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内源性大麻素系统激活调节抑郁症的作用机制

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摘 要:抑郁症是一种常见的神经精神疾病,其发病机制错综复杂,涉及生物、心理和社会等多个层面。内源性大麻素系统(endocannabinoid system,ECS)广泛分布于生物体内,参与调节情绪、认知和行为等多方面的功能。ECS在改善抑郁症中扮演重要角色,调节ECS可以通过抑制神经炎症、维持下丘脑-垂体-肾上腺轴(hypothalamic-pituitary-adrenal axis,HPA轴)稳态和改善神经可塑性异常等途径缓解抑郁症症状。本文综述了ECS在抑郁症中的调控作用,并探讨了其作为治疗靶点的潜在应用。未来,基于ECS开发的治疗手段有望成为抑郁症治疗的新方向。

关键词:内源性大麻素系统;抑郁症;神经炎症;HPA轴;神经可塑性
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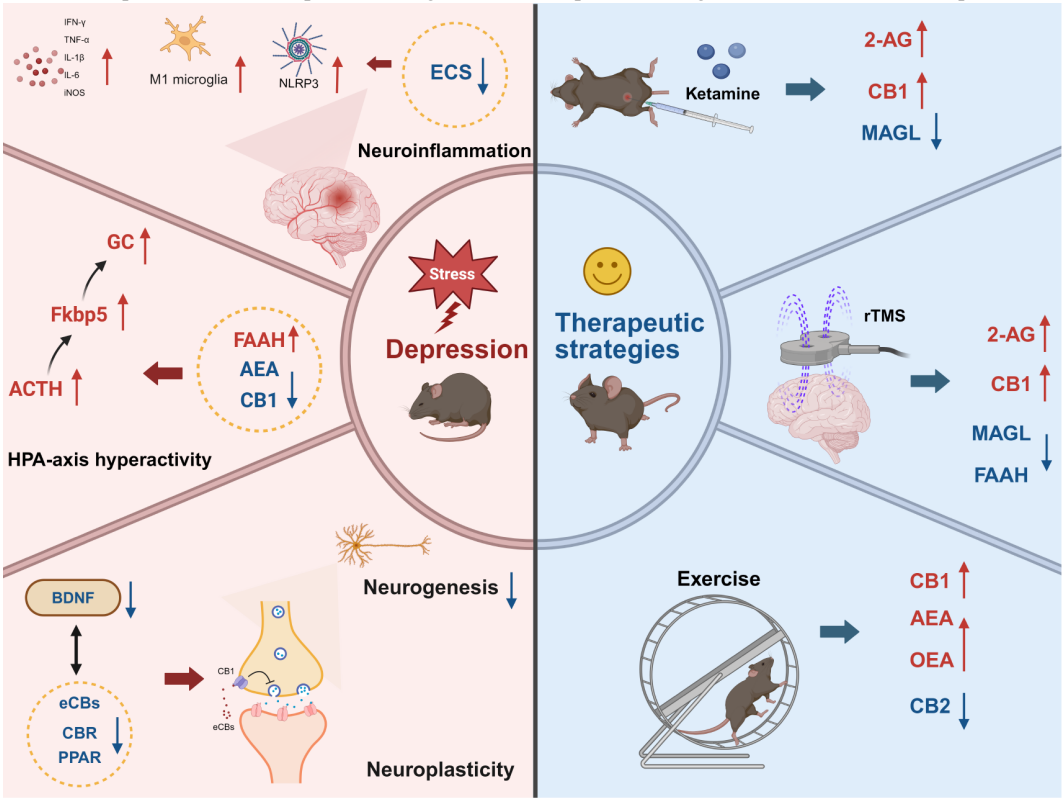
Mechanism of endocannabinoid system activation in regulating depression

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Abstract: Depression is a prevalent neuropsychiatric disorder with complex and heterogeneous pathogenesis, involving interactions among chronic stress, immune activation, endocrine dysregulation, impaired neuroplasticity, and psychosocial factors. Although the monoamine hypothesis has long guided antidepressant development, delayed therapeutic onset and limited efficacy in some patients indicate that additional biological mechanisms and therapeutic targets should be considered. The endocannabinoid system (ECS), consisting mainly of endogenous ligands such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG), cannabinoid receptors including CB1 and CB2, and metabolic enzymes such as FAAH and MAGL, is widely distributed in the central nervous system and peripheral tissues. It participates in the regulation of mood, cognition, stress responses, immune activity, and synaptic transmission, making it a promising target for understanding and treating depression. This review summarizes current evidence on ECS alterations in depressive states and discusses the mechanisms by which ECS activation may alleviate depressive symptoms. First, ECS signaling can suppress neuroinflammation by regulating microglial polarization, inhibiting NLRP3 inflammasome activation, and reducing the release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. CB2 receptor activation appears particularly important in limiting excessive microglial activation and restoring immune balance. Second, ECS activity contributes to the maintenance of hypothalamic-pituitary-adrenal (HPA) axis homeostasis. Stress-induced disruption of the FAAH-AEA-CB1 receptor pathway may increase the release of adrenocorticotropic hormone and glucocorticoid, whereas enhancing endocannabinoid tone may reduce HPA-axis hyperactivity. Third, ECS signaling interacts with brain-derived neurotrophic factor (BDNF) and related pathways to improve neuroplasticity, including hippocampal neurogenesis, synaptic remodeling, and neural circuit adaptation. In addition to its role in depression pathophysiology, ECS may also mediate the effects of current and emerging therapeutic strategies. Pharmacological treatments such as ketamine may influence ECS-related targets, while non-pharmacological interventions, including repeated transcranial magnetic stimulation (rTMS) and exercise, can enhance endocannabinoid signaling and improve mood-related outcomes. Exercise, in particular, may exert

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antidepressant effects by increasing endocannabinoid levels, reducing neuroinflammation, promoting neurogenesis, and improving synaptic function. Nevertheless, existing findings remain inconsistent across brain regions, disease models, and detection methods, and peripheral endocannabinoid changes may not fully reflect central ECS activity. Overall, ECS does not act through a single pathway but may serve as an integrative regulatory system linking neuroimmune responses, endocrine stress regulation, and neural plasticity. Future studies should clarify brain region-, cell type-, and circuit-specific ECS mechanisms, examine interactions between ECS and other systems such as the gut microbiota, and explore ECS-based pharmacological and non-pharmacological interventions for depression.



