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抑郁症研究的发展和趋势——从菌-肠-脑轴看抑郁症

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摘要 抑郁症是现代社会最常见的心理疾病, 该病不仅降低个人的生活质量, 还给家庭和社会带来巨大的经济负担. 但由于经济文化和医疗资源等因素限制, 目前大部分抑郁症患者并没有进行过任何治疗, 已有疗法效果的有限性又进一步加剧了这种困境. 研究发现, 抑郁症患者的大脑、内分泌、免疫和肠脑功能都出现异常, 脑-肠轴功能失常可能是抑郁症的主要病理机制. 以往的抑郁症治疗主要针对大脑, 如药物治疗和心理治疗, 而忽视了患者的其他症状. 近年来, 全世界范围随生活水平的提高抑郁症患病率也随之升高的现象提示, 食品添加剂、药物、环境压力及不良饮食等均可为肠道菌群异常的直接诱因, 而肠道菌群改变导致菌-肠-脑轴功能异常更可能促进抑郁症发生; 通过益生菌、益生元、健康饮食以及粪便菌群移植等方式重建肠道菌群平衡, 改善菌-肠-脑轴功能则能减轻甚至治疗抑郁. 通过调节肠道微生物来改变抑郁焦虑等心理疾病已成为神经科学和心理学的热点, 维护良好的肠道菌群可能是未来抑郁症预防和治疗的重要方向.

关键词 抑郁症, 脑-肠轴, 菌-肠-脑轴, 肠道微生物, 益心菌

抑郁症是一种以显著而持久的情绪低落、兴趣减退为主要临床特征的心理疾病, 是现代社会最常见的心理疾病, 也被称为“精神感冒”. 世界上平均每5个人中可能就有一个在生命的某阶段遭受抑郁折磨[1,2]. 在不同国家和地区, 抑郁症的患病率有差别, 但近年来大都呈上升趋势[3,4]. 据2014年保守估计, 抑郁症患病率在美国约为4.45%, 在中国约为3.02%, 世界范围内影响着超过3亿5千万人的健康和生活[5,6].

抑郁症的核心症状是持续的愉快感缺乏和意志行为减退(两周以上), 还包括有不适宜的负罪感、自杀念头、注意力不集中、失眠和食欲障碍等症状. 抑郁症的主要特点是高发病、高复发、高自杀率和高致残率. 患者往往具有明显的复发倾向或趋于慢性化, 首发患者85%以内会在未来10年内出现复发, 大部分患者会出现自杀想法和行为, 最终15%~20%会自杀成功[7,8]. 抑郁症不仅严重危害着个体的健康和生命, 还给家庭和社会带来了沉重的经济负担. 2014年的研究显示, 在2013年全球医疗经济负担中, 抑郁症带来的伤残损失生命年(years lost due to disability, YLDs)居第一位, 远超其他疾病, 占10.3%[3,5]. 2017年的研究也显示, 从1990到2016年, 抑郁症带来的医疗疾病负担(伤残调整生命年(disability adjusted life years, DALYs))不断增加[9].

1 抑郁症的认识发展

抑郁(depression或melancholia)很早就吸引了人们的注意. 2000多年前, 古希腊医生希波克拉底就描述了这种精神症状, 核心特征是持续的恐惧和沮丧. 文艺复兴后, 随着19世纪心理学和生物学的发展, 人们对抑郁症的认识也不断深化.

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1917年, 精神分析学派创始人弗洛伊德发表了《哀伤与抑郁》一书, 揭开了人们从心理学角度研究抑郁的序幕. 心理动力学理论认为, 无意识冲突和童年早期形成的敌意情绪在抑郁的形成中起了关键作用. 行为主义理论认为, 当个体生活中的丧失或变更受到不充分的正强化且经历很多惩罚, 就会出现抑郁. 认知理论则认为, 抑郁症病人在生活中思考他们自己和事件的方式可能使他们抑郁下去. 患者可能具有多种消极认知, 如对自己的消极看法、消极的当前体验、对未来的消极看法和习得性无助等. 基于对于个体心理结构和心理特征的认识, 目前已经发展了多种抑郁症心理治疗方法[10,11].

现代生物学认为, 抑郁症不仅是一种心理疾病, 更是一种生理疾病. 抑郁症具有明显的生物学因素, 患者大脑发生了重要改变, 如脑内神经递质失衡、神经生长受损、神经可塑性降低、神经环路异常[12,13]. 调整这些结构和功能异常是抑郁症治疗的根本[1,13]. 目前已开发出多种抗抑郁药物, 药物治疗成为抑郁症治疗的主流[14,15]. 抑郁具有一定的遗传性, 大规模全基因组研究发现, 重性抑郁的遗传力为46%, 轻度抑郁为37%[16]. 个体的第二基因组(即肠道微生物基因组)在抑郁发生中可能也发挥了重要作用[17~21].

目前, 一般认为, 抑郁是由遗传基因和环境应激的累积效应引起, 易感个体遭受应激从而出现抑郁. 应激性生活事件(童年阴影、失业、丧偶、不幸婚姻和长期受挫等)是抑郁的重要诱因, 遗传基因和心理特征决定了个体的易感性. 科学家提倡通过生物心理社会医学模式来更好地预防和治疗抑郁症[1,22,23].

2 抑郁症的治疗

目前已经被纳入抑郁症标准治疗方案中的主要有药物治疗、心理治疗及一些其他疗法[15,24,25].

