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慢性应激诱导动物抑郁样行为机制研究进展

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【摘要】 抑郁症是影响范围广、人数多的精神/心境障碍,其经典致病机制假说包括 HPA(hypothalamic-pituitary-adrenocortical axis)轴功能异常、单胺类和神经可塑性缺陷等。要充分阐明抑郁症多种致病因素,及不同病因之间复杂的相互作用关系,仍需更加深入的研究。慢性应激是抑郁症主要临床诱因,利用此动物模型可充分揭示发病过程中复杂的病理机制及其变化趋势,且利于将转化医学研究结果快速有效地向临床转化,对疾病预防和治疗有重要意义。目前现有相关综述主要围绕经典的 HPA 轴异常、单胺类和神经可塑性缺陷、大脑神经元结构功能、中枢神经递质和因子及其受体等方面异常展开。本文综述了近年抑郁症研究热点和新发现,包括基因变异和表观遗传修饰、神经胶质细胞(星形胶质细胞和小胶质细胞)结构功能异常、线粒体功能障碍、机体系统水平异常(氧化应激、免疫炎症反应和微生物-肠-脑轴),旨在系统呈现慢性应激诱导动物抑郁样行为机制研究进展,为后续有针对性地深入研究致病机制,及其临床预防和治疗提供新思路。

【关键词】 慢性应激;抑郁症;神经胶质细胞;免疫炎症反应;微生物-肠-脑轴
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Research progress on mechanisms underlying chronic-stress-induced depressive-like behavior in animals

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【Abstract】 Depression is a serious mental disorder that affects a wide range and a large number of people. Pathogenic hypotheses for the condition include classical hypothalamic-pituitary-adrenocortical (HPA) axis dysfunction and monoamine and neural plasticity deficiencies. More in-depth investigations are required to fully reveal the complexities of the pathogenesis and interactions between multiple pathogenic factors. Chronic stress is the main clinical factor that induces depression; therefore, it is vital to fully reveal the complex pathological mechanisms and the changes that occur during chronic stress exposure for the rapid and effective transformation of translational findings and the efficient prevention and treatment of the disease. Existing reviews related to depression pathogenesis have mainly focused on the classical hypotheses of HPA axis dysfunction and monoamine deficiency, as well as morphological and functional abnormalities of different brain subregions, neurons, central neurotransmitters, factors, and the corresponding receptors. The present review summarizes

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current depression research hotspots and new findings that have surfaced in recent years, such as genetic variants and epigenetic modifications, structural and functional abnormalities of glial cells (astrocytes and microglia), mitochondrial dysfunction, and systematic abnormalities (oxidative stress, immune inflammatory response, microbial-gut-brain). This paper systematically presents the research progress made into the mechanisms underlying chronic-stress-induced depressive-like behavior in animals, to benefit further in-depth studies into the pathogenesis, and to provide novel ideas for the clinical prevention and treatment of the disease.

【**Keywords**】 chronic stress; depression; glia cells; immune inflammatory response; microbial-gut-brain axis
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1 抑郁症

抑郁症是一种影响范围广、人数多的精神/心境障碍。世界卫生组织国际疾病分类 11(ICD 11)和美国精神疾病分类与诊断标准第 5 版(DSM-5),都将抑郁心境(至少持续 2 周)和快感缺失列为其核心症状[1]。据《柳叶刀》2018 年对 195 个国家和地区的调查报道,全球抑郁症患者约为 2.7 亿人(2018 年为此系列报道最新数据)[2]。《柳叶刀精神病学》2019 年发表北京大学学者研究,表明中国抑郁症患病率为 6.9%,则有超过 9500 万人患有此病[3]。上述数据表明,抑郁症广泛且严重地影响人类身心健康,且重度抑郁症患者会反复出现自杀念头和行为,为家庭和社会带来沉重负担,是亟待解决的社会问题。