Key words: endocannabinoid system (ECS); depression; neuroinflammation; HPA axis; neuroplasticity

抑郁症是一种对社会产生广泛影响的精神障碍性疾病。世界卫生组织最新数据显示，在全球范围内约3.22亿人患有抑郁症，约占世界总人口的4.4%[1]。抑郁症已经成为导致残疾的主要原因之一。抑郁症患者常伴随睡眠障碍、进食障碍、情绪持续低落及自杀倾向等特征，这些不仅给患者个人带来沉重的痛苦，也给社会造成了巨大的负担。抑郁症发病机制错综复杂，致病假说包括：单胺类神经递质假说、神经炎症假说、下丘脑-垂体-肾上腺轴（hypothalamic-pituitary-adrenal axis，HPA轴）功能障碍假说以及神经可塑性假说等[2]。长期以来，单胺类神经递质的减少被视为抑郁症的主要致病因素，但相关抗抑郁药物往往存在起效慢、治疗周期长及对重症患者疗效不佳等问题。这说明抑郁症可能并非单一因素所致，因此，探索新的抗抑郁靶点及开发新型治疗方法在抑郁症的临床治疗中显得尤为重要。越来越多的研究表明，内源性大麻素系统（endocannabinoid system，ECS）在人体情绪调节中发挥重要作用，增强ECS信号传导具有抗抑郁潜力。重复经颅磁刺激（repeated transcranial magnetic stimulation，rTMS）和运动等非药物疗法也被证明是治疗抑郁症的有效手段，而且这些非药物疗法均可调节ECS。本文首先概述了ECS在情绪调节中的关键作用，随后探讨了ECS在抑郁症发病中的作用机制及当前研究中存在的问题（图1），最后分析了当前抑郁症药物治疗及非药物疗法对ECS的影响，为深入研究ECS在抑郁症中的作用机制提供新思路，并为抑郁症的药物和非药物治疗提供新靶点。