2.1 药物治疗

20世纪50年代初期, 治疗肺结核的药物异丙异烟肼被偶然发现可以改善情绪, 从而开启了药物治疗抑郁症的大门. 异丙异烟肼及随后发现的异丙肼、苯乙肼、沙夫肼等均属于单胺氧化酶抑制剂(monoamine oxidase inhibitor, MAOI), 具有抗抑郁效果, 但因其副反应大、起效缓慢, 很快被三环类抗抑郁药(tricyclic antidepressant, TCA)取代. 1957年发现的第一个TCA——丙咪嗪具有良好的抗抑郁效果, 随后又有氯丙咪嗪、阿米替林和多塞平等TCA用于临床. TCA属于单胺再摄取抑制剂, 能抑制5羟色胺(5-hydroxytryptamine, 5-HT)和去甲肾上腺素(noradrenaline, NA)的重吸收, 适用于各种抑郁症. TCA是公认的第一代抗抑郁药物, 但具有抗胆碱的不良反应和心血管不良反应, 20世纪80~90年代后逐渐被取代. 70年代后出现了四环类抗抑郁药物(如马普替林), 随后又出现了多种新型抗抑郁药物, 包括选择性5-HT重吸收抑制剂(selective serotonin reuptake inhibitors, SSRIs)、5-HT和NA重吸收抑制剂(selective norepinephrine reuptake inhibitors, SNRIs)、选择性NA再摄取抑制剂(selective inhibitor noradrenalin inhibitor, NARI)、α-受体阻断四环类抗抑郁药, 5-HT平衡抗抑郁药等. 其中最常用的抗抑郁药物是SSRIs, 包括氟西汀、帕罗西汀、氟伏沙明、舍曲林和西酞普兰等[15,26]. 传统抗抑郁药主要针对单胺类神经递质(包括5-HT, NA和多巴胺(dopamine, DA)等), 而最新的抗抑郁药主要针对谷氨酸(Glu)和γ-氨基丁酸(gamma-aminobutyric acid, GABA), 如氯胺酮(ketamine), 就是一种*N*-甲基-*D*-天冬氨酸(*N*-methyl-*D*-aspartic acid, NMDA)受体拮抗剂, 具有快速又持久的抗抑郁效果, 其长期抗抑郁效果还在研究中[27~29].

药物治疗是目前最常用和最有效的抑郁症治疗方法, 见效快、易操作、更容易被大量人群采用, 但存在一定比率的不良反应[15]. 且现有药物基本上都是二十世纪五六十年代药物的改进品, 全新药物很少, 主要针对单胺类神经递质异常进行治疗[6,13]. 在接受治疗的患者中, 有将近1/2效果不明显[6,13]. 例如, 难治性抑郁症(treatment resistant depression), 此类型患者即便使用公认的两种抗抑郁药, 剂量足够, 且药物治疗依从性良好, 治疗6周以上仍无明显改善[30]. 未来针对其他神经递质如GABA和Glu的药物可能会给这一情况带来改善[31], 遗憾的是这些药物的关注点仍然集中在大脑.

2.2 心理治疗

在现代心理学的发展中, 不同心理学流派根据自己的理论创立了不同的心理治疗方法, 如心理动力学治疗、行为疗法、认知治疗等. 目前, 抑郁症最常用的心理治疗方法有人际心理治疗(interpersonal psychotherapy, IPT)、认知行为治疗(cognitive-behavioral therapy, CBT)和家庭治疗等. IPT是根据研究

发现抑郁发作与人际关系变化相关这一结果而提出的. 它强调“此时此地”以及与病人抑郁状态有关的许多人际困难问题. CBT应用最为广泛, 它基于“情感状态”是继发于思维和认知之后所产生的这一前提. 这两种治疗方法目前已被多个国家纳入抑郁症标准治疗体系[10,24,32].

经验显示, 心理治疗对抑郁症具有良好的效果且无副作用. 但心理治疗不适用于伴有其他精神状态的抑郁症, 花费偏高, 疗效高度依赖于治疗师的个人能力, 难以用科学方法验证, 这些原因使得心理治疗高度依赖于经济文化和精神医疗状况, 阻碍其普遍应用和推广[24].

2.3 其他疗法

在药物治疗和心理治疗无效的情况下, 患者还可以考虑其他疗法, 如电抽搐治疗(electroconvulsive therapy, ECT)、重复经颅磁刺激(repetitive transcranial magnetic stimulation, rTMS)、迷走神经刺激(vagus nerve stimulation, VNS)等. ECT是一种无创性脑刺激疗法, 具有良好的抗抑郁效果[27,33], 但直接刺激大脑对患者和家属而言, 仍是一种挑战[24]. 也有研究表明, 运动和饮食疗法对于抑郁症有一定效果, 但由于证据不够充分, 仅被部分人认可[24,34,35].

抑郁症往往并非独立发生, 患者还同时出现其他疾病状态. 抑郁患者共病其他心理疾病非常常见, 如抑郁和焦虑共病超过60%, 约1/3的抑郁患者也患有人格障碍[21,25,36]. 抑郁症与消化系统疾病具有极高的共病性, 甚至可能完全重合. 例如, 在肠易激综合征患者中, 50%~60%以上伴有抑郁或者焦虑[37]. 在炎症性肠病患者中, 21.6%会出现抑郁, 31.5%出现焦虑[38]. 在其他功能性肠病和胃肠病中, 患者的抑郁风险也明显升高[21,39,40]. 此外, 抑郁患者还可能共病其他躯体疾病(如糖尿病等代谢性疾病和心脏病等心血管疾病)及神经系统疾病(如阿尔兹海默症和帕金森综合征)[21,25,41]. 这些要求在抑郁症的治疗中, 同时还需要考虑共病症的治疗, 进一步增加了抑郁症治疗的难度.

