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Hans汉斯

# 微生物群肠脑轴与酒精依赖综合征的研究进展

**魏　巍[1*]，杨　朔[1*]，卢晓筱[1,2]，张　柠[1]，张旭兰[3,4]，黎　宽[1]，连心情[1]，徐冲冲[1]，钟树荣[1,5#]**

[1]昆明医科大学法医学院，云南　昆明
[2]北京通达首诚司法鉴定所，北京
[3]昆明医科大学附属精神卫生中心，云南　昆明
[4]云南省精神病医院，云南　昆明
[5]昆明医科大学司法鉴定中心，云南　昆明

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## 摘　要

**酒精依赖综合征是一种较为严重的精神疾病，导致患者躯体受损，心理改变，甚至危害社会等。研究表明，酒精依赖综合征患者由于长期饮酒，导致肠道内微生物的种类和数量发生明显变化，诱发机体免疫炎症等反应，影响情绪和认知，增加患者对酒精的渴求，导致患者躯体和精神的依赖。研究表明，“微生物群－肠－脑轴”在酒精依赖综合征的发生发展过程中发挥着重要作用，有望成为酒依赖治疗的新靶点。本文结合国内外最新的研究进展，首先综述了微生物群－肠－脑的概念及相互作用，其次阐述了微生物群－肠－脑轴与酒精依赖综合征的研究进展，为酒精依赖的预防和治疗提供新思路。**

## 关键词

**酒精依赖综合征，肠道微生物，微生物群－肠－脑轴**

# Advances in Microbiota-Gut-Brain Axis and Alcohol Dependence Syndrome

**Wei Wei[1*], Shuo Yang[1*], Xiaoxiao Lu[1,2], Ning Zhang[1], Xulan Zhang[3,4], Kuan Li[1], Xinqing Lian[1], Chongchong Xu[1], Shurong Zhong[1,5#]**

[1]School of Forensic Medicine, Kunming Medical University, Kunming Yunnan
[2]Beijing Tongda Shoucheng Institute of Forensic Science, Beijing
[3]Mental Health Center Affiliated to Kunming Medical University, Kunming Yunnan
[4]The Mental Hospital of Yunnan Province, Kunming Yunnan
[5]Judicial Identification Center of Kunming Medical University, Kunming Yunnan

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[*]共一作者。
[#]通讯作者。

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## Abstract

**Alcohol dependence syndrome is a serious mental disease, which leads to physical damage, psychological change, and even harms the society. Studies have shown that long-term drinking in patients with alcohol dependence syndrome will lead to significant changes in the type and number of gut microbiota, induce immune inflammation and other reactions, affect emotion and cognition, increase patients' thirst for alcohol, and lead to physical and mental dependence of patients. Studies have shown that the "Microbiota-Gut-Brain Axis" plays an important role in the occurrence and development of alcohol dependence syndrome, and is expected to become a new target for the treatment of alcohol dependence. Based on the latest research progress at home and abroad, this paper firstly reviewed the concept and interaction of Microbiota-Gut-Brain Axis, and then described the research progress of Microbiota-Gut-Brain Axis and alcohol dependence syndrome, providing new ideas for the prevention and treatment of alcohol dependence.**

## Keywords

**Alcohol Dependence Syndrome, Gut Microbiota, Microbiota-Gut-Brain Axis**



## 1. 引言

酒精依赖综合征(Alcohol Dependence Syndrome, ADS)，也称为酒精依赖、酒精成瘾、酒精中毒等，指反复大量饮酒引起的一系列行为、认知和生理现象，表现为对酒精的渴求和经常需要饮酒的强迫性体验，可连续或间断出现，停止饮酒常出现戒断症状，恢复饮酒则症状消失，是饮酒导致的精神和躯体依赖[1]。研究表明，ADS 是遗传和环境因素共同作用的一种复杂疾病[2]。肠道作为人体重要的消化吸收器官，与人体的健康息息相关。随着人类微生物组计划(Human Microbiome Project, HMP)第二阶段研究的完成，人们发现肠道中的微生物对人体健康有着重要的影响[3]。越来越多的研究表明，肠道菌群紊乱与机体多种疾病存在相关性，如肥胖[4]、糖尿病[5]、心血管疾病[6]、帕金森病[7]、焦虑[8]、抑郁[9]、精神分裂症[10]、阿尔茨海默病[11]、自闭症[12]等。肠道和大脑之间存在着复杂的双向交流，对疾病的产生有重要影响。因此了解微生物群－肠－脑轴的作用机制，有助于我们对 ADS 的深入了解与研究，对酒依赖的预防和治疗具有重要意义。本文就微生物群－肠－脑轴与酒依赖综合征的研究进展作一综述。

