衡是肝性脑病发生发展的根本

中医古籍中并无肝性脑病病名记载,可根据其意识障碍、行为异常、昏迷等临床表现,将其归属于“神昏”“肝厥”等疾病,二者病机迥异。《温病条辨》言“湿温邪入心包,神昏肢逆”,强调湿热浊毒蒙窍致神识昏愦,属肝病失治。《伤寒论》言“凡厥者,阴阳气不相顺接,便为厥;厥者,手足逆冷是也”。明确指出肝性脑病多因阴阳气机逆乱,阴阳相离或不相顺接,导致清窍失养而神志昏迷。“肝厥”属肝病致厥,其病机根于肝气横逆,《证治汇补》载“肝厥之证,状如痫疾,僵仆不醒”,描述肝风挟痰瘀上冲脑络之猝然昏仆、肢体强直,与肝性脑病急性期肝气冲逆、气血紊乱之象相应。肝性脑病即浊毒壅窍与肝气冲逆并现,终归“厥”之气血逆乱,以阴阳失衡作为疾病本质。目前多认为肝性脑病病位在脑,可涉及心肝脾肾诸脏^[5]。历代医家认为此病病性虚实夹杂,病机复杂,病属危重。

钱英教授提出肝性脑病属本虚标实之证,其核心病机在于阴阳失衡、痰瘀闭窍。盖因肝病日久,湿热毒邪蕴结肝胆,久稽不去,一则灼伤肝阴致虚风内动,二则下耗肾水使相火妄动,终致肝肾阴虚、虚阳上扰清窍,久病及肾,阳损及阴,肾阳衰微则气化失司,浊毒壅滞三焦,上蒙清窍。此阴阳互根互制之机既败,脾土失于斡旋,中州运化无权,湿浊酿生痰毒,血滞成瘀,终致痰瘀互

结、络阻窍闭^[6]。王明刚教授认为肝性脑病缘由肝体损伤,反乘脾胃,湿、痰、瘀交阻,加重肝损伤,二者互为因果,痰浊上蒙心神脑窍而为病^[7]。笔者团队则认为肝性脑病之病机本于阴阳失衡而浊毒为标,主病位在心脑,原发病位在肝,涉及肺脾肾诸脏,盖因肝失疏泄,枢机不利,致三焦气化失司,肺失宣肃、脾失健运、肾失开阖,诸脏气机逆乱则阳不制阴,阴不涵阳,虚火炼液成痰,瘀血阻络,在湿、热、痰、瘀等病邪的基础上积聚成浊,浊盛成毒,终致痰瘀浊毒壅滞血脉、上蒙清窍,则肝性脑病神昏诸症骤现^[8-9]。综上所述,肝性脑病的病机关键在于阴阳失衡,湿、热、痰、瘀互结,酿生浊毒,蒙闭清阳。

2 BA/SCFA代谢紊乱是肝性脑病发病的重要机制

2.1 BA失衡与肝性脑病 BA是肝脏以胆固醇为原料合成的一类具有消化和信号调控功能的重要代谢分子,是胆汁的主要成分之一。根据来源,BA可分为胆酸、鹅脱氧胆酸等初级BA,和经肠道菌群转化生成的脱氧胆酸、石胆酸等次级BA。近年来,BA在“肠-肝-脑轴”中的作用受到广泛关注,为肝性脑病的研究和治疗提供了新的靶点。

生理条件下,BA通过肝肠循环维持肠道稳态。其激活肠道法尼醇X受体(FXR)负反馈抑制顶端钠依赖性胆汁酸转运蛋白(apical sodium-dependent bile acid transporter, ASBT)表达,限制BA过度重吸收,维持“肝-肠轴”动态平衡^[10]。其次,其通过抑制革兰阴性菌增殖,促进有益菌定植,稳定肠道菌群稳态^[11]。此外,BA通过激活FXR信号上调occludin(闭锁蛋白)、ZO-1(闭锁小带蛋白-1)表达,维持上皮屏障完整性^[12]。在肝硬化进展为肝性脑病时,BA代谢失衡触发肠道级联损伤。代谢组学研究发现,乙型肝炎肝硬化患者血清游离BA水平显著升高,且与肝硬化的病理进展密切相关^[13]。FXR信号被抑制后,其对ASBT的负反馈作用减弱,BA重吸收效率增强,而未被重吸收的BA在革兰阴性菌作用下生成毒性次级BA,蓄积于肠道,直接损伤肠黏膜^[14]。BA蓄积通过抑制FXR活性,下调紧密连接蛋白表达,增加脂多糖(LPS)及氨易位风险,并解除对核因子 κ B(NF- κ B)通路的抑制,激活巨噬细胞分泌肿瘤坏死因子- α (TNF- α)等促炎因子,加剧肠黏膜炎症^[12,15]。此外,BA通过干扰Wnt信号通路抑制潘氏细胞分泌抗菌肽,削弱抑菌作用,并降低有益菌丰度,加剧菌群紊乱^[16]。肠道屏障的完整