除了治疗方法, 抑郁症治疗还受精神医疗资源和社会文化因素影响[5,10,11]. 一般来说, 精神医疗资源越丰富, 心理疾病患者越容易得到恰当治疗和帮助, 主要指标为每10万人中的精神科医生数量. 在不同国家, 受经济文化因素影响, 精神医疗资源差异巨大, 一般发达国家更丰富而发展中国家较为匮乏. 2013年统计, 美国每10万人中有7.79名精神科医生; 瑞士每10万人中有41.42名精神科医生; 中国每10万人中1.53有名精神科医生; 阿富汗则每10万人中仅有0.16名精神科医生[5]. 中国精神科医生官方数字近年来有显著提升, 2016最新统计为每10万人1.7名, 但14%的中国注册精神专科医生没有接受过任何训练, 另外有29%的人只有3年的大专教育证书, 仍有2/3的农村地区没有心理疾病床位.

在中高收入国家, 阻止心理疾病患者接受适当治疗的最大障碍不是医疗体系的缺陷, 而是人们自身的态度. 在多个国家和文化中, 心理疾病会带来社会歧视, 患者往往有病耻感, 不希望别人知道自己患有心理疾病, 或者自欺欺人, 不愿承认自己患有心理疾病, 因而不进行治疗. 不发达国家和高速发展国家情况尤为严重, 而发达国家情况稍好一些[5,11]. 2016年, *The Economist*智库发布的《亚太地区精神卫生综合评价指数研究报告》指出, 在中国, 只有8%的心理疾病患者进行了治疗, 而92%的患者从未接受过治疗. 即使在发达的英国, 也只有25%的抑郁症患者接受了治疗, 而75%患者未受治疗或诊断[6].

以上内容可以看出, 不同于其他疾病, 抑郁症患者的治疗主动性偏低, 而治疗体系尚待完善; 现有治疗的有效性还需要提高, 但目前已有方法, 改进较为缓慢; 患者常伴随其他躯体症状, 但治疗却往往只关注大脑.

3 抑郁症的病理生理机制

抑郁症的治疗是在病理机制的研究中发展而来, 随着神经科学和生物信息学的发展, 抑郁症的病理机制逐渐明晰, 已有研究结果提示, 抑郁可能主要涉及4个方面, 包括大脑、下丘脑-垂体-肾上腺(hypothalamic-pituitary-adrenal, HPA)轴、免疫系统和肠脑的功能改变. 大脑的变化主要表现在神经递质失衡、神经可塑性降低和神经环路异常[1,13]; HPA轴异常主要表现在负反馈机制失调[42,43]; 免疫系统变化主要表现为慢性炎症[44,45]; 肠脑功能异常主要是胃肠功能失调和肠道微生物异常[1,23,37,40,46].

3.1 大脑异常

神经递质是神经细胞交流的信使, 在个体心理和行为中发挥着重要作用, 抑郁症与神经递质失衡

密不可分[47,48]. 单胺类神经递质缺乏假说认为, 幸福和快乐等积极情绪情感离不开单胺类神经递质(如5-HT和DA), 抑郁是由于脑内单胺类神经递质缺乏引起, 而增加这些神经递质水平, 就能产生抗抑郁效果[47,49]. 但SSRIs大都起效慢, 只对一部分患者有效, 提示抑郁还涉及其他机制[12]. 随后的研究发现, 抑郁患者的其他神经递质可能也发生了改变, Glu能系统和乙酰胆碱能系统过于兴奋, 而GABA能系统受到抑制, 各个神经递质系统相互影响, 这些研究对于开发新的抑郁症治疗方法具有重要意义[48,50,51].

前额叶、海马和杏仁核在调节情绪、心理应激反应、自我控制、动机和认知反应中发挥重要作用, 但在一些抑郁症患者中, 海马和前额叶功能受损, 而杏仁核功能增强, 甚至可能出现海马萎缩[52]. 传统脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)假说认为, BDNF是神经生长的重要调节因子, BDNF水平降低, 神经凋亡增加会引起抑郁症状; 长期抗抑郁治疗能够增加脑中BDNF和其他神经营养和生长因子的含量, 减少海马神经元的凋亡, 促进神经元生长, 改善认知和情绪[1,43,53]. 进一步研究发现, 抑郁患者不仅神经生长受损, 神经胶质细胞生长也受影响, 突触可塑性降低, 神经髓鞘受损, 总体神经可塑性降低[12,13,52]. 新的神经可塑性理论认为, 神经递质失衡(如单胺类和Glu能)和BDNF降低等都会引起相关脑区神经可塑性降低, 从而引起抑郁症状, 而抗抑郁治疗(不管是纠正神经递质失衡还是进行脑刺激)都可通过抑制神经凋亡、增加神经可塑性从而改善抑郁[2,27,29,54]. 以上理论都偏重于分子细胞水平, 而有的理论更侧重功能如神经环路理论. 这种理论认为, 抑郁症可能是由于大脑中多个神经环路间的异常交流引起, 可通过脑刺激等方式重塑异常神经环路进行治疗, 中脑腹侧被盖区的DA能神经元和中缝背核的5-HT能神经元及其投射区可能在其中发挥了重要作用[13,55].

3.2 HPA轴异常

HPA轴功能异常是抑郁病理生理机制的重要组成部分之一[44,46,56,57]. HPA轴是机体应激反应的主要组成部分, 不管是生理应激还是心理应激都会激活HPA轴, 促进下丘脑释放促肾上腺皮质激素释放因子(corticotropinreleasing factor, CRF)和后叶加压素(arginine vasopressin, AVP), CRF和AVP会引起垂体前叶促肾上腺皮质激素(adrenocorticotropic hormone, ACTH)释放增加, 而ACTH则促使肾上腺增加糖皮质激素(glucocorticoid, GC)释放, 循环GC反过来又会促使下丘脑减少CRF和AVP的释放, 从而形成一个负反馈通路[56,58]. 但在1/2以上的重度抑郁患者体内, HPA轴负反馈机制失调, 循环GC和ACTH水平持续升高, 不少患者甚至出现高皮质醇血症[44,56]. 早期研究认为, 糖皮质激素受体(glucocorticoid receptor, GR)在抑郁的HPA轴功能中发挥重要作用, 循环GC水平过高以致超出了GR的负荷从而导致对GR敏感性降低, 而抗抑郁治疗能够增加GR表达, 增强GR功能, 进而增强了GR介导的对于糖皮质激素的负反馈[56,57]. 随后研究发现, HPA失调会减少BDNF表达[58], 抑制5-HT合成[59], 减少Glu受体表达[60], 甚至影响神经可塑性和神经环路功能[13,61].