## 2. 微生物群－肠－脑轴

肠道微生物群(Gut microbiota)，又称为肠道菌群，是指肠道内与之共生的微生物群，由影响正常生理和改变宿主对疾病易感性的数以万亿计的微生物组成[13]，包括细菌、古细菌、病毒和噬菌体等[14]。肠道与肠道共生的微生物群落构成了复杂的微生态系统，不论在数量上还是种类上都维持着相对稳定的状态。肠道微生物群的组成在生命初期建立，受个体遗传、母亲垂直传播、饮食、胃肠道感染、精神压力和包括抗生素在内的药物等多因素影响。肠道微生物通过分解食物中复杂的多糖来影响人体代谢，除此之外，肠道微生物还能调节肠道屏障系统功能、肠道蠕动和脂肪分布，防止病原菌定植以及利用肠道相关淋巴组织影响免疫功能[15]。

肠道微生物群、肠道以及大脑共同构成了微生物群－肠－脑轴(Microbiota-Gut-Brain Axis, MGB 轴)[16]。研究表明，微生物群－肠－脑轴是一个复杂的双向交流系统。肠道微生物群及其代谢物不仅可以通过免疫和内分泌等多种途径影响肠神经系统，也可通过迷走神经、免疫以及下丘脑－垂体－肾上腺轴等对中枢神经系统发挥调控作用[17] [18]。此外，中枢神经系统及肠神经系统也会发挥调控作用影响肠道微生物的功能和组成。中枢神经系统对肠道微生物的影响作用途径主要包括两条，一条是直接途径，通过信号分子释放直接作用肠道固有层细胞，中枢系统可控制肠神经系统的神经元、免疫细胞、肠嗜铬细胞等分泌的儿茶酚胺、5-羟色胺等物质进入肠腔，进而影响肠道微生物的种类和数量[19]。另一条是间接途径，通过调节胃肠蠕动和分泌功能调节肠道微生物组成[20]。

### 2.1. 微生物对肠神经系统的影响

在哺乳动物中，肠神经系统由镶嵌于肠道内壁数以百万计的神经元和神经胶质细胞组成[21]。研究表明，无菌小鼠肠神经系统的数量及其形成的网络复杂性严重减少。当给无菌小鼠移植正常的肠道微生物群 4 周后，可观察到粘膜肠神经系统网络的数量和复杂性显着增加[22]。De Vadder 等[23]研究表明，无菌小鼠表现出未成熟的肠道神经系统，但将正常小鼠的粪菌移植到无菌小鼠后，肠道微生物群将通过影响 5-HT 的释放，作用于肠神经元的 5-羟色氨 4 受体(5-HTR4)促进肠道神经系统的成熟。肠神经系统可以调节肠道蠕动，肠道微生物也可以通过短链脂肪酸等代谢产物刺激肠神经系统，进而影响肠道蠕动[24]。肠道微生物及其代谢物可通过免疫和内分泌等多种途径影响肠神经系统。

### 2.2. 微生物对中枢神经系统的影响

肠道微生物群组成在个体之间变化很大，肠道微生物的组成改变可能会影响神经递质 γ-氨基丁酸产生以及发酵产物短链脂肪酸产生。以上证据表明，肠道微生物组成改变可能与神经系统正常功能变化有关，这种途径包括迷走神经传入、免疫和 HPA 轴调控。

#### 2.2.1. 迷走神经通路

迷走神经由大约 80%的传入神经构成，控制几个器官的功能，如调节心率和胃肠运动。其主要收集从食道到结肠的感觉信号，传入到中枢神经系统。Lyte 等[25]研究发现，将枸橼酸杆菌(*Citrobacter*)移植到小鼠胃肠道一段时间后，小鼠表现出明显焦虑样行为，并且在此阶段机体主要免疫反应尚未发挥作用。此后的研究[26]发现，枸橼酸杆菌(*Citrobacter*)可增加迷走神经通路活性，快速激活孤束核和外侧旁核及杏仁核等内脏感觉和焦虑的大脑区域。实验结果表明，神经系统可以感知肠道急性变化以及识别病原体存在。切断迷走神经能够消除微生物调节的行为改变。Bravo 等[17]研究发现，切断老鼠的迷走神经，用益生菌进行治疗，未发现受试老鼠行为改变，同时将双歧杆菌(*Bifidobacterium*)移植到迷走神经切断的大鼠体内，其行为也未发生改变。只有在完整的迷走神经系统存在的前提下，乳酸杆菌(*Lactobacillus*)才可对小鼠的神经生物学和行为产生影响[27]。进一步证实了迷走神系统在微生物－肠－脑轴中的重要性。