性和通透性损伤促使游离氨和内毒素等易位到门静脉系统和肠外部位,引发全身性炎症风暴^[17]。

肝脏 FXR 与 SHP(小异源二聚体伴侣蛋白)结合后,负反馈抑制胆固醇 7 α -羟化酶(recombinant cytochrome P450 7A1, CYP7A1)活性,调控初级 BA 合成;同时, BSEP(胆汁酸输出泵)介导 BA 排泄至胆管,防止肝内淤积^[18]。生理浓度的 BA 激活 FXR 信号抑制 Toll 样受体 4(TLR4)/NF- κ B 通路,减少肝 Kupffer 细胞释放 TNF- α 、IL-6 等促炎因子,并抑制肝星状细胞活化,发挥抗炎及抗纤维化作用^[19]。然而,在肝性脑病阶段,BA 代谢失衡加重肝损伤。肝 FXR-SHP 代偿性激活,抑制初级 BA 合成;另一方面, BSEP 功能障碍导致毒性 BA 排泄受阻,引发肝内淤积^[18]。过量的 BA 直接损伤肝细胞膜结构,诱导线粒体氧化应激和功能障碍,触发凋亡或坏死^[20];也可激活肝 Kupffer 细胞和肝星状细胞上的 TLR4/NF- κ B 通路,释放 TNF- α 、IL-6、IL-1 β 等促炎细胞因子,加重肝损伤^[19]。肠屏障功能受损致内毒素入肝,进一步抑制 FXR 信号并下调氨代谢关键酶,导致血氨蓄积^[21]。

BA 可通过调节血脑屏障紧密连接蛋白 occludin 的磷酸化状态,维持屏障完整性,限制外周毒性入脑^[22]。此外,BA 激活脑内武田 G 蛋白偶联受体 5(Takeda G-protein coupled receptor 5, TGR5),抑制神经元中 CCL2(趋化因子配体 2)的表达,下调小胶质细胞活化并减少促炎因子释放,发挥神经保护作用^[23]。BA 代谢紊乱与高氨血症和炎症反应协同作用导致神经损伤,构成肝性脑病核心病理机制。胆汁淤积的胆管结扎大鼠模型研究发现,游离 BA 可使 Rac1(Ras 相关 C3 肉毒杆菌底物 1)激活和下游的紧密连接蛋白 occludin 磷酸化,从而破坏血脑屏障,使 BA 及肠源性 LPS 侵入中枢神经系统^[24],然而 BA 激活 Rac1 的机制尚未阐明。BA 介导 S1P2R(1-磷酸鞘氨醇受体 2)上调 CCL2 表达,进而导致小胶质细胞的激活以及促炎性细胞因子的进一步释放, TGR5 激活不足则加剧炎症级联^[25]。其次,肠道来源的氨可直接通过血脑屏障,由星形胶质细胞摄取并转化为谷氨酰胺,引发星形胶质细胞肿胀及脑水肿^[26]。氨激活小胶质细胞线粒体活性氧依赖性 NLRP3(核苷酸结合寡聚化结构域样受体蛋白 3)通路,促进 IL-1 β 释放^[27]。肠源性毒素与 BA、氨共同激活脑内炎症,最终导致神经元坏死及认知障碍。