1　ECS概述

ECS是广泛存在于中枢神经系统的生物调节系

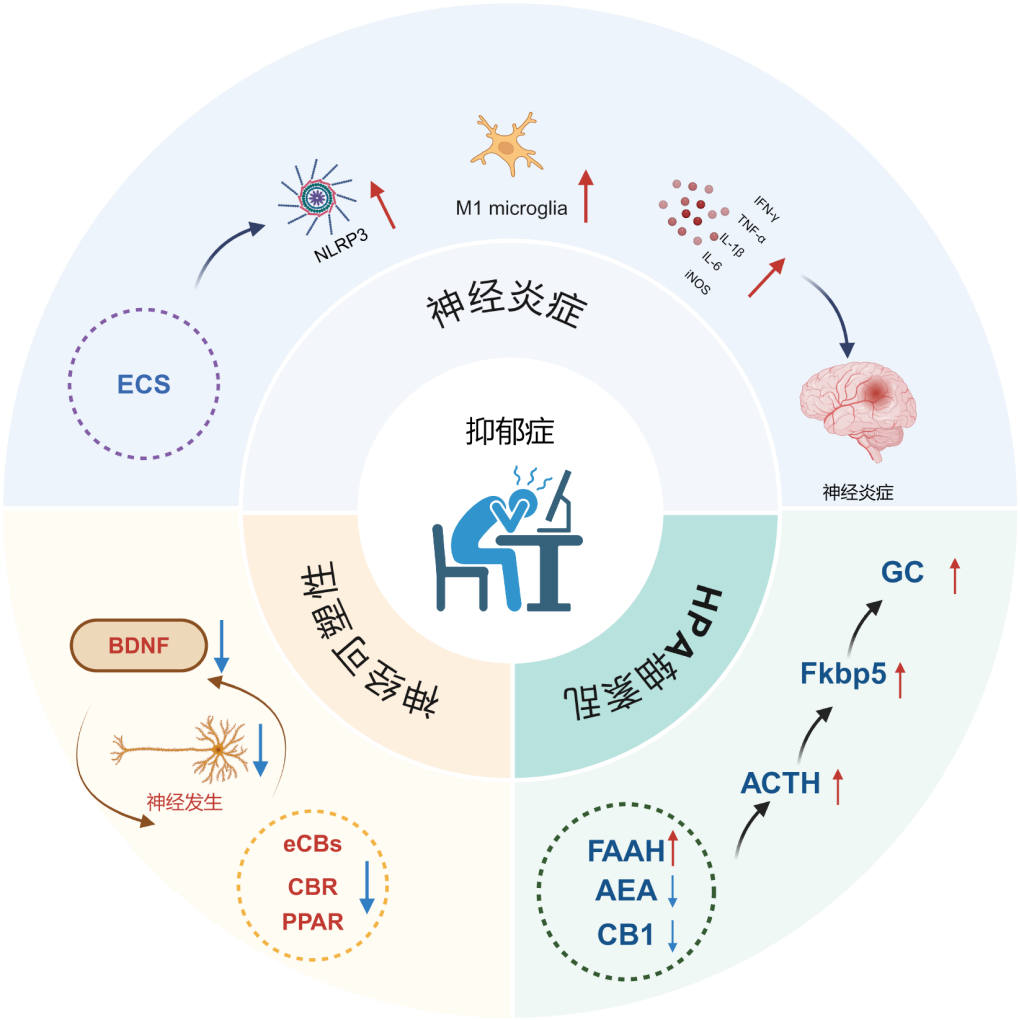


图1 ECS信号参与抑郁症发病的机制

抑郁症的发病机制错综复杂，而单胺类神经递质减少假说无法完全解释抑郁症的发病机制。神经炎症假说、HPA轴功能障碍假说以及神经可塑性假说从不同角度解释了抑郁症的病理机制。ECS信号衰退导致M1型小胶质细胞和NLRP3炎症小体过度激活，促炎因子释放增加，诱发神经炎症。负面情绪引起ECS中FAAH-AEA-CB1受体信号通路紊乱，诱导ACTH水平升高，引起外周GC释放增加，HPA轴稳态失衡。抑郁情绪诱发ECS与BDNF协同作用异常，导致神经发生水平下降，最终引发抑郁症。

Figure 1 ECS signaling in the pathogenesis of depression

The pathogenesis of depression is complex and multifactorial, and the monoamine neurotransmitter deficiency hypothesis cannot fully explain its underlying mechanisms. The neuroinflammation hypothesis, HPA-axis dysfunction hypothesis, and neuroplasticity hypothesis provide complementary perspectives on the pathological mechanisms of depression. Impaired ECS signaling may promote excessive activation of M1 microglia and the NLRP3 inflammasome, leading to increased release of pro-inflammatory cytokines and neuroinflammation. Negative emotional states may disrupt the FAAH-AEA-CB1 receptor signaling pathway within the ECS, resulting in elevated ACTH levels, increased peripheral glucocorticoid release, and impaired HPA-axis homeostasis. In addition, depressive states may disturb the interaction between ECS signaling and BDNF-related pathways, thereby reducing neurogenesis and ultimately contributing to the development of depression.

统，主要由内源性大麻素(endocannabinoids，eCBs)、大麻素受体(cannabinoid receptors，CBRs)，以及负责合成和降解内源性大麻素的酶组成，在调节情绪、认知、记忆以及免疫等方面起着至关重要的作用[3]。(1)eCBs：N-花生四烯酸乙醇胺(anandamide，AEA)和2-花生四烯酸甘油(2-arachidonoylglycerol，2-AG)是最主要的两种内源性配体。AEA由N-酰基-磷脂酰乙醇胺-磷脂酶D(N-acyl-phosphatidylethanolamine hydrolyzing phospholipase D，NAPE-PLD)水解N-酰基磷脂酰乙醇胺(N-acyl-phosphatidylethanolamine，NAPE)生成；磷脂酶Cβ(phospholipases C beta，PLCβ)催化磷脂酰肌醇-4，5-二磷酸(PIP_2)生成二酰基甘油

(diacyl glycerol，DAG)，DAG再经二酰基甘油脂肪酶α和β(diacylglycerol lipase α and β，DAGLα&β)水解生成2-AG。AEA和2-AG在突触后膜受到刺激时按需合成，扩散至突触间隙，并结合突触前膜上的大麻素受体发挥作用。(2)CBRs：包括大麻素受体1型(cannabinoid receptor 1，CB1)和大麻素受体2型(cannabinoid receptor 2，CB2)。CB1受体主要分布在海马、前额叶皮层(prefrontal cortex，PFC)、基底外侧杏仁核(basal lateral amygdala，BLA)和中央杏仁核等区域，在神经胶质细胞中也有表达；CB2受体主要在被激活的小胶质细胞中表达，最新研究发现CB2受体也存在于海马、腹侧被盖区和红核等脑区。(3)负责eCBs合成和降解的内源性大麻素代谢酶，如DAGLα/β、NAPE-PLD、脂肪酸酰胺水解酶(fatty acid amide hydrolase，FAAH)和单酰基甘油脂肪酶(monoacylglycerol lipase，MAGL)等。

2　ECS在情绪调节中的变化

诸多研究表明，精神障碍模型或精神疾病患者的ECS信号出现显著变化(表1)。然而，目前ECS在情绪调节中的作用尚不清晰，诸多精神障碍模型的中枢神经系统ECS信号的变化结果并不一致。例如，动物研究发现，大多数精神障碍模型的eCBs水平(尤其是AEA)显著降低，但在慢性不可预测轻度应激模型(chronic unpredictable mild stress，CUMS)的杏仁核中eCBs无显著变化[4,5]。大多数精神障碍模型中枢神经系统中的CB2受体水平明显升高，但CB1受体的变化并不一致[6-9]。以上研究结果提示，ECS信号变化不一致可能是由于被检测脑区功能不同、检测方法不同、ECS作用位点不同及各种精神障碍模型的建模方式不同。在突触部位，eCBs在突触后膜受刺激后按需产生，经“合成-释放-受体”全过程对突触前递质释放进行抑制，因此eCBs含量未发生改变，并不一定代表ECS的调节能力未出现变化。CB1受体主要定位于突触前膜，但上述研究检测的主要是总蛋白中CB1受体的水平或CB1受体基因转录水平，并不能反映膜上发挥功能的CB1受体的变化特征。此外，CB1受体定位于兴奋性或抑制性突触末梢，会对神经环路的兴奋/抑制产生不同影响，但上述研究并未特异性检测是兴奋性还是抑制性突触末梢CB1受体发生了变化，因此后期实验需针对性探究不同脑区特异性神经环路上CB1受体的功能变化特点。临床研究发现，重症抑郁症(major depressive disorder，MDD)患者的血浆中AEA水平