3.3 免疫异常

炎症是抑郁症的主要病理特征之一, 患者往往存在免疫失调和慢性炎症[44,62,63]. 细胞因子假说认为, 抑郁患者体内促炎症细胞因子水平(如IL-6和TNF-α)升高, 而抗炎症细胞因子(如IL-10和TGF-β)水平降低, 免疫反应整体倾向于炎症方向[62,64,65]. 高水平的促炎症细胞因子可抑制HPA轴负反馈功能, 提高血脑屏障渗透性, 降低5-HT合成, 扰乱Glu能系统, 从而引发抑郁[59,62,66,67]. 早期理论主要集中于外周炎症, 最新理论很多, 但都认为中枢炎症在抑郁发生中发挥重要作用, 如神经炎症假说和炎性体假说[61,66]. 神经炎症假说强调心理应激、疾病和感染等各种因素引起小胶质细胞释放过量促炎症细胞因子对中枢神经系统(central nervous system, CNS)的不利影响[61], 而炎性体假说则更关注炎性体引发的中枢炎症的影响[68,69]. 神经胶质细胞在中枢免疫和神经可塑性调控中发挥重要作用, 虽然不同假说侧重点不同, 但都认为神经胶质细胞功能受损引起的神经炎症和神经可塑性降低可引发抑郁[61]. 传统抗抑郁治疗的抗炎症效果并不理想[63], 在抑郁症治疗中考虑抗炎症可能会有更好的效果[66].

3.4 肠脑功能异常

由于具有自己的神经系统(肠神经系统(enteric nervous system, ENS)), 并能对外界信号作出独立反应而不完全依赖于CNS, 哺乳动物的肠道也被称为

肠脑[21]. 肠脑是一个微生物器官, 肠道内细胞的90%~95%为微生物(包括细菌、古细菌、真菌、病毒和一些原生动物), 而且肠道的代谢、免疫和信号传递等主要功能均与微生物有关, 可以把肠道和肠道微生物作为一个整体, 对其他器官的信号做出反应, 并影响其他器官的功能[70~73]. 抑郁症患者往往存在肠脑功能异常, 如食欲障碍、代谢异常、功能性胃肠病和肠道微生物异常[18,23,40,74~76].

可以看出, 抑郁症并不是一种单纯的心理疾病或CNS疾病, 患者不仅出现大脑分子结构异常和功能失调, 外周系统功能也受到损伤, 如HPA轴功能失调, 免疫失调和肠脑功能紊乱. 这些异常并非独立发生, 而是相互联系、彼此影响的, 如应激可降低大脑5-HT含量, 而5-HT的合成和分泌受免疫、HPA轴和肠脑影响, 又反过来影响这些系统的功能[43,59,77]. 因此, 综合考虑中枢和外周更能阐明抑郁症的生理异常, 即脑-肠轴功能异常更能全面说明抑郁症的病理基础.

脑-肠轴是指哺乳动物大脑和胃肠道间存在的双向信号交流网络, 通过神经、HPA轴和免疫等途径把大脑和肠脑联系起来[17,21]. 心理应激或者疾病等因素损害某条途径功能, 即可能造成整个脑-肠轴功能异常, 从而出现抑郁[23,78,79]. 随着肠道微生物研究的深入, 研究者不仅关注脑-肠轴自上而下(即从脑到肠)的影响, 同时开始关注自下而上(即从肠到脑)的作用[23,40,80]. 个体的代谢、免疫、内分泌和神经等各个系统的功能都与肠脑密切相关, 肠脑的变化(如肠道微生物异常)会影响大脑和行为, 大脑的变化也会影响肠脑功能和结构, 结合肠脑和大脑是未来神经科学发展的新方向, 针对肠道微生物来治疗心理疾病和神经系统疾病可能是未来神经科学发展的新趋势[21,81~89].

肠道微生物可通过肠-脑轴(为强调肠道微生物的重要性也称菌-肠-脑轴)来影响宿主的大脑和心理行为, 在心理疾病中发挥重要作用[82,83]. 肠道微生物是肠脑的重要组成部分, 决定肠脑正常结构和功能[70~73], 影响HPA轴的发育和功能成熟[90~93], 调节免疫系统发育和功能[94~96], 调控血脑屏障的结构[97], 调节神经递质的合成分泌和识别[77,90,98], 影响神经细胞生长[99]、神经胶质细胞发育和功能[100,101]以及神经髓鞘形成[102], 影响大脑发育和功能[84,96,103,104]. 因此, 调节肠道微生物, 不仅能改善肠脑功能失调, 还能调节免疫、HPA轴和大脑异常, 从而全面改善脑-肠轴功能, 这可能是未来抑郁症等心理疾病预防和治疗的重要方向, 这就是抑郁症的肠道微生物假说.

4 抑郁症的最新研究进展——肠道微生物假说

肠道微生物假说认为, 抑郁症与个体肠道微生物密切相关, 肠道微生物改变及随之的肠-脑轴功能异常是抑郁症发生的病理基础, 肠道微生物异常是隐藏在环境和遗传之下的独立因素, 也是抑郁症的直接诱因, 调节肠道微生物可能是预防和治疗抑郁症的有效方法. 十几年来, 随着肠脑研究的深入, 不断增加的研究从多个方面支持了这项假说[21,83,85,86,105~110].