2.2 SCFA 失衡与肝性脑病 SCFA 是肠道菌群发酵膳食纤维生成的代谢产物,主要包括乙酸、丙酸和丁酸,在维持肠道健康和全身代谢中发挥重要作用。近年研究表明, SCFA 可能通过“肠-肝-脑轴”在肝性脑病中发挥关键作用。

丁酸不仅为肠道上皮细胞提供能量,还通过激活肠道上皮细胞的 GPR41(G 蛋白偶联受体 41)和 GPR43(G 蛋白偶联受体 43)等,上调 ZO-1 和 occludin 的表达,有助于维护肠道屏障的完整性^[28]。正常情况下, SCFA 通过活化 GPR43 和调控调节性 T 淋巴细胞的功能,增强抗炎反应及抑制过度的免疫反应,并通过抑制组蛋白去乙酰化酶(histone deacetylase, HDAC)调节肠道细胞的表现遗传状态,从而控制肠道炎症和细胞周期^[29]。肝性脑病患者的肠道微生物群通常处于失调状态,乳酸菌科、瘤胃科等产 SCFA 的益生菌减少,而产氨菌、拟杆菌等致病菌增多,导致 SCFA 的生成减少^[30]。研究发现,肝性脑病患者血清中的戊酸、丁酸等 SCFA 浓度较高,而粪便中的水平则未必发生变化,表明可能由于肠道屏障功能的损伤使 SCFA 更易进入循环,肠道通透性增加使得毒性物质如氨和 LPS 通过门静脉系统进入肝脏,进一步加剧肝性脑病的病理进程^[31]。SCFA 介导的调节性 T 淋巴细胞功能抑制和 HDAC 活性失控,加剧肠道黏膜的炎症损伤。

肠道菌群来源的 SCFA 代谢紊乱与多种肝脏疾病的发病机制有关,目前针对非酒精性脂肪性肝病的研究发现其可导致肝脏炎症反应。SCFA 可维持肠道屏障完整性,减少 LPS 入肝,间接保护肝细胞免受炎症损伤。SCFA 生成减少,肠道通透性增加使 LPS 通过门静脉进入肝脏,激活肝 Kupffer 细胞和肝星状细胞上的 TLR4/NF- κ B 炎性小体通路,释放促炎细胞因子^[32]。由于 SCFA 减少,可能导致产乙醇菌过度增殖,内源性乙醇生成增加,并通过细胞色素 P450 代谢产生活性氧,直接损伤肝细胞^[33]。肝性脑病患者肠道菌群失调可能较非酒精性脂肪性肝病患者更为严重, SCFA 减少加剧上述病理过程,同时与氨等毒素的积累共同促进神经功能障碍。

SCFA 的缺乏通过多种机制加剧神经系统损伤。丁酸盐抑制 HDAC 促进紧密连接蛋白表达,对维持血脑屏障的低通透性具有关键作用^[34]。肝性脑病患者 SCFA 减少导致血脑屏障破坏,血氨、炎症因子及肠道菌群代谢产物更易进入脑组织,直接损伤星形胶质细胞和神经元功能。临床数据显示^[35],肝性脑病患者粪便氨水平无显著差异,但血脑屏障破坏可能放大氨的神经毒性效应。SCFA 通过抑制 HDAC 和激活 GPR43,下调小胶质细胞 NF- κ B 和 JNK(c-Jun 氨基末端激酶)通路磷酸化,减少促炎因子 IL-1 β 、IL-6 释放^[36]。肝性脑病患者 SCFA 减少导致小胶质细胞过度活化,引发神经炎症级联反应。SCFA 作为 HDAC 抑制剂,减少后导致 HDAC 活性升高,组蛋白乙酰化水平下降,抑制神经保护基因表达,神经元可塑性和突触功能受损,加剧认知功能障碍^[37]。

3 BA/SCFA代谢紊乱与阴阳失衡

中医阴阳学说认为,人体健康的核心在于阴阳二气的动态平衡与互根互用,阳主推动、温煦,阴主滋养、收敛,二者协调则脏腑功能调和,反之则百病丛生。肝性脑病作为终末期肝病的严重并发症,其核心病机可归结为“阴阳失衡、浊毒上犯”。BA与SCFA在生理上互为根基,病理上互为因果,二者的代谢互作失衡贯穿肝性脑病发生发展的全过程。

BA源于肝之余气,藏于胆腑,其性刚烈,主疏泄而助决渎,推荡肠胃秽浊,正如《医学见能》所言“胆者,肝之腑,属木,主升清降浊,疏利中土”,其主升发,燮理三焦气机,为阳中之少阳。SCFA生于水谷精微,其性柔润,主濡养固护络脉,滋养脏腑形骸,恰合《素问·阴阳应象大论》“阴味出下窍……味厚者为阴”,其性敛降,调和营卫气血,乃阴中之至阴。二者一阳一阴,少阳相火与太阴湿土相济,升降相因,刚柔互制,维系阴平阳秘。若少阳之火亢而无制,太阴之土衰而失荣,则阴阳乖戾,清浊混淆,浊毒内生,上犯清阳,此为肝性脑病之枢机。