2 抑郁症慢性应激动物模型

动物模型是研究人类疾病(致病机制和治疗方法)不可或缺的工具,抑郁动物造模方法有急/慢性应激、嗅球切除、药物诱导和遗传学操作等[4]。慢性应激(chronic stress)是抑郁症主要临床诱因,此方法所造动物模型因具有与临床患者相似致病原因而结构效度(construct validity)较高,且用此模型进行研究可充分阐明应激过程中复杂的神经生物学变化,利于将动物实验结果快速有效地向临床转化[5]。慢性应激暴露可在动物发育早期或后期(青年/成年)进行,早期应激以母婴分离(maternal separation, MS)为主,青年/成年期应激根据刺激强度不同,可分为较为缓和的慢性可预测性应激如社会隔离(social isolation, SI)、慢性束缚应激(chronic restraint stress, CRS)、慢性不可预测性应激(chronic unpredictable stress, CUS)和刺激强度较高的慢性社会挫败应激(chronic social defeat stress, CSDS)等[4,6-7]。这些应激方法可有效诱导动物出现与临床患者相似的抑郁样行为(核心症状抑郁心境和快感缺失),因此模型表面效度较高(face validity);常用临床抗抑郁药物可有效改善其诱发的抑郁样行为,因此模型预测效度较高(predictive validity)[5,7]。此 3 种效度的满足,使慢性应激动物模型成为理想的抑郁症模型。多年临床和动物研究发现,抑郁症与 HPA 轴(hypothalamic-pituitary-adrenocortical axis)功能异常、大脑(前额叶和海马等关键脑区)神经元结构功能异常、中枢神经递质和因子(如 5-羟色胺(5-HT)、谷氨酸和脑源性神经营养因子(brain derived neurotrophic factor, BDNF))及其受体功能异常均有密切关系,因此多种致病假说被提出,包括经典单胺(5-HT)假说、神经内分泌(HPA 轴)假说和神经可塑性(BDNF)假说等[1,8-11]。近年研究陆续发现抑郁症还与基因变异和表观遗传修饰、胶质细胞结构功能异常、线粒体功能障碍、氧化应激(oxidative stress, OS)、免疫炎症反应和微生物-肠-脑轴(microbiota-gut-brain axis, MGB 轴)功能异常密切相关,本文综述了慢性应激引起动物抑郁样行为背后的上述多方面机制研究进展。

3 慢性应激诱发抑郁症机制

3.1 基因变异和表观遗传修饰

研究发现抑郁症可遗传性在 35%左右,随着基因检测技术发展,抑郁症相关基因变异和单核苷酸多态性位点(single nucleotide polymorphisms, SNPs)被陆续发现[12]。2015 年,对 5303 名中国汉族女性患者的 DNA 序列分析结果,发现两个疾病相关突变部位[13]。2016 年,全基因组关联分析筛选出的 17 个欧洲人群 SNPs[14],2018 年又报道了对 13.5 万多名患者的 DNA 进行序列分析发现的 44 个基因变异[15]。所发现的变异基因与 SNPs,主要与大脑神经元和胶质细胞结构和功能、神经递质和激素及受体表达等相关,其中与 5-HT 和 BDNF 系统的密切相关性支持经典单胺和神经可塑性等致病机制假说[16-18]。如 BDNF 基因第 66 位密码子由缬氨酸

(Val)突变为甲硫氨酸(Met)会导致脑内 BDNF 分泌减少,增加携带者患抑郁症的风险[18],此发现与临床患者和抑郁模型动物大脑前额叶和海马 BDNF 水平显著降低结果一致[10,19]。

外在环境因素会在不改变基因序列和引起变异的情况下,通过表观遗传学修饰(包括 DNA 甲基化、组蛋白修饰、染色质异构和非编码 RNA 等)影响基因表达。临床研究发现抑郁患者蓝斑星形胶质细胞(astrocytes)谷氨酸相关基因(如 SLC1A2 和 SLC1A3 等)转录水平显著降低,且多个脑区胶质细胞缝隙连接通道蛋白 CX30 和 CX43 基因转录下调[20-21]。这些基因表达下调是由 DNA 甲基化异常引起的,如 H3K9me3(组蛋白 h3 上第九个赖氨酸三甲基化)水平升高[20,22]。慢性应激引起的动物抑郁样行为也伴随着基因表达和表观遗传学修饰异常:CUS 降低大鼠海马基因表达,如下调 BDNF mRNA 和蛋白水平[23-24],以及引起多种抑郁症生物学标志物 miRNA 异常表达[25-26];早期逆境抑制大鼠海马糖皮质激素受体(glucocorticoid receptor, GR)基因表达,降低 GR 基因启动子周围 H3K9 乙酰化水平,而增加甲基化水平[27];CSDS 升高小鼠前额叶 H3K14 乙酰化水平,而脑内给予 MS-275(Ⅰ类组蛋白去乙酰化酶抑制剂)则产生抗抑郁效应[28]。随着科学技术的进步,更多表观遗传修饰机制被陆续发现,可能会提供新的抑郁症预防策略和治疗靶点,如研究发现通道蛋白 CX43 的异常表观遗传修饰与抑郁症有关,因而有可能作为抗抑郁药物的新靶点[29]。