4.1 抑郁症患者拥有不同于健康个体的肠道微生物

临床证据显示, 抑郁症患者的肠道菌群发生了明显改变. 有研究认为, 总体上抑郁患者的菌群多样性和丰度都有所下降[75,105]. 与健康个体相比, 在门水平, 抑郁患者粪便中拟杆菌门(*Bacteroidetes*)和变形菌门(*Proteobacteria*)含量升高, 而厚壁菌门(*Phylum Firmicutes*)含量降低; 在科水平, 普雷沃氏菌科含量增加; 在属水平, 普氏菌属含量增加, 粪菌属(*Faecalibacterium*)和瘤胃球菌属(*Ruminococci*)含量降低[75,111]; 双歧杆菌属(*Bifidobacterium*)和乳酸杆菌属(*Lactobacillus*)含量降低[112]. 虽然这些研究都发现, 抑郁症患者与健康个体的粪便菌群不同, 但具体差异部分仍有分歧[76,113,114], 这可能与研究者采用不同诊断标准、入组标准以及粪便菌群检测方法等因素有关.

动物实验发现, 啮齿类抑郁模型动物的肠道微生物也与其健康对照组有明显区别. 在嗅球切除模型、母子分离模型、社交挫败模型、慢性可变应激模型以及本研究组的慢性束缚应激模型中都发现了这种现象, 甚至抑郁动物的菌群组成与抑郁患者有相似之处, 如门水平拟杆菌门含量增加而厚壁菌门含量降低, 属水平乳酸杆菌属含量减少[115~118].

这些证据均提示抑郁可能与特定的菌群表型(菌群组成和结构)有关.

4.2 抑郁患者粪便菌群移植可传递抑郁症

抑郁这种“精神感冒”似乎也具有流感的传染特性(即通过流感病毒从个体传播给另一个体), 但抑郁的传播介质更为复杂, 为抑郁患者的肠道微生物, 传

播条件也更为苛刻, 在自然条件下很难实现.

Zheng等人[113]把抑郁症患者和健康人的粪便移植到无菌动物(没有肠道微生物)体内, 发现接受抑郁症患者粪便菌群的小鼠(*Mus musculus*)抑郁样行为增加, 菌群表型与接受健康人粪便菌群的小鼠明显有差异, 且这种差异与各自供体间差异一致, 提示菌群表型通过影响代谢引发抑郁. Kelly等人[105]使用抗生素鸡尾酒法处理, 使大鼠(*Rattus norvegicus*)处于一种微生物缺乏状态, 再把人的粪便微生物通过灌胃的方法接种给大鼠. 结果表明, 与接受健康志愿者粪便的大鼠相比, 接受了抑郁患者粪便菌群移植的大鼠表现出快感缺失, 焦虑样行为增加, 同时色氨酸代谢发生改变, 其表现与抑郁供体的症状一致[105]. 这两项研究显示, 抑郁患者的心理和生理异常可通过其粪便菌群传递给其他个体, 进一步提示个体的心理状态受肠道菌群调控.

在自然条件下, 子代通过垂直传递和水平传递, 也会获得与亲代相似的肠道微生物[119]. 本研究组发现, 抑郁的遗传效果可能是由于遗传获得了亲代抑郁易感的肠道微生物引起.

4.3 破坏肠道菌群会增加抑郁风险

抗生素破坏菌群增加抑郁风险. 尽管抗生素曾在人类抗感染治疗中发挥过重要作用, 但抗生素不仅针对病原体, 同时也严重破坏个体的有益共生微生物, 引起菌-肠-脑轴功能紊乱, 反而增加其他疾病风险, 甚至是心理疾病风险[120~123]. 大规模人群研究发现, 抗感染治疗中使用的抗生素会明显增加个体罹患抑郁等心理疾病的风险. 这种风险呈现出剂量依赖效应和时间依赖效应——即风险与抗生素的使用剂量和时间长短呈正相关, 即使在使用结束10年后, 这种风险提高影响依然存在[124,125]. 婴幼儿研究也发现, 在出生后一年内使用抗生素的孩子, 更易出现行为问题和抑郁症状, 这种现象在3岁半时就已非常明显[126]. 动物研究也表明, 抗生素使用会增加动物出现行为和认知异常的风险[121,127].

应激破坏肠道菌群增加抑郁风险. 应激性生活事件是抑郁症的重要诱因, 动物研究常用各种慢性应激来诱使实验动物抑郁. 应激不仅影响心理和应激系统, 还会破坏肠道菌群[128~134]. 本研究组研究表明, 慢性应激可通过改变肠道菌群, 进而引起菌-肠-脑轴功能失调(包括海马5-HT含量降低、BDNF mRNA表达减少、血浆应激激素水平增加、循环IL-10水平降低、肠道菌群改变等), 从而引起抑郁[135].

不良饮食方式破坏菌群, 增加抑郁风险. 断奶以后, 饮食是影响个体肠道菌群的最重要因素之一, 不健康的饮食明显破坏肠道菌群[119,136~138]. 研究发现, 西方饮食或精加工饮食或工业化使用大量饱和脂肪酸、糖和添加剂(防腐剂乳化剂调味剂等)的饮食方式会破坏菌群平衡, 增加个体的抑郁风险[139~141]. 食物的这种风险提高可能是由于破坏肠道菌群平衡从而影响菌-肠-脑轴功能引起的[142,143].

抗生素、应激和饮食等因素均会破坏肠道菌群, 使原本健康的肠道菌群趋近于抑郁患者的菌群结构, 从而增加宿主的抑郁风险. 更为严峻的是, 这些破坏因素常常同时出现[144,145], 却被宿主忽视.