#### 2.2.2. 免疫系统通路

进入机体的微生物都有免疫原性，会被人体免疫系统识别诱发各种免疫反应。人类经过数千万年进化，肠道微生物达到了平衡状态，可以与机体共生，也可以识别病原体激活免疫反应。神经系统与免疫系统有不断的双向交流，以至于微生物对神经系统的影响不能脱离免疫系统[28]。微生物在肠道内将膳食纤维分解代谢成短链脂肪酸(SCFA)调节肠道适应性免疫反应[29]，并在调节中枢神经系统功能中发挥关键作用[30]。MacFabe 等[31]将 SCFAs 直接注入啮齿类动物大脑并检测其行为，发现丙酸可增加损害社会的行为，而丁酸可减少抑郁样行为，同时组蛋白乙酰化和脑源性神经营养因子(BDNF)表达也发生变化

[32]。许多实验观察到肠道微生物群多样性越高，免疫水平越稳定；肠道微生物群多样性越低，免疫水平越不稳定，共生细菌可以改变免疫系统反应[33]。

#### 2.2.3. 下丘脑－垂体－肾上腺轴(HPA 轴)调控

众所周知，HPA 轴对学习和记忆功能非常重要，当 HPA 轴紊乱时可导致海马记忆功能损害，因此 HPA 轴也是微生物影响中枢的重要途径。日本一项研究表明，肠道早期暴露于特定微生物群会减少成年无菌小鼠 HPA 轴过度反应[34]。饲喂益生菌可以减弱 HPA 轴对压力的反应[35]。Tillisch 等[36]通过核磁共振检查发现，女性受试者饮用含有益生菌的酸奶后，控制脑记忆和感觉处理脑区域的内在活动发生了改变。同时 Messaoudi 等[37]在实验中也发现，健康成年人服用益生菌后情绪可获得改善，同时尿皮质醇水平减低。Sudo [38]等人利用无菌小鼠模型证实了肠道微生物群对行为和大脑化学的影响，实验中雄性无菌小鼠表现出 HPA 轴应激反应升高。HPA 轴在应激暴露期间激活下丘脑释放促肾上腺皮质激素释放激素(CRH)，HPA 轴激活导致糖皮质激素释放，糖皮质激素显著增高又可进一步影响胃肠生理。

### 2.3. 中枢神经系统对肠道微生物的影响

肠道微生物可以影响肠神经系统和中枢神经系统功能，同时肠神经系统和中枢神经系统也会发挥调控作用影响肠道微生物的功能和组成。中枢神经系统对肠道微生物的影响作用途径主要包括两条，一条是直接途径，通过信号分子释放直接作用肠道固有层细胞，中枢系统可控制肠神经系统的神经元、免疫细胞、肠嗜铬细胞等分泌的儿茶酚胺、5-羟色胺等物质进入肠腔，进而影响肠道微生物的种类和数量。另一条是间接途径，通过调节胃肠蠕动和分泌功能调节肠道微生物组成。

当机体情绪发生变化时，肠道微生物的种类和数量也会发生变化。交感神经和副交感神经、HPA 轴及调节疼痛不适的内源性通路组成一个系统，不论是单独或者组合激活该系统组份，都可改变肠道环境，进一步影响肠道微生物群的种类和数量。肠道微生物群主要寄生在肠黏液层，而上述系统对肠黏液层形成至关重要，从而直接或间接改变肠道微生物群的定植。Alverdy [39]等证实外科手术创伤引起去甲肾上腺素进入肠腔后，铜绿假单胞杆菌(*Pseudomonas aeruginosa*)繁殖速度迅速增加，导致机体出现脓毒血症。Demaude [40]等通过研究发现，在压力刺激下，肠道胶质细胞和肥大细胞被激活，产生过量 TNF-γ，使紧密连接蛋白含量降低减弱肠上皮细胞的屏障作用，肠道上皮细胞渗透性增加，细菌进入肠道上皮触发肠道黏膜层免疫反应。出生后与母亲分离的子代动物表现出焦虑的同时伴随乳酸杆菌(*Lactobacillus*)水平下降，机体抵抗力也弱于正常对照组，Bailey 等[41]推测出现这种现象的原因可能是出生不久的子代动物与母亲分离后产生应激反应，导致肠蠕动加快，乳酸杆菌(*Lactobacillus*)排除增多导致。