3.2　神经胶质细胞结构功能异常

神经胶质细胞是大脑中除神经元外的另一大类细胞,主要包括星形胶质细胞、小胶质细胞和少突胶质细胞。传统认为胶质细胞主要起支持、营养神经元及调节神经递质稳态的功能,但研究逐渐发现星形胶质细胞和小胶质细胞结构功能异常与抑郁症有密切关系[30-31]。早期临床发现抑郁患者大脑前额叶和扣带回胶质细胞密度显著降低[32-33],而海马胶质细胞密度显著升高[34],但这些研究没有具体区分胶质细胞类型。利用星形胶质细胞分子标记物进行的研究发现,抑郁患者海马齿状回和 CA1 区星形胶质细胞标记物 GFAP(glial fibrillary acidic protein)和 S100β 蛋白水平显著降低[35-36]。动物研究也发现慢性应激诱发动物抑郁样行为伴随着星形胶质细胞形态以及星形胶质细胞标志物 mRNA 和蛋白水平异常[37]。形态异常包括 CRS 降低树鼩海马星形胶质细胞体积[38]和大鼠前额叶星形胶质细胞突起长度、分支和体积[39],而 CUS 降低大鼠海马星形胶质细胞体积和突起长度[40]。标志物水平异常包括 CRS 降低树鼩海马[38]和大鼠杏仁核(而非海马)[41] GFAP 水平,MS 降低大鼠内侧前额叶(而非海马)GFAP 和 S100β 水平[42],而 CUS 降低大鼠海马和前额叶 GFAP mRNA 和蛋白水平[43-44]。但也有少数报道发现抑郁动物脑内星形胶质细胞标志物水平升高(如 CUS 升高大鼠海马和前额叶 GFAP 水平等)[45],或不同星形胶质细胞标记物之间的差异性变化(如 MS 和 CRS 升高大鼠前额叶 S100β 和 S100ss,但降低 GFAP 水平等)[39,46]。上述不一致结果可能是由多种影响因素所致,如不同类型的慢性应激和不同星形胶质细胞标志物的自身特性,其也进一步提示单一分子标记物不足以反映星形胶质细胞数量,需要两种以上标记物同时标记才能准确反映真实变化情况。除了影响星形胶质细胞形态和标志蛋白水平,慢性应激还影响星形胶质细胞膜上功能蛋白表达和功能,如谷氨酸转运体 1(GLT-1),其负责摄取清除大脑突触间隙谷氨酸从而维持稳态平衡[47]。研究发现,慢性应激诱导的动物抑郁样行为伴随着脑内星形胶质细胞膜上 GLT-1 表达水平显著降低,而 GLT-1 功能促进药物则有抗抑郁作用。如 CUS 诱导小鼠抑郁样行为,同时显著抑制海马和前额叶星形胶质细胞膜上 GLT-1 表达水平[48],而 GLT-1 活性促进药物利鲁唑有抗抑郁作用,同时挽救 CUS 引起的星形胶质细胞标志物 GFAP mRNA 水平异常[43]。研究发现,小鼠脑内星形胶质细胞源性 ATP 水平降低会使其更容易受 CSDS 影响从而出现抑郁样行为,而通过刺激升高星形胶质细胞源性 ATP 水平则有抗抑郁样作用[49]。此研究表明星形胶质细胞源性 ATP 与抑郁症发病和恢复密切相关,但其所涉及的具体生物学机制、不同脑区星形胶质细胞源性 ATP 的影响及星形胶质细胞源性和神经细胞源性 ATP 作用是否不同,这些问题的答案尚不清楚。