4.4 重建肠道菌群平衡可改善抑郁症

肠道微生物与宿主健康和疾病息息相关, 肠道菌群紊乱引发多种生理和心理疾病, 而重建肠道菌群平衡有改善和治疗作用[83,84,146~148]. 目前, 已经证明有效改善肠道菌群紊乱的方法主要有益生菌、益生元、健康饮食和粪便菌群移植4种[138,149~151].

益生菌(probiotics)是指足量服用时能对机体产生有益影响的、活的微生物. 这种有益影响不仅局限在胃肠道, 甚至可能达到整个菌-肠-脑轴, 研究者把这种能够改善行为和心理状态的益生菌称为益心菌(psychobiotics)[152]. 临床研究和动物实验均发现, 补充益心菌可减轻抑郁症状, 甚至能达到与传统治疗相似的效果. 在抑郁患者的随机对照安慰剂研究中, 补充益心菌, 能够减轻患者的抑郁和焦虑症状, 改善认知和代谢异常[153~155]. 抑郁的动物模型研究进一步验证了这种效果, 提示益心菌可能是通过菌-肠-脑轴改善行为和认知[135,156,157]. 目前已经报道的益心菌基本都属于乳酸杆菌和双歧杆菌, 如干酪乳杆菌(*Lactobacillus casei*)和瑞士乳杆菌(*Lactobacillus helveticus*)以及两歧双歧杆菌(*Bifidobacterium bifidum*)等特定菌株.

益生元(prebiotics)是指食用后能促进肠道有益细菌生长的营养或食物成分, 可以说是肠道益生菌的食物. 研究者发现, 补充益生元不仅能够促进有益菌生长, 重建肠道微生物平衡, 还能产生类似于益心菌的行为和认知改善效果, 这种健康增益可能是通过调节菌-肠-脑轴功能实现的[149,158~160]. 目前益生元

的研究很受关注, 其中研究较多的主要有以下3种: 低聚果糖、低聚半乳糖和Ω-3多不饱和脂肪酸等[161].

与不良饮食相反, 健康饮食可以增加肠道菌群多样性和稳定性, 促进身心健康[19,149,162,163]. 健康饮食, 主要指食物中含有丰富的膳食纤维、不饱和脂肪酸和发酵食品(酸奶奶酪酸豆汁等等); 而含有较少的精制碳水化合物、饱和脂肪酸、糖和添加剂(防腐剂、乳化剂、调味剂、着色剂等)的食物, 如地中海式饮食. 健康饮食可以重塑肠道菌群平衡, 通过菌-肠-脑轴促进行为和认知改善[19,138,143,151,162]. 这些数据也为从前一直被人忽视的抑郁症饮食疗法提供了有力的支持.

粪便菌群移植, 将健康个人的粪便移植到患者肠道内, 整体替换患者原有的菌群, 在艰难梭菌感染、炎症性肠病和溃疡性结肠炎等疾病治疗中已经发挥着重要作用[164]. 目前国内外已经有研究者尝试, 通过移植健康人的粪便菌群, 来治疗抑郁症、自闭症等心理疾病.

就当前研究应用来看, 针对肠道菌群, 通过益生菌或益生元、健康饮食或者粪便菌群移植, 重建菌群平衡, 调节菌-肠-脑轴功能, 可能在未来抑郁症等心理疾病的治疗中发挥重要作用[86,152,165].

4.5 传统抗抑郁疗法发挥作用可能与肠道微生物有关

一般认为, 传统抗抑郁治疗能够改善认知和大脑功能, 从而治疗抑郁. 但最新研究发现, 传统治疗方法, 不仅影响大脑, 还会影响肠道菌群, 这些疗法发挥作用似乎与对菌-肠-脑轴的影响有一定关系[19,166,167].

抑郁症的药物疗法可调节肠道菌群. 第一个抗抑郁药物——异烟肼, 最初就是用来治疗结合分枝杆菌感染; 第一代抗抑郁药物TCA, 也能抑制大肠杆菌(*Escherichia coli*)、鼠疫耶尔森杆菌(*Yersinia pestis*)、疟原虫(*Malaria Parasite*)等生长; 目前常用的SSRIs类, 能够抑制革兰氏阳性细菌生长; 甚至最新的抗抑郁药氯胺酮, 也能抑制一些葡萄球菌(*Staphylococcus*)、肠球菌(*Enterococcus*)和白假丝酵母(*Candida albicans*)的增殖. 常用抗生素, 如头孢曲松钠和二甲胺四环素, 都显示出了一定的抗抑郁特性[166]. 本研究组的实验也发现, 西酞普兰对慢性束缚应激抑郁模型大鼠具有治疗效果, 同时还能改变抑郁大鼠的肠道菌群, 尽管改变后的菌群并未恢复到对照水平. 这些结果表明, 抗抑郁药物发挥作用可能与其对肠道微生物的作用有关. 同时, 这些发现也提示, 对于难治性抑郁, 从肠道微生物角度研究, 可能会提供更多认识.

其他抑郁症疗法也可改变肠道菌群. 除了上文所说的饮食疗法, 运动疗法可能也是通过影响肠道菌群, 改善菌-肠-脑轴功能实现的, 久坐不动、缺乏运动的不良生活方式会增加抑郁风险, 而充分运动则能改善抑郁[167,168].