中医认为,肝具有体阴用阳的特点。肝体阴主司藏血濡养、固守精微,其属阴特性通过肠道菌群衍生的SCFA实现阴血濡养之功,滋养肠黏膜屏障,并以阴主静的特性抑制炎症反应,为肝用阳提供物质基础;肝用阳主司疏泄气机、解毒化浊,其属阳特性则依赖BA激活FXR受体,通过阳主动调控代谢功能,驱动SCFA生成,形成“阴得阳助而生化无穷”的生理循环。从分子机制而言,BA的生物合成始于肝细胞内由CYP7A1介导的经典途径与CYP27A1(胆固醇27 α -羟化酶)介导的替代途径,这一过程以胆固醇为原料,经阳化气作用转化为具有表面活性的两性分子^[38]。初级BA进入肠道后,经菌群代谢为次级BA,不仅通过激活FXR、TGR5受体调控糖脂代谢及炎症反应,体现阳主温煦的生理功能,还选择性抑制肠道致病菌并促进有益菌增殖,间接增强菌群对膳食纤维的发酵能力,从而增加SCFA生成,即“阳生阴长”。SCFA作为膳食纤维的菌群代谢产物,不仅是结肠上皮细胞的主要能量来源,还可通过激活GPR41/43受体增强肠上皮紧密连接蛋白ZO-1和occludin表达,维持肠屏障完整性,体现阴主濡养的生理功能,同时抑制HDAC活性以减少促炎因子释放,拮抗BA过度激活的炎症反应,即“阴制阳亢”。在正常生理状态下,BA与SCFA通过“FXR-GLP1轴”与“GPR43-CYP7A1轴”形成负反馈调节:BA激活肠道FXR促进GLP-1(胰高血糖素样肽-1)分泌以刺激SCFA生成,而SCFA通过激活GPR43信号抑制CYP7A1,

反馈减少BA合成^[39-41]。二者为阴阳双方,既相互制约又相互促进,参与维持“肠-肝-脑轴”稳态。然而,当肝病进展至肝性脑病时,BA与SCFA阴阳失衡,表现为阴阳对立制约失衡、互根互用失衡、消长失衡以及发生阴阳转化。

肝性脑病阴阳失衡,根源于少阳相火亢盛劫阴与太阴湿土虚衰不制之阴阳对立制约失衡。肠道为病机之始,少阳属阳,其性燔灼升发,若肝失疏泄,相火妄动,燔灼肠腑,劫夺太阴脾土,则SCFA生化衰微,肠道营卫失守,腠理洞开,湿热浊毒胶结中焦,此即“阳亢阴损”。肝胆为肝性脑病枢机之要,中医认为“肝体阴而用阳”,肝阴不足则阴不敛阳,相火炼液成痰,血络凝滞,痰瘀互结,终致癥瘕内生,加重肝脏炎症及纤维化损害。脑络为肝性脑病终末之变,少阳火毒携湿热浊邪上蒙清窍,太阴精微衰极不升,清阳陷而浊阴逆,髓海失养,神明失守,终致“浊毒蒙窍,阴阳离决”之危象,出现肝性脑病神识昏蒙的临床症状。少阳与太阴本应制约平衡,今阳亢无阴可守,阴衰无制阳之能,对立制约机制崩溃,三焦气机壅塞。

中医认为阴阳互根,即孤阴不生、独阳不长。BA属少阳之精,SCFA为太阴之血,二者本应精血同源,少阳之精有赖太阴之血濡润以制其燥烈,太阴之血需少阳之精温煦以资生化。然肝病日久,少阳相火亢而无制,劫夺太阴脾土之阴血,抑制SCFA生化,肠道阴精枯涸,营卫失守,湿热浊毒蕴结。太阴血虚则肝络失养,精不归位,相火挟痰瘀化毒,血络凝滞成癥,阴不涵阳,终致肝脏癥瘕之顽疾。精不化血,血不荣精,阴阳互根互用失职,精血俱竭,少阳火毒上冲髓海,太阴精微不升,神明失守。