小胶质细胞是中枢神经系统的免疫细胞,其在大脑免疫监视、神经发生、突触修剪等过程中起重要作用[50]。临床研究发现抑郁患者大脑小胶质细胞被过度激活[30,51],动物研究也发现慢性应激诱发动物抑郁样行为的同时,会引起大脑(前额叶和海马等脑区)小胶质细胞结构功能异常和过度激活[30,52],提示小胶质细胞异常很可能参与了抑郁症

发病。如 CRS 增加大鼠前额叶小胶质细胞近端分支,而 MS 增加小鼠体感皮层小胶质细胞突起数量和运动性[53-54],而 CUS 增加大小鼠海马和前额叶小胶质细胞激活(小胶质细胞标志物 IBA1 水平升高)[45,55]。新近研究还发现抗抑郁药可调节小胶质细胞功能,从另一个方面说明小胶质细胞与抑郁症的密切关系[56]。除了影响星形胶质细胞和小胶质细胞结构和功能,研究还发现慢性应激会影响新胶质细胞发生(gliogenesis)和胶质细胞增生(gliosis),如 CUS 加剧了大小鼠海马和皮层星形胶质细胞和小胶质细胞增生,以及大鼠海马新星形胶质细胞发生异常[45,55,57],再次表明星形胶质细胞和小胶质细胞参与介导了慢性应激诱发抑郁症的过程。

3.3 线粒体功能障碍

线粒体既是活性氧(reactive oxygen species, ROS)和活性氮(reactive nitrogen species, RNS)主要来源之一,也是最容易受 OS 影响的细胞器,近期研究发现线粒体结构功能异常可能与抑郁症发病密切相关。临床发现抑郁患者大脑线粒体出现结构改变、酶活性降低和 ATP 生成减少等异常[58-59],而健身运动则会通过改善海马线粒体功能改善精神障碍[60]。动物研究则发现皮质酮诱导的小鼠抑郁样行为与线粒体能量代谢受损有关[61],而烟酰胺单核苷酸的抗抑郁作用正是通过减轻线粒体代谢受损[62]。线粒体代谢产生的 ATP 是机体主要能量来源,我国学者发现小鼠大脑星形胶质细胞源性 ATP 降低会导致抑郁样行为产生,增加星形胶质细胞源性 ATP 有抗抑郁作用,而小鼠前额叶 ATP 水平也在抑郁行为调控中起重要作用[49,63],表明大脑 ATP 水平异常是线粒体功能障碍参与抑郁症发病的重要途径。动物研究发现慢性应激诱发的抑郁样行为伴随着大脑线粒体功能障碍,如 MS 显著降低大鼠中缝背核线粒体呼吸功能[64]。但慢性应激是否通过降低前额叶和星形胶质细胞源性 ATP 水平诱发动物抑郁样行为?应激降低 ATP 水平以及脑内 ATP 减少导致抑郁样行为的具体机制是什么?需要大量研究来解答这些问题,从而进一步揭示线粒体功能障碍在抑郁症发病中的作用。

3.4 OS

氧化和还原是细胞的基本反应,氧化产生 ROS 和 RNS 等自由基,而体内抗氧化系统(抗氧化酶如超氧化物歧化酶,小分子抗氧化剂如谷胱甘肽)负责清除多余自由基,从而保持氧化还原反应稳态平衡。当体内氧化功能过剩或抗氧化系统功能不足时,氧化还原反应稳态失调,ROS/RNS 等自由基大量积蓄形成 OS 状态,使核酸、脂质和蛋白质发生过氧化,导致细胞损伤和机体病理反应[65]。OS 参与抑郁症发病是近年研究热点之一[66]。临床发现抑郁患者体内过氧化标志物水平显著升高[67],如 DNA 过氧化标志物 8-羟基脱氧鸟苷[68]和脂质过氧化标志物 F2-异前列腺素[69]。动物研究也发现慢性应激导致的抑郁样行为伴随着脑内过氧化标志物水平升高和抗氧化酶水平降低:CRS 升高大鼠海马和前额叶脂质过氧化标志物丙二醛(MDA)和蛋白质过氧化标志物羰基水平,降低超氧化物歧化酶活性[70];CUS 升高大鼠海马和皮层 ROS 和 MDA 水平,降低谷胱甘肽水平[45]。另外,临床和动物研究都发现抗抑郁药能显著降低过氧化标志物水平,如抑郁药氟西汀拮抗 CRS 引起的大鼠抑郁样行为,同时显著降低脑内 MDA 和羰基水平[67,70]。同时,研究还发现抗氧化剂具有抗抑郁作用,如二丙烯基二硫能逆转脂多糖诱导的小鼠抑郁样行为[71]。这些研究表明 OS 与抑郁症有密切关系,且是介导慢性应激诱发抑郁症的途径之一,其会通过影响神经内分泌系统,如引起 HPA 轴功能失调、GR 水平异常和谷氨酸兴奋毒性等,参与抑郁症发病[66,72]。