以上研究证明胃肠道与大脑之间存在持续双向信息交流，一旦这个强大的网络出现差错，将导致机体疾病产生。

## 3. MGB 轴和 ADS

ADS 患者肠道菌群紊乱，有益菌减少，有害菌增多。伴随肠通透性的增加，有害代谢物从肠道进入外周血液循环，甚至进入中枢神经系统，对人体造成进一步的损害。

### 3.1. ADS 肠道微生物群及其代谢物发生改变

Dubinkina 等[42]对 ADS 患者肠道微生物进行宏基因组测序分析发现，ADS 患者瘤胃球菌(*Ruminococcus*)显著增加($P < 0.05$)，粪便杆菌(*Faecalibacterium*)和阿克曼氏菌(*Akkermansia*)明显减少($P < 0.05$)。Mutlu 等[43]将健康对照组与有或没有肝病的酒精中毒者进行比较研究发现，酒精中毒者肠道微生物组中拟杆菌属(*Bacteroidetes*)的丰度显著低于健康对照组($P = 0.035$)，而变形杆菌属(*Proteobacteria*)丰度

则明显高于健康对照组($P = 0.001$)。而动物模型的研究结果则与人的不同，Kosnicki 等[44]对酒精消耗大鼠和健康对照大鼠肠道微生物进行 $\alpha$ 多样性和 $\beta$ 多样性比较发现，对照组具有比酒精消耗组大鼠更高的物种丰富度和系统发育多样性，食用酒精的大鼠肠道微生物群的生物多样性显著下降(加权 UniFrac, $P = 0.033$)，同时，酒精消耗大鼠特定微生物的相对丰度在门水平和属水平均存在显著的差异，在门水平上表现为厚壁菌门(*Firmicutes*)的相对减少($P < 0.05$)和拟杆菌门(*Bacteroidetes*)的相对增加($P = 5.1E{-}05$)，在属水平上，则表现为乳酸杆菌属(*Lactobacillus*)的明显降低($P = 4.9E{-}12$)。ADS 患者除了肠道微生物群组成发生改变外，肠道中的代谢物也会发生显著的改变。Leclercq 等人[45]的研究表明，酒依赖患者与健康人群的肠道代谢物存在显著的差异($P < 0.05$)。在酒依赖患者中醇类、酚类、吲哚类、烷烃类和苯类代谢物显著高于健康人群。一项针对慢性过度酒精消费者的研究提示，慢性过度酒精消费者肠道中的丁酸盐的含量显著低于健康人群，相关性分析表明，粪杆菌属(*Faecalibacterium*)丰度与丁酸盐水平呈正相关($r = 0.4$, $P = 0.05$)，而变形杆菌属(*Protebacterium*)的丰度与丁酸盐水平呈负相关($r = -0.61$, $P = 0.002$) [46]。

### 3.2. ADS 患者肠通透性改变

在一项针对酒依赖患者与健康对照人群的研究中，Leclercq 等人[45]采用乙二胺四乙酸的检测方法来判断酒依赖患者的肠道通透性，结果表明酒依赖患者的肠道通透性显著高于健康人群($P < 0.001$)。Donnadieu-Rigole 等[47]的研究结果显示，戒酒前酒精使用障碍患者连蛋白(Zonulin)和脂肪酸结合蛋白(I-FABP)的血浆水平显著高于健康对照组($P < 0.001$); 而戒酒 6 周后，二者的血浆水平显著下降($P < 0.05$)。结果提示酒精使用障碍患者肠道通透性增加。Barr 等[48]研究表明，慢性酒精消耗可通过肠固有层白细胞产生的免疫因子 IFN-$\gamma$、TNF-$\alpha$、IL-6 和 CCL2 介导空肠和回肠免疫炎症反应，从而改变肠道通透性和肠道功能。综上所述，ADS 患者肠道生态失调、肠道屏障功能被破坏，导致肠道通透性增加[49] [50]。