表1　不同精神障碍模型与精神疾病患者ECS信号变化的部分研究结果

Table 1　Partial research findings on changes in ECS signals in different mental disorder models and patients with psychiatric disorders

精神障碍模型/精神障碍患者	检测部位	研究方法	ECS信号	参考文献
孤独症大鼠模型	海马、前额叶皮层	液相色谱质谱法、定量PCR和免疫印迹	海马中eCBs(AEA、2-AG)水平↓；CB1受体水平↑，CB2受体mRNA水平↑，CB2受体蛋白水平↔；FAAH和DAGL mRNA水平↑，FAAH和MAGL蛋白水平↑；前额叶皮层中eCBs水平↔	[10]
吗啡成瘾小鼠模型	中脑腹侧被盖区	免疫印迹、定量PCR	AEA和2-AG水平↔；CB2受体mRNA水平↓，CB1受体水平↔；DAGLα和MAGL水平↔	[6]
慢性不可预测轻度应激模型	杏仁核	液相色谱质谱法	eCBs(AEA、2-AG、PEA和OEA)水平↔	[11]
焦虑小鼠模型(129S1/SvImJ)	杏仁核、前额叶皮层和海马	定量RT-PCR	CB2受体水平↑	[4]
恐惧消除受损模型	基底外侧杏仁核、海马	液相色谱质谱法、定量RT-PCR	2-AG水平↑，小胶质细胞中CB2受体水平↑	[7]
慢性社交挫败压力模型	伏隔核	液相色谱质谱法	2-AG水平↓	[8]
Wistar-Kyoto抑郁大鼠模型	额叶皮层、海马	免疫印迹	AEA水平↓；CB1受体水平↑；FAAH水平↑，NAPE-PLD水平↔	[12]
早期生活压力诱导的抑郁模型	内侧前额叶皮层	定量RT-PCR	CB1受体mRNA水平↓	[5]
孤独症儿童	血浆	液相色谱质谱法、定量PCR和免疫印迹	eCBs(AEA、2-AG、PEA和OEA)水平↓；CB2受体水平↑；FAAH和MAGL水平↑，DAGL mRNA水平↑	[10]
重症抑郁症患者	血浆	液相色谱质谱法	AEA水平↑；2-AG水平↓	[9]

注：PEA，棕榈酰乙醇酰胺(palmitoylethanolamide)；OEA，油酰乙醇酰胺(oleoylethanolamide)。

Note: PEA, palmitoylethanolamide; OEA, oleoylethanolamide.

升高,2-AG水平显著降低[9]。由于ECS既存在于外周也存在于中枢,因此血浆中AEA和2-AG的变化并不一定能准确反映MDD患者中枢中eCBs的变化。由此可见,抑郁症中ECS的变化特征十分复杂,而且具有脑区特异性。但总体而言仍能从中寻得规律:ECS信号下调可能是导致精神障碍的关键。eCBs代谢酶活性增强致使eCBs水平显著下降是ECS信号下调的重要原因,而CBRs增加可能是精神障碍后的代偿性反应。因此,增强ECS信号可能是治疗压力和焦虑等精神障碍的新靶点。

3 ECS在抑郁症发生中的作用机制

3.1 ECS抑制抑郁症中的神经炎症反应

神经炎症假说认为,长期压力刺激诱导的神经炎症导致中枢神经系统出现不可逆转的损伤,最终导致抑郁症的形成。研究发现,在脂多糖(lipopolysaccharides,LPS)诱导的抑郁模型中神经炎症水平升高,而抗抑郁药物氟西汀同时具有减轻神经炎症的作用[13]。另有研究发现,MDD患者表现出持续的慢性神经炎症,包括核苷酸结合寡聚化结构域样受体含pyrin结构域蛋白3(nucleotide-binding oligomerization domain-like receptor family, pyrin domain-containing 3,NLRP3)表达增加,以及血清中白细胞介素-1β(interleukin-1β,IL-1β)和白细胞介素-18(interleukin-18,IL-18)水平升高[14]。此外,临床研究表明非甾体抗炎药、米诺环素等抗炎类药物对MDD具有显著的抗抑郁作用[15]。以上研究证明,神经炎症与抑郁症的发病过程密切相关。目前,抑郁模型和抑郁症患者神经炎症相关研究主要集中在以下几个方面。(1)小胶质细胞过度激活。这是神经炎症的重要特征,大多数抑郁模型中小胶质细胞M1/M2极化失衡,可能是抑郁情绪的重要诱因。研究发现,CUMS诱导的抑郁模型海马脑区中M1型小胶质细胞水平升高,M2型小胶质细胞水平下降,并表现出抑郁样行为[16]。而在LPS诱导的抑郁模型中,通过抑制小胶质细胞核因子-κB(nuclear factor kappa-B,NF-κB)和丝裂原活化蛋白激酶(mitogen-activated protein kinase,MAPK)通路,可以降低小胶质细胞活化水平,缓解抑郁情绪[13]。(2)NLRP3炎症小体过度激活。NLRP3炎症小体由NLRP3蛋白、caspase-1前体(precursor caspase-1, pro-caspase-1)和凋亡相关斑点样蛋白(apoptosis speck-like protein containing a caspase recruitment domain,ASC)组成。研究发现,CUMS抑郁模型海马脑区NLRP3炎症小体过度激活,并伴随快感缺失和抑郁情绪[17],而NLRP3炎症小体抑制剂被认为是潜在的新型抗抑郁治疗药物[18]。(3)促炎因子释放增加,例如IL-1β、IL-6、肿瘤坏死因子-α(tumour necrosis factor-alpha,TNF-α)等。压力等因素诱导M1型小胶质细胞和NLRP3炎症小体过度激活,并释放出更多的促炎性细胞因子,而促炎性细胞因子反过来促进M1型小胶质细胞和NLRP3炎症小体过度激活,最终形成恶性循环,产生快感缺失等抑郁样行为[14]。