4.6 肠道微生物的整合疗法

目前已经有研究者尝试针对肠道菌群, 结合传统疗法的整合疗法来治疗心理疾病. 2016年, Schnorr和Bachnerb[169]尝试结合饮食和心理疗法, 给一位惊恐发作患者进行心理治疗, 并去除饮食中能持续升高血糖的食物, 增加富含益生菌的食物, 结果发现, 患者焦虑症状和失眠情况都有明显改善, 粪便中的有益微生物乳酸杆菌增加, 而一些有害的梭菌类减少, 粪便菌群组成和多样性都发生了明显改善. 2017年, Bambling等人[170]进行了一项预实验: 12名难治性抑郁症患者, 同时进行益生菌和乳清酸镁联合治疗, 8周后患者的抑郁状况得到明显改善, 转为常规SSRIs治疗, 但16周后重新检测发现患者症状又出现复发. 这两项研究提示, 在传统抗抑郁治疗中注意改善肠道菌群, 可能会产生更好的效果.

综上所述, 抑郁症患者的菌群发生了改变, 这种改变可能由多种因素引起, 如抗生素、应激、不良饮食和遗传型易感等. 且这种改变具有稳定性, 在一定条件下可把抑郁的表型传递给其他个体. 破坏健康个体的肠道菌群, 会增加抑郁风险; 而重建患者的肠道菌群平衡, 不管是使用益心菌、益生元、健康饮食、粪便菌群移植、运动或者药物, 都能产生抗抑郁效果.

5 结论与展望

一百多年来, 随着现代心理学和生物学的发展, 人们对抑郁症的认识取得了巨大进步, 开发了多种治疗抑郁症的方法. 例如, 心理疗法、药物疗法、脑刺激和运动饮食等方法, 其中最常用的是药物治疗和心理治疗. 但由于治疗有效性、患病人数和社会文化经济等多种原因, 87.5%以上患者没有得到有效帮助[5,6,171]. 消极性格和认知、大脑神经递质失衡、神经可塑性降低和神经环路异常、HPA轴功能失调、慢

性炎症及肠脑功能异常在抑郁症患者中经常同时出现，暗示患者的脑-肠轴功能失调，这可能是抑郁症的主要病理基础. 人们对抑郁症的关注从心理到大脑，到其他系统(内分泌和免疫)，再到脑-肠轴，肠-脑轴，最后转向菌-肠-脑轴[87~89,172~174]，具体可见图1所示. 肠道菌群异常是抑郁的直接诱因，肠道微生物可通过菌-肠-脑轴影响个体的行为和心理，菌-肠-脑轴功能失调才是抑郁症的真正病理基础，这就是抑郁症的肠道微生物假说. 根据这种假说，针对肠道微生物，调节菌-肠-脑轴功能，就能改善和治疗抑郁症. 截至目前已经积累了多种有效促进肠道菌群平衡的方法，如调整饮食、补充益生菌制剂或者益生元，在上述方法无效时，还可以考虑粪便菌群移植.

长久以来，抑郁症的治疗多为“头痛医头”，直接针对大脑异常(如5-HT，Glu或神经环路)，而其他躯体异常则往往被忽视或默认为会随着大脑功能改善而改善. 而调节肠道微生物，进而全面改善菌-肠-脑轴功能，可能会给抑郁症等心理疾病的防治带来无法估量的影响. 且这种方法具有更大的灵活性和可操作性，对于患者而言，更易接受实施；对于高风险人群，也更易于预防. 一百多年前，就提出抑郁等精神疾病的根源可能在肠道微生物，补充益生菌可能有改善，但

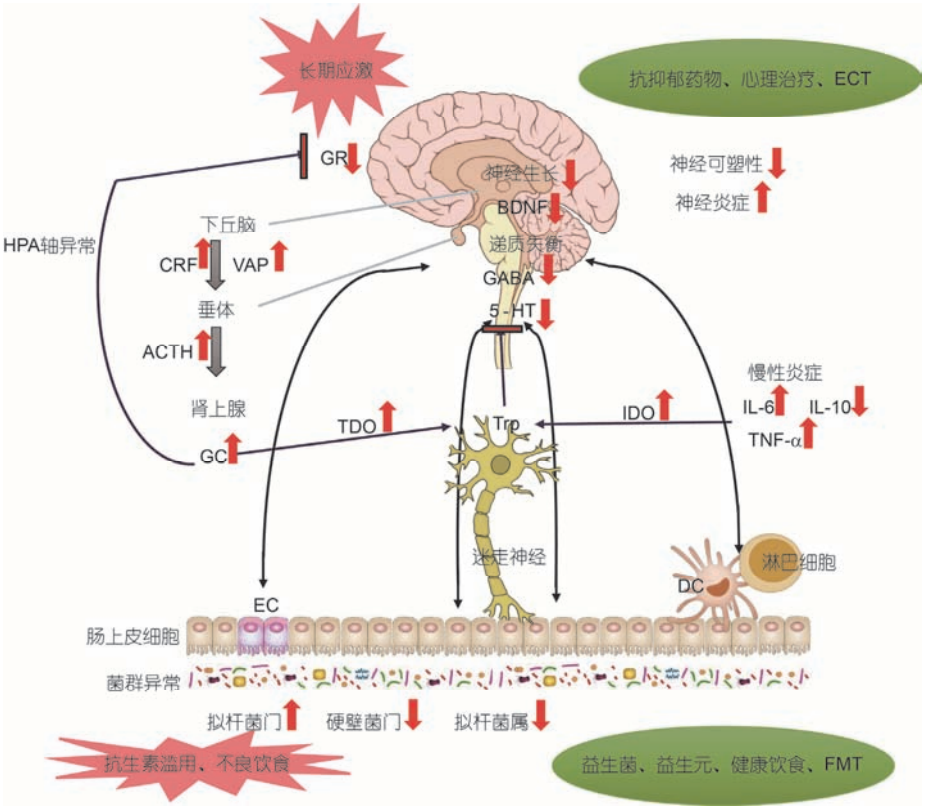

图 1 抑郁症的病理机制和治疗策略. 长期应激、抗生素滥用、不良饮食等多种因素可导致抑郁症患者的脑肠轴功能失调. 大脑异常可通过神经、内分泌和免疫途径自上而下影响肠脑，肠道微生物异常亦可损害肠脑，并通过以上 3 条途径自下而上影响大脑，进而诱发抑郁. 传统治疗策略主要关注改善大脑生理异常和功能异常，而最新治疗策略更倾向通过肠道微生物整体调节菌-肠-脑轴功能. 图中：GR为糖皮质激素受体; CRF为促肾上腺皮质激素释放因子; VAP为后叶加压素; ACTH为促肾上腺皮质激素; GC为糖皮质激素; EC为肠内分泌细胞; Trp为色氨酸; TDO为色氨酸 2,3-双加氧酶; IDO为吲哚胺 2,3-双加氧酶; ECT为电抽搐治疗; DC为树突状细胞; FMT为粪便菌群移植