肝性脑病病程进展中BA/SCFA二者对立制约、互根互用失衡可导致二者动态消长失衡。《素问·六微旨大论》云“亢则害,承乃制”,生理状态下BA与SCFA二者之间保持阳生阴长以资化源。然肝病传变,一方面,少阳相火亢极无制,陷太阴湿土于下,太阴虚极,水谷不归正化,而生秽浊,致肠道湿浊蒸腾,SCFA生化不及,营阴衰微;另一方面,湿浊壅遏中焦,反遏脾阳,致肝络痰瘀凝滞,阴不涵阳,相火挟浊毒上窜,炼液为痰,痰湿瘀毒痼结肝络,三焦气化逆乱,清阳不升则髓海失濡,浊阴不降则脑窍蒙蔽,症见神识昏蒙,正如《灵枢·五乱》载“清浊相干,乱于头则为厥逆”。肝性脑病传变中,少阳升发无制,太阴敛降失司,阳长阴消终致气机逆乱。

肝性脑病的终末阶段,BA与SCFA的阴阳失衡核心在于阴阳属性发生逆转。《素问·阴阳应象大论》云“重阴必阳,重阳必阴”,少阳相火本属阳热,然其亢盛至极,气化失司,阳热毒邪无法通过正常代谢途径疏泄,反因“亢

则害”而化为阴浊,致毒性次级 BA 的淤积,与痰瘀胶结深伏三焦血分,即为“阳毒入阴”。太阴湿土本属阴柔,然其虚极衰败,阴精枯竭,失却濡润之性,反因“阴损及阳”而生燥火,导致“阴竭化燥”。BA/SCFA 阴阳转化的本质在于二者阴阳动态平衡的彻底崩溃:少阳火毒因无阴制阳而由实转虚,阳热之性逆变为阴浊之毒;太阴湿土因无阳化气而由润转燥,阴柔之质转化为焚阴之火,终致阴阳离决,少阳火毒化为蒙蔽清窍之阴浊,太阴燥火反成灼伤髓海之阳邪。

肝性脑病病机演变以“肠-肝-脑轴”为传变枢纽,始自肠道少阳相火亢盛,燔灼太阴湿土,致湿热蕴结、阳亢阴损,清阳不升而浊阴不降;继则病传于肝,肝体失于太阴阴血濡润,相火挟湿热浊毒炼液成痰,瘀阻肝络,导致痰瘀化火、阴不制阳;终致浊毒循三焦上蒙清窍,阴阳离决,神明失守(图1)。

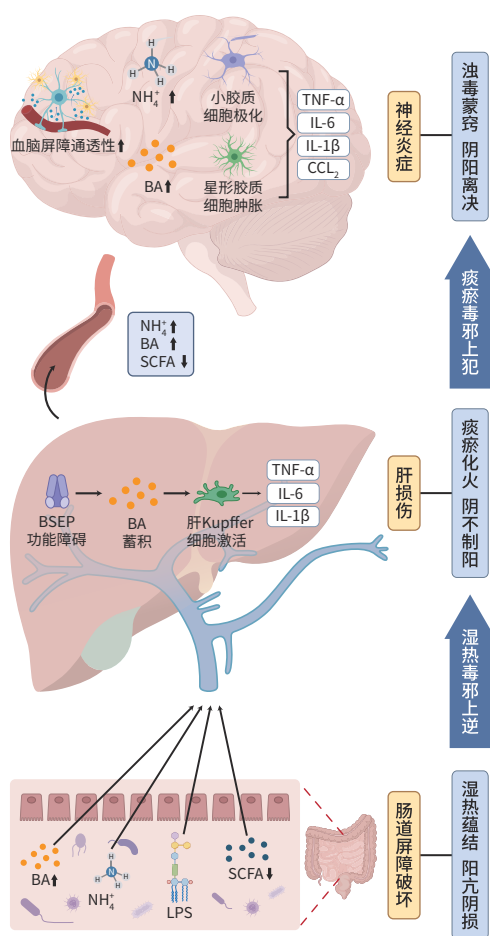


图1 中医阴阳失衡视域下BA/SCFA代谢紊乱与肝性脑病的关系

Figure 1 The relationship between BA/SCFA metabolism disorder and hepatic encephalopathy from the perspective of yin-yang imbalance in traditional Chinese medicine

此外,肝性脑病的发病不仅与BA/SCFA核心阴阳失衡相关,更受个体差异因素的调控。先天禀赋如FXR、CYP7A1等基因多态性可致少阳相火升发无制或太阴湿土生化无权,形成阳亢阴损的体质偏颇,表现为BA代谢亢进或SCFA生成不足。后天调摄如高脂饮食、酗酒等习惯,助湿生热,劫夺脾阴,加剧少阳相火燔灼肠道、抑制太阴湿土运化,湿热浊毒壅塞三焦;而久坐少动、昼夜节律紊乱则通过气机郁滞、阳不入阴进一步破坏少阳与太阴的动态平衡。个体差异因素与核心病机交互作用,先天禀赋奠定阴阳失衡之基,后天失养加速肝性脑病病程,终致“肠-肝-脑轴”清浊逆乱、神明蒙蔽,可为HE的个体化防治提供理论依据。