ECS信号的调节具有抗炎和抗抑郁作用,被认为是一种内源性保护机制。CB2受体在激活的小胶质细胞中广泛存在。有研究报道,在活化的小胶质细胞中CB2受体mRNA水平升高20倍[19]。目前普遍认为CB2受体在抗炎过程中发挥重要作用(图2),其机制可能包括以下几个方面。(1)激活的CB2受体通过调节小胶质细胞表型极化改善神经炎症。CB2受体激动剂JWH-133(一种合成大麻素)通过调节cAMP/PKA和PI3K/Akt/Nrf2信号通路促进小胶质细胞由M1型向M2型转化,增加抗炎细胞因子释放,发挥抗炎作用[20,21]。此外,阻断CB2受体可以消除安非他命对LPS诱导的M1型小胶质细胞过度激活的抑制作用,而非阻断CB1受体[22]。另有研究结果显示,合成大麻素还通过激活CB2受体抑制小胶质细胞中的MAPK通路,抑制促炎细胞因子的释放,降低小胶质细胞的促炎活性[23]。(2)激活的CB2受体通过抑制NLRP3炎症小体改善神经炎症。例如,CB2受体激动剂β-石竹烯(β-caryophyllene,BCP)通过抑制NLRP3炎症小体活化来降低神经炎症水平[24];类似地,在慢性酒精暴露模型中CB2受体激动剂AM1241通过抑制PFC中的小胶质细胞NLRP3炎症小体活化,改善慢性酒精暴露诱导的戒断期间的焦虑样行为[25];CB2受体激动剂JWH-133通过促进NLRP3清除来减轻由小胶质细胞极化介导的神经炎症[26]。研究发现,CB2受体激活促进NLRP3清除可能与膜相关环指蛋白7(membrane associated ring-CH-type finger 7,MARCHF7)表达增加有关[27,28]。(3)激活的CB2受体通过抑制促炎因子释放改善神经炎症[29]。CB2受体激动剂JWH-133可抑制应激诱导的额叶皮层促炎因子和NF-κB的表达,从而改善神经炎症,而CB2受体过表达模型表现

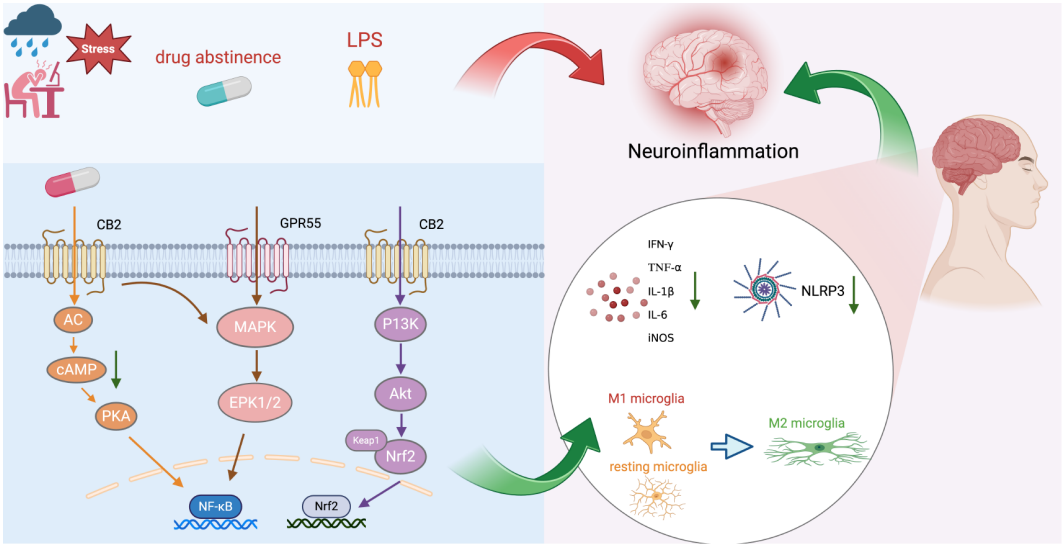


图2　ECS信号在抑郁症诱导的神经炎症中的分子机制

压力、成瘾药物戒断以及脂多糖(LPS)等是抑郁症的重要诱因，同时这些刺激会导致中枢神经系统免疫系统过度激活，诱发神经炎症。抑郁症中的神经炎症主要表现为M1型小胶质细胞和NLRP3炎症小体过度激活，导致促炎因子释放增加。CB2受体激动剂JWH-133通过cAMP/PKA通路以及PI3K/Akt/Nrf2信号通路抑制M1型小胶质细胞的过度激活，减轻神经炎症。激活的CB2受体还可以通过MAPK通路减少促炎因子的释放。此外，大麻素受体GPR55激活后通过抑制MAPK通路，发挥与CB2受体相似的抗炎作用。

Figure 2　Molecular mechanisms of ECS signaling in depression-induced neuroinflammation

Stress, withdrawal from addictive substances, and lipopolysaccharides (LPS) exposure are important factors contributing to depression. These stimuli can also induce excessive activation of the central nervous system immune response, leading to neuroinflammation. Neuroinflammation in depression is mainly characterized by overactivation of M1-like microglia and the NLRP3 inflammasome, accompanied by increased release of pro-inflammatory cytokines. The CB2 receptor agonist JWH-133 may inhibit excessive M1-like microglial activation through the cAMP/PKA pathway and the PI3K/Akt/Nrf2 signaling pathway, thereby attenuating neuroinflammation. Activation of CB2 receptors may also reduce the release of pro-inflammatory cytokines through the MAPK pathway. In addition, activation of the cannabinoid-related receptor GPR55 may exert anti-inflammatory effects similar to CB2 receptor activation by modulating the MAPK signaling pathway.