Figure 1 The pathophysiological mechanisms and treatment strategies of depressive disorder. Variety of factors may induce the brain-gut axis dysfunction of depressed patients, including chronic stress, antibiotic abuse, and poor diet. Brain dysfunction impacts the gut brain through neuron, neuroendocrine and immune pathways from up to down, and gut microbiota dysbiosis impairs gut brain function, and influences the brain and behavior via the three pathways from down to up. Traditional treatment strategies mainly focus on brain and mental improvement, while the most advanced strategies tend to gut microbiota and dephasing the improvement of whole microbiota-gut-brain axis. GR, glucocorticoid receptors; CRF, corticotropin releasing factor; VAP, vasopressin; ACTH, adrenocorticotropic Hormone; GC, glucocorticoid; EC enteroendocrine cell; 5-HT, serotonin; Trp, tryptophan; GABA, gamma-aminobutyric acid; TDO, tryptophan 2,3 dioxygenase; IDO, indoleamine 2,3-dioxygenase; ECT, electroconvulsive therapy; IL, interleukin; TNF-α, tumor tumor nectosis factor-alpha; DC, dendritic cell; FMT, fecal microbiota transplantation

由于各种因素限制, 这种观点并未受到关注[175~177]. 2005年, Logan和Katzman[74]提出补充益生菌可作为抑郁症的辅助疗法. 2009年之后, 科学家们开始注意肠-脑轴在抑郁等心理疾病中的作用[17,21,40,80,178,179]. 2013年, Dinan等人[152]直接提出益心菌概念来强调益生菌在心理疾病治疗中的潜能. 与此同时, 益生菌在动物实验中被证明具有治疗抑郁症的作用[135,157], 随后直接使用益生菌改善抑郁症治疗的临床研究也不断增加[153~155]. 最近, 有临床工作者开始尝试结合菌群干预和传统疗法治疗难治性抑郁症[170]. 可以预期, 不久的将来, 针对肠道微生物和肠-脑轴的治疗将会在抑郁症的预防和治疗中发挥重要作用.

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Summary for “抑郁症研究的发展和趋势——从菌-肠-脑轴看抑郁症”

The development and tendency of depression researches: Viewed from the microbiota-gut-brain axis

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Depressive disorder is the most prevalent mental disease, not only it has impaired the life and wellbeing of patients, but also brought great economic burden for family and society. Yet depressive disorder is widely undiagnosed and untreated because of stigma, inadequate mental-health resources, complex comorbidities, and lack of effective therapies. Increasing researches indicate that depressive disorder is more a physiological disease rather than a psychological illness. For most patients, the brain-gut axis function is impaired, including the imbalances in brain neurotransmitters, the decline in brain neuroplasticity, the dysfunction in hypothalamic-pituitary-adrenal axis, the chronic periphery inflammation and neuro-inflammation, as well as gastrointestinal diseases and the gut microbiota dysbiosis. Traditional treatments for depression have been focusing on the brain itself, and/or also, using variety of medications and psychotherapy. Almost half of the patients have not acquired effective help. New treatment strategies underlining the whole brain-gut axis dysfunction will shed light on the dilemma.

In recent years, more and more studies have presented the important role played by gut microbiota in brain and behavior, promoting the appearance of new theories for mental disorders. According to current gut microbiota hypothesis, gut microbiota is a crucial component of gut brain, gut microbiota disruption and the following brain-gut axis dysregulation are the main pathophysiology of depression, and which will be the promising target of future therapies. Patients and model animals with depressive disorder share some similarities in gut microbiota, which are obviously distinctive with their healthy controls, indicating that depression is probably related with certain gut microbiota phenotype. Both the physiological symptoms and behavioral symptoms can transfer to germ-free and microbiota-deficient animals through fecal microbiota transplantation from depressed patients, further confirming the relationship between depression and abnormal microbiota. Various factors like antibiotics use, chronic stress, and long-term unhealthy diet disturb gut microbiota, while the abnormal microbiota probably induce microbiota-gut-brain axis dysfunction and increase the incidence of depression and other mental disorders. Several methods have presented good effects in gut microbiota regulation, including probiotics, prebiotics, healthy diet, and fecal microbiota transplantation, all of which possibly alleviate and treat depression via improving the microbiota-gut-brain axis function. Additionally, traditional adjuvant treatments like diet therapy and exercise therapy also possibly work through microbiota-gut-brain axis regulation. Even the effects of common antidepressants are probably related with gut microbiota, too. And the integrative therapy attempts emphasizing gut microbiota regulation present promising effects. All of the above results indicate that depression is strongly linked with gut microbiota abnormalities, and it may be treated through gut microbiota intervention using effective methods like psychobiotics supplement. Now-a-day the application of gut microbiota interventions has been becoming a hot point in treatment of mental disorders. And maintaining the normal condition of gut microbiota probably play vital part in the prevention and therapy of mental disorders in the future.

depressive disorder, brain-gut axis, microbiota-gut-brain axis, gut microbiota, psychobiotics

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