在治疗学层面,恢复BA与SCFA的阴阳平衡展现出广阔前景。针对“阳亢”,现代医学采用熊去氧胆酸等亲水性BA置换毒性BA,或使用奥贝胆酸等FXR激动剂恢复代谢稳态^[42-43];针对“阴亏”,补充丁酸盐可直接增加SCFA,修复肠屏障。最新研究表明,含有低聚果糖的益生元制剂通过促进双歧杆菌等有益菌增殖,提升粪便丁酸水平以滋阴,又竞争性抑制7 α -脱羟酶活性,降低脱氧胆酸浓度以潜阳,这种双向调节作用印证了中医“治阴不忘阳,调阳必顾阴”的治疗原则^[44]。针对肝性脑病阳亢阴衰为本,湿、热、痰、瘀、毒互结为标的病机,治疗当以“通腑泻浊、调和阴阳”为核心,可选用由大黄、乌梅组成的大黄煎剂进行辨证施治。目前,大量研究证实,大黄煎剂保留灌肠治疗肝性脑病效果显著^[45]。方中大黄苦寒沉降,善入阳明胃肠,通腑泻热、逐瘀解毒,专攻肠腑湿热浊毒之壅滞,荡涤燥屎、疏利胆腑,使阳毒从下而泄;乌梅酸涩柔润,滋阴生津、敛肝和胃,既缓大黄峻下之性以防伤正,又酸甘化阴以滋被灼之阴液,柔肝体而制肝用。二者刚柔相济,大黄泻湿热痰瘀,乌梅补阴液亏耗,共奏清热不伐胃、通下不伤阴之效,使三焦气机得畅,痰瘀浊毒分化,阴阳渐归平衡,体现中医“祛邪扶正、标本兼顾”的治疗思想。药理学研究显示,大黄中大黄素等蒽醌类成分可激活肠道FXR信号通路,减少BA重吸收,降低血氨及内毒素水平^[46];其抗炎作用通过调控TLR4/NF- κ B等多条信号通路减轻神经炎症,修复血脑屏障^[47]。乌梅富含咖啡酸等有机酸类成分,能调节肠道菌群稳态,促进产SCFA肠道菌群增殖,进而增加SCFA含量,修复肠黏膜紧密连接蛋白^[48];乌梅提取物的生物活性成分梅素可抑制小胶质细胞过度活化,降低脑内IL-1 β 、TNF- α 等阳毒^[49]。二者协同减少BA、氨和内毒素等毒性物质生成,增加SCFA生成,同时修复肠肝屏障、调节神经炎症,从多层次打破肝性脑病病情进展中BA/SCFA的恶性循环。

4 小结与展望

现代医学认为,BA/SCFA代谢紊乱是肝性脑病发生发展的重要因素。生理状态下,属阳的BA与属阴的SCFA通过“肠-肝-脑轴”协同调控代谢稳态;病理条件下,BA异常蓄积而SCFA合成不足,二者失衡通过激活小胶质细胞引发神经炎症级联反应,与中医“阴阳失衡”的病机本质深度契合。基于BA与SCFA代谢紊乱,肝性脑病的关键病机可概括为二者阴阳对立制约、互根互用、消长、转化失衡,湿、热、痰、瘀互结,酿生浊毒,上犯清阳,病理传变以“肠-肝-脑轴”为枢纽,表现为肠道湿热蕴结、肝络痰瘀化火、髓海浊毒蒙蔽的三焦逆乱过程。

笔者团队前期已研究探讨肝性脑病与BA代谢之间的关系及大黄煎剂的干预效应^[50],揭示肝性脑病和轻微型肝性脑病中BA代谢紊乱表现为初级BA减少、未结合BA增加及FXR信号异常,大黄煎剂通过调节肠道菌群结构、恢复结合BA水平、抑制FXR过度激活等多途径,改善BA代谢紊乱,减轻肝损伤和神经炎症,从而发挥对肝性脑病的干预作用。未来研究将继续探索肝性脑病与SCFA的关系,并通过构建肝性脑病体内外模型,深入探讨二者之间的阴阳平衡关系,以期促进肝性脑病的防治,推动中医药理论与现代科技的深度融合。

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