3.5 免疫炎症反应

临床研究发现,抑郁症患者体内免疫炎症反应会增强,大脑小胶质细胞会被过度激活产生大量小分子蛋白质(cytokine,细胞因子)来调节免疫应答,其中最受关注的是促炎细胞因子(pro-inflammatory cytokines)白介素-1β(IL-1β)、白介素-6(IL-6)和肿瘤坏死因子-α(TNF-α)[30,50-51]。进一步研究发现,抑郁患者和动物外周及脑内的促炎细胞因子水平均显著升高,而抗抑郁药会显著降低其水平,且抗炎药物有抗抑郁效果,因此抑郁症的细胞因子假说近些年被提出并备受关注[73-75],如抑郁患者大脑前额叶和海马等多个脑区的促炎细胞因子(TNF-α、IL-1 和 IL-6)均显著升高,而抗抑郁药和行为治疗则降低其水平[76-77]。动物研究也发现慢性应激诱发的抑郁样行为常伴随着促炎细胞因子水平显著升高[78]:MS 升高小鼠前额叶 IL-1β 水平[79];CUS 升高小鼠前额叶 IL-1β、TNF-α 和 IL-6 mRNA 水平[80],海马 IL-1β 及炎症小体 NLPR3(NOD-like receptor thermal protein domain associated protein 3)水平[81]和 TNF-α、IL-1 和 IL-6 水平[82],以及大鼠海马 TNF-

α 和 NF-κB(nuclear factor-κB)水平[45]。抗炎药物拮抗慢性应激诱发的动物抑郁样行为,而抗抑郁药则会显著降低促炎细胞因子水平:抗炎药物香叶醇和青藤碱显著降低 CUS 引起的促炎细胞因子高水平,并拮抗小鼠抑郁样行为[80,82];抗抑郁药显著降低多种促炎细胞因子水平,如氟西汀降低脂多糖诱导的抑郁小鼠 TNF-α、IL-1β 和 IL-6 mRNA 高水平[83-84]。上述研究表明免疫炎症反应(尤其是高促炎细胞因子水平)是介导慢性应激诱发动物抑郁样行为的途径之一(神经生物学机制有待进一步揭示),同时也是潜在的抑郁症预防和治疗靶点,如学者近期提出抗 TNF-α 化合物可作为潜在的新型抗抑郁药[85]。