出类似的抗炎作用[30]。相反，CB2受体敲除转基因模型(CB2-KO小鼠)加剧了压力诱导的神经炎症[31]。以上研究表明，激活ECS，尤其是CB2受体，可通过抑制M1型小胶质细胞和NLRP3炎症小体的过度激活，减少促炎因子释放，进而减轻神经炎症，这可能是ECS参与调节抑郁症神经炎症的作用机制之一。但是近年也有研究发现了矛盾的结果：在先天高焦虑水平小鼠(129S1/SvImJ小鼠)的杏仁核、海马、PFC中CB2受体表达升高，腹腔注射CB2受体拮抗剂SR144528可缓解焦虑样行为[4]。这可能与以下因素有关：(1)该研究采用了天然的高焦虑水平模型，与接受不可预测应激刺激导致的抑郁模型在行为学表型、受累脑区、神经炎症特点和HPA轴激活模式上存在显著不同；(2)在天然焦虑模型中，CB2受体表达升高可能是代偿性反应，即小鼠天生表现出较高水平的神经炎症，这与后天接受应激刺激导致CB2受体表达升高和功能异常不同；(3)腹腔注射SR144528也会对外周的CB2受体产生拮抗作用，从而减少外周免疫细胞向中枢的浸润[32]；(4)除CB2受体外，SR144528也可能作用于A3腺苷受体(adenosine A3 receptor，A3AR)和5型磷酸二酯酶(phosphodiesterase 5，PDE5)，也可能通过非受体途径(如膜胆固醇调节)发挥抗炎作用[33]。最新研究发现，非典型大麻素受体GPR55也能够改善抑郁症神经炎症(图2)。GPR55的激活可以通过抑制甲基苯丙胺(methamphetamine，METH)戒断期小胶质细胞的活化和增殖以及NLRP3炎症小体蛋白的表达，抑制METH所诱导的神经炎症，改善抑郁情绪[34]；此外，也可以通过抑制MAPK通路发挥与CB2受体相似的抗炎功能[35]。综上所述，ECS对神经炎症的调节作用主要通过CB2受体实现，CB2受体激活能够抑制抑郁症相关神经炎症中的促炎效应，而非典型大麻素受体GPR55的激活也具有改善神经炎症的作用。

3.2 ECS缓解抑郁症中的HPA轴过度激活

HPA轴由下丘脑、垂体、肾上腺组成，是应激反应的核心调节系统。长期的压力会诱发HPA轴过度激活，导致糖皮质激素(glucocorticoid，GC)分泌增加，最终导致抑郁症[36]。GC是HPA轴过度激活的最终产物，高水平GC是抑郁症的重要诱因之一。研究发现，CB1受体拮抗剂AM251显著上调应激诱导的血浆中促肾上腺皮质激素(adrenocorticotropic hormone，ACTH)和GC的水平[37]。此外，在慢性社会挫败应激(chronic social defeat stress，CSDS)诱导的CB1受体缺陷模型小胶质细胞中，GC调节因子FKBP脯氨酰异构酶5(FKBP prolyl isomerase 5，FKBP5)表达增加，诱发HPA轴紊乱[38]。连续3周抗抑郁药地昔帕明治疗后，海马和下丘脑CB1受体密度显著增加，血浆GC水平显著降低，且CB1受体激动剂表现出与抗抑郁药相似的治疗效果[39]。另有研究发现，20 min约束应激可诱导BLA内FAAH活性增加，抑制AEA/CB1受体通路，最终导致HPA轴过度激活[40]。此外，FAAH抑制剂URB597可以降低慢性应激(chronic unpredictable stress，CUS)模型肾上腺重量和血清皮质酮水平，抑制CUS诱导的HPA轴过度激活，改善抑郁情绪[41]。综上所述，ECS与抑郁症HPA轴过度激活密切相关，压力等负面情绪可造成ECS中FAAH-AEA-CB1受体信号通路紊乱，诱导ACTH水平升高，进而引起外周GC释放增加，最终HPA轴稳态失衡，导致抑郁症发生。以上结果虽然表明了ECS在调节GC中的重要性，然而GC主要作用于糖皮质激素受体(glucocorticoid receptor，GR)和盐皮质激素受体(mineralocorticoid receptor，MR)，GR/MR的失调也是HPA轴稳态失衡的重要原因，因此ECS是否参与调节GR和MR激活还需要进一步探究。