### 3.3. ADS 患者免疫炎症反应改变

ADS 患者因长期大量饮酒引起肠道微生物组成和肠道通透性发生改变，导致肠道内毒素产生增加，内毒素与肠粘膜上的细胞结合，引起局部炎症，并转移到肠外部位，引起全身性炎症[51]。肠道炎症是免疫系统对酒精及其代谢产物的炎症反应。ADS 患者表现为肠道免疫系统对病原体敏感性增加[52]，同时酒精会触发免疫系统反应并促进炎症反应分子上调，释放炎性免疫细胞。酒精还抑制肠道对细菌的防御，即调节分泌抗菌化合物的 Paneth 细胞，来影响粘膜免疫力[53]。ADS 患者除了肠道炎症，还有外周的免疫炎症。ADS 患者线粒体内产生的活性氧，促进炎症小体 NLRP3 的过度激活，过度激活的炎症小体 NLRP3 可促进促炎细胞因子 IL-1$\beta$ 和 IL-18 的合成和分泌[54]，并可引起外周炎症反应，如痛风[55]、糖尿病[56]和慢性胰腺炎[57]。在 ADS 患者表现为肠道脂多糖和肽聚糖增加，增加的脂多糖和肽聚糖进入外周，两者都激活外周血单核细胞中各自的 Toll 样受体，引起外周炎症反应[58] [59]。在中枢水平上，ADS 患者同样也存在中枢神经系统的炎症反应。Leclercq 等[60]研究表明，将酒依赖患者的粪便微生物移植到经抗生素处理的小鼠，经抗生素处理的小鼠额叶皮层和纹状体中髓鞘形成相关基因(*Mobp* 和 *Mog*)表达的下调，纹状体中促炎细胞因子(TNF-$\alpha$ 和 IL1$\beta$)和趋化因子(Cxcl15 和 Ccl2)的 mRNA 表达显着上调。Lowe 等[61]通过对慢性饮酒急性发作小鼠进行抗生素治疗发现，抗生素极大地减少了酒精喂养小鼠肠道微生物组负荷，并且酒精引起的神经炎症和小肠细胞因子表达增加在用抗生素治疗的小鼠中也得到减轻，从而缓解酒精引起的大脑变化。

### 3.4. ADS 患者焦虑抑郁样行为与肠道微生物群相关

ADS 患者经常共病其它精神疾病，尤其以抑郁症、焦虑症多见，约占 30% [62] [63]。ADS 患者伴随的严重焦虑抑郁样反应与大脑中重要的神经递质 5-HT 有关，肠道微生物可能通过影响该受体在不同脑区

的分布及脑内 5-HT 水平，从而加重 ADS 的严重程度，恢复肠道微生物水平能纠正小鼠焦虑、抑郁状态[64]。在一项临床病例对照研究中，ADS 患者表现出肠道菌群的改变和出现焦虑抑郁样行为，并且在酒精戒断 3 周后部分 ADS 患者任然表现出与健康人群存在显著差异的焦虑抑郁样行为[45]。Xiao 等人[65]的研究中发现，过量饮酒的小鼠酒精戒断后可引起小鼠焦虑样行为，将过量饮酒的小鼠粪菌移植到健康小鼠，健康小鼠也出现了同样的焦虑样行为。此外，在一项慢性酒精暴露的小鼠实验中，将健康小鼠的粪菌移植到慢性酒精暴露的小鼠肠道中，小鼠的肠道微生物群得到改善，同时接受粪菌移植的慢性酒精暴露小鼠的焦虑抑郁样行为与慢性酒精暴露小鼠存在显著差异，而与健康小鼠无显著差异[66]。

## 4. 展望

2021 年 4 月 10 日，上海交通大学携手 Science 杂志发布了“新 125 个科学问题”，这其中就包括“我们的微生物组在健康和疾病中扮演什么角色？”“什么是成瘾？”。由此可见，成瘾以及包括肠道微生物在内的微生物组学的研究，现已成为全球关注的热点问题。目前对于“微生物群－肠－脑轴”与 ADS 的研究主要集中于肠道微生物群及其代谢物与 ADS 的关联分析上。ADS 患者肠道微生物群及其代谢物发生改变与 ADS 的精神行为存在密切的联系，但 ADS 患者与健康人群间的差异菌群及其代谢物引起 ADS 患者脑功能及行为改变的机制仍然是不明确的。未来可以通过建立啮齿类以及非人灵长类等动物 ADS 模型，移植外源的特异性菌株或者菌群，或者添加外源的差异代谢物等干预手段，进一步验证特异性菌株或者菌群，以及差异代谢物在 ADS 发生发展中的作用。采用微生物组学、代谢组学、细胞生物学、分子生物学、免疫学以及形态学等多组学联合，研究“微生物群－肠－脑轴”在 ADS 发生发展中的作用机制，将会为酒精依赖的预防和治疗提供新的思路和依据。

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