3.6　MGB 轴

MGB 轴指大脑和胃肠道之间双向作用关系,肠道微生物菌群是其关键组分,肠道菌群通过迷走神经、免疫调节和色氨酸代谢等途径影响大脑功能,而大脑则通过神经内分泌和免疫调节等途径影响菌群组成(丰度和多样性)和代谢[86-87]。近年来,临床和动物研究发现,抑郁患者和动物肠道菌群组成和代谢异常,提示 MGB 轴功能异常与抑郁症有密切关系,其也成为抑郁症研究热点之一[88-90]。如临床研究发现抑郁患者双歧杆菌和乳酸杆菌丰度下降,而拟杆菌门、变形菌门和放线菌门丰度上升[89-90]。动物研究也发现慢性应激诱发的抑郁样行为常伴随着菌群丰度和多样性的显著异常:MS 降低小鼠肠道菌群多样性[91],CUS 降低大鼠乳杆菌属、梭状芽孢杆菌属和粪球菌属相对丰度[92],而 CSDS 增加小鼠梭菌属菌群丰度[93]。菌群多样性和相对丰度的不一致变化与多种影响因素有关,如慢性应激类型和菌群种属多样性。另外,抗抑郁药显著影响菌群丰度和多样性,挽救慢性应激诱发的动物抑郁样行为所伴随的菌群失调。多种抗抑郁药改变小鼠肠道菌群组成,如氟西汀降低菌群(变形杆菌和瘤胃球菌)丰富度,增加其 β-多样性[94],氯胺酮降低 CSDS 对梭菌属菌群的影响[93],而中药配方开心散拮抗慢性应激引起的小鼠肠道菌群异常[95]。动物研究还发现给予益生菌恢复肠道菌群稳态有抗抑郁效果,如双歧杆菌和鼠李糖乳杆菌改善 MS 引起的大小鼠抑郁样行为[96-97],而双歧杆菌也增强小鼠对 CSDS 的抵抗力[98]。上述研究说明肠道菌群与抑郁症有密切相关,以菌群失调为代表的 MGB 轴功能异常很可能是介导慢性应激诱发抑郁症的重要途径之一。

菌群失调诱发抑郁以及益生菌恢复菌群稳态的抗抑郁效果,主要通过调节脑内神经递质水平和功能发挥作用,如 5-HT、谷氨酸和 GABA 等[99]。动物研究发现益生菌可以调节脑内神经递质水平:双歧杆菌降低大鼠脑内去甲肾上腺素水平[96];长双歧杆菌和鼠李糖乳杆菌升高大鼠海马和前额叶 5-HT 水平[100],而乳酸乳球菌则升高小鼠脑内 5-HT 前体 5-羟基色氨酸(5-HTP)水平[101];鼠李糖乳杆菌降低小鼠海马和杏仁核 GABA mRNA 水平(但增加其皮层水平)[97],而乳酸杆菌则增加小鼠脑内 GABA 水平[102];乳酸杆菌增加小鼠脑内谷氨酸水平[102]。近期动物研究进一步发现益生菌能逆转慢性应激引起的神经递质异常,从而拮抗抑郁样行为:鼠李糖乳杆菌升高 CUS 引起的大鼠脑内 GABA、谷氨酸和谷氨酰胺低水平[103-104];长双歧杆菌、鼠李糖乳杆菌和乳酸乳球菌升高 CUS 引起的大小鼠海马和前额叶 5-HT、5-HTP 和 BDNF 低水平[100-101]。以肠道菌群影响脑内 5-HT 系统为例,体内约 90% 的 5-HT 是由肠道嗜铬细胞合成,其生理条件下不会穿过血脑屏障(前体色氨酸则可以),因而肠道菌群会通过影响色氨酸代谢影响脑内 5-HT 递质水平[87,105]。要全面揭示肠道菌群和中枢神经递质变化的对应关系,尤其是不同种属菌群、不同脑区和不同神经递质的一一对应关系,还需要进行大量研究工作。但通过给予益生菌和健身运动等方式恢复肠道菌群稳态和 MGB 轴功能,无疑是一条有前景的抑郁症预防和治疗路径[106-107]。

4　总结和展望

抑郁症影响人群范围越来越广、人数越来越多,成为严重影响患者及家人身体、精神健康且亟待解决的社会问题。慢性应激是抑郁症主要临床诱因,利用慢性应激动物模型进行致病机制和治疗研究,有助于快速有效地将动物实验结果向临床应用转化。现有综述主要围绕经典的 HPA 轴异常、单胺类和神经可塑性缺陷、大脑不同脑区和神经元结构功能、中枢神经递质和因子及其受体等方面异常展开。为充分阐明慢性应激诱导动物抑郁样行为机制的研究进展,本文综述了慢性应激引起的基因变异和表观遗传修饰、神经胶质细胞(星形胶质细胞和小胶质细胞)结构功能异常、线粒体功能障碍、机体系统水平异常(OS、炎症反应和 MGB 轴),旨在

系统呈现近年相关研究热点和新发现,为后续有针对性地深入研究致病机制,及其临床预防和治疗提供新思路和靶点。

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