3.3 ECS改善抑郁症神经可塑性异常

神经可塑性是指大脑适应环境变化和学习新事物的能力，神经元的生长、突触可塑性和神经回路重塑等均可调节神经可塑性。在抑郁症患者中，神经可塑性通常发生显著损伤，尤其是在关键脑区如海马和PFC，研究表明这些区域的神经发生显著下降，导致情绪调节能力减弱、认知功能受损以及抑郁症状加重。脑源性神经营养因子(brain-derived neurotrophic factor，BDNF)是调节突触可塑性、海马神经发生的关键因子。研究发现，在CUMS、慢性束缚应激(chronic restraint stress，CRS)以及LPS诱导的抑郁模型中，海马以及前额叶皮质等脑区BDNF水平显著下降，抑制神经发生，并诱发抑郁情绪[42-45]。目前ECS与BDNF协同改善抑郁症的证据主要包括以下几个方面。(1)eCBs与BDNF协同发挥抗抑郁作用。研究发现，MAGL抑制剂JZL184通过减少2-AG的降解显著增加BDNF表达，改善早期生活压力(early life stress，ELS)诱导的抑郁情绪[46]。另有研究发现，FAAH抑制剂URB597通过增强AEA/CB1受体信号传递，激活TrkB/BDNF信号，改善认知功能[47]。类似地，URB597在社会隔离模型和WKY抑郁大鼠模型中也能提高BDNF水平，发挥抗抑郁作用[48,49]。此外，BDNF还可以选择性激活突触后原肌球蛋白受体激酶B(tropomyosin receptor kinase B，TrkB)，继而激活PLCγ/DGL通路释放eCBs，eCBs逆行并激活突触前的CB1受体，通过抑制AC/PKA信号转导抑制突触间传递，发挥神经保护作用[50]。(2)CBRs与BDNF协同发挥抗抑郁作用[51]。研究发现，激活CB1受体能够增强突触可塑性并促进神经元的生长和连接，其机制可能是CB1受体激活通过调节ERK/CREB信号通路磷酸化上调了BDNF的表达[52]。研究发现，CB1受体敲除小鼠对压力更加敏感，对其海马局部施用 BDNF可改善CB1受体敲除诱导的压力敏感，减少敲除小鼠的绝望行为[53]。CB2受体与BDNF的协同同样值得关注。激活CB2受体不仅能够减少神经炎症，还能通过调节BDNF的表达促进神经发生。研究发现，CB2受体阻断剂AM630可阻断大麻二酚(cannabidiol，CBD)在雌性抑郁大鼠中的抗抑郁作用，并逆转CBD诱导的BDNF表达增加[54]。此外，与对照组相比，CB2受体过表达的转基因小鼠海马中BDNF基因表达水平更高，并表现出更强的抗压能力[55]。(3)其他CBRs的传导。近年来，过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptors，PPARs)在神经可塑性和抗抑郁治疗中的作用逐渐受到关注。PPARs被认为是非典型CBRs，可以被PEA、AEA和2-AG等eCBs激活[56]。研究发现，海马PPAR-α介导了抗抑郁药物氟西汀在CSDS抑郁模型中的抗抑郁作用[57]。此外，PPAR-α的选择性激动剂逆转了CSDS诱导的抑郁模型海马中的BDNF信号通路以及成人海马中的神经衰退，改善了抑郁情绪[58]。在LPS诱导的抑郁模型中，

PPAR-γ激动剂通过调节CREB/BDNF通路减少了抑郁样行为[59]。2019年的一项研究发现，PEA通过激活PPAR-α恢复海马BDNF水平，改善CUMS诱导的抑郁样行为，而PPAR-α拮抗剂MK886可消除PEA对海马BDNF的影响[60]。综上所述，ECS与BDNF协同调节海马神经发生，发挥突触传递调节、神经保护等作用。未来针对ECS与BDNF协同作用的研究或许能够为抑郁症的治疗提供新的思路。

3.4 ECS在三大机制交互中的作用

抑郁症的发生过程可能并非单一因素所致。研究发现，压力可导致活化小胶质细胞产生促炎细胞因子，诱导HPA轴过度激活，以及促肾上腺皮质激素释放激素（corticotropin releasing hormone，CRH）、ACTH和GC增加[61]。另有研究发现，在腹腔注射LPS诱导的慢性神经炎症模型中，PFC和海马中BDNF基因和蛋白质表达显著降低并导致抑郁样行为[62]。这提示，在抑郁症发病过程中，神经炎症、HPA轴紊乱和神经可塑性异常存在一定的交互作用。ECS作为串联三大机制的桥梁，可能是治疗抑郁症的新靶点。如上所述，CB2受体激动剂JWH-133治疗具有抗炎作用，同时还能显著增加大鼠海马BDNF基因的表达[63]。此外，研究发现ECS信号增强可抑制HPA轴过度激活，同时调节海马CREB-BDNF通路磷酸化，促进BDNF的表达[64]。以上结果表明，ECS不是仅靶向抑郁症的单一病理机制，而是从整体调节抑郁症病理条件下的神经炎症、HPA轴紊乱和神经可塑性，进而改善抑郁情绪。

4 ECS是当前抑郁症临床治疗的重要靶点

4.1 药物治疗手段

新型“速效”抗抑郁药氯胺酮（ketamine，KET）已被批准用于治疗难治性抑郁症，而ECS可能参与氯胺酮抗抑郁的过程[65]。最新研究发现，急性艾司氯胺酮（S-ketamine，S-KET）治疗显著上调弗林德斯敏感系（Flinders sensitive line，FSL）抑郁模型PFC脑区中2-AG的水平，但对AEA无影响；其可能机制是：通过促进MAGL基因负转录因子PRDM5的表达，抑制MAGL活性，导致2-AG水平增加[66,67]。进一步研究发现，S-KET可降低CB1受体基因表达，并提高CB1受体利用效率，但CB1受体拮抗剂利莫那班（Rimonabant）不会干扰S-KET诱导的抗抑郁行为[66]。这可能是由于S-KET通过直接调节ECS的其他靶点发挥抗抑郁作用，例如脂肪酸结合蛋白5（fatty acid-binding protein 5，FABP5）、FAAH和MAGL[66]。而另一种CB1受体抑制剂AM251表现出不同的作用，其可逆转KET诱导的CB1受体上调，消除KET的神经保护作用[68]。还有一项研究发现，无效剂量的KET和AM251联合给药也能诱导出抗抑郁样效应[69]。综上所述，KET可能通过作用于ECS多个靶点发挥抗抑郁作用，但其机制尚不清晰。不同CB1受体抑制剂表现出不同的作用，可能与Rimonabant和AM251的作用机制存在差异有关：Rimonabant是CB1受体的中性阻断剂，而AM251是CB1受体的反向激动剂，不仅能阻断CB1受体与内源性配体结合，还能影响其基础活性[37,70]；不同CB1受体抑制剂作用上的差异还可能与动物模型、抑制剂应用剂量和KET治疗方案不同有关。因此，ECS在KET快速持续的抗抑郁中的作用机制值得进一步深入研究。

4.2 非药物治疗手段

4.2.1 重复经颅磁刺激

rTMS是一种临床上有效的抑郁症治疗手段，能够通过调节大脑特定区域的神经活动改善抑郁症状。人体研究发现，rTMS治疗10 d后，MDD患者抑郁、焦虑和快感缺失等症状明显改善，同时血清中2-AG水平显著增加[71]。动物实验发现，在CUMS诱发的大鼠抑郁模型中，7 d的rTMS治疗明显改善大鼠海马齿状回中的CB1受体表达和细胞增殖水平降低，减少CUMS模型抑郁样行为[70]。CB1受体拮抗剂 AM251可以消除rTMS对CUMS模型海马齿状回中神经发生的增强，减弱rTMS治疗诱导的抗抑郁作用[70]。另有研究发现，高刺激频率的rTMS治疗（≥5 Hz）是最有效的抑郁症治疗方案[72]。还有研究发现，只有高刺激频率的rTMS治疗可上调CUMS模型海马中星形胶质细胞和神经元中DAGLα和CB1受体的表达，下调MAGL和FAAH的表达，改善CUMS模型抑郁样行为，而低刺激频率的rTMS治疗可降低CB1受体表达[73]。高刺激频率的rTMS治疗还可以改善CUMS诱导的PFC和海马中θ振荡的减少，CB1受体拮抗剂AM281以及谷氨酸能神经元CB1受体缺失可阻断rTMS治疗作用[74]。以上结果表明，高刺激频率rTMS治疗的抗抑郁作用可能是通过增强ECS信号实现的，CB1受体可能是rTMS发挥抗抑郁作用的重要靶点。但目前研究依然存在一定的局限

性,动物研究主要集中于海马、PFC等脑区,rTMS治疗对其他脑区ECS的影响尚未可知。诸多研究发现,rTMS治疗具有抗炎作用[75],而CB2受体与神经炎症密切相关,rTMS治疗对CB2受体激活的影响需进一步深入研究。

4.2.2 运动

诸多研究表明,运动具有抗抑郁作用[76-78]。近年一项涉及218项实验研究、14 170名参与者的荟萃分析显示,运动是治疗抑郁症的有效方法,如步行或慢跑、瑜伽和力量训练等[79]。动物实验发现,与安静组相比,6~8周有氧运动可以增强雄性大鼠海马的神经发生水平,提高认知能力。最新研究发现,在CSDS和CRS两种抑郁模型中,有氧运动通过激活薄束核(gracile nucleus,GR)-中缝背核(dorsal raphe,DRN)-内侧前额叶皮层(medial prefrontal cortex,mPFC)通路,减少抑郁样行为[80]。运动对ECS信号的调节可能是运动抗抑郁的作用机制之一。一项关于运动调控情绪的系统综述研究认为,运动通过提高eCBs水平进而发挥欣快、镇静和减少抑郁情绪的作用,俗称"跑步者高潮"[81]。另一项随机临床试验发现,一次性20 min的中等强度运动就可使重度抑郁症女性患者血浆中AEA和OEA水平显著升高;运动后10 min和运动后30 min,患者的情绪状态均得到明显改善[82]。eCBs为亲脂性分子,运动后eCBs分泌迅速增加,可以快速通过血脑屏障并与CBRs结合发挥作用。动物实验发现,跑轮运动可上调CSDS抑郁模型伏隔核星形胶质细胞血管周围CB1受体的表达,从而提高对压力的适应能力[83]。为进一步探究运动通过调节ECS实现抗抑郁作用的机制,Rodrigues等[84]进行了运动联合药物治疗抑郁症的研究,结果发现,2周运动联合CB2受体拮抗剂AM630减少了8周不可预测性慢性温和应激(unpredictable chronic mild stress,uCMS)诱导的抑郁样行为,而2周运动联合CB2受体激动剂HU308对抑郁样行为没有影响。进一步研究发现,2周运动联合CB2受体拮抗剂AM630显著促进uCMS模型海马神经母细胞增殖,改善成人海马神经发生(adult hippocampal neurogenesis,AHN)[84]。此外,uCMS诱导小胶质细胞标志物离子钙结合衔接分子1(ionized calcium binding adapter molecule 1,Iba1)显著上调,表明小胶质细胞激活增强。2周运动联合CB2受体拮抗剂AM630显著下调Iba1、TNF-α表达,抑制小胶质细胞过度激活,改善神经炎症。2周运动联合CB2受体拮抗剂AM630还可显著上调uCMS模型海马BDNF表达,促进突触传递功能,减少抑郁样行为[84]。本课题组前期研究发现,在青春期间歇性酒精暴露(adolescent intermittent ethanol exposure,AIE)模型中,8周跑步机运动显著降低海马IL-1β、IL-6和TNF-α水平,提高IL-10水平,抑制小胶质细胞过度激活,改善神经炎症,改善认知能力;此外还发现,运动可进一步降低AIE大鼠海马CB2受体的表达,与Rodrigues等[84]的结果一致,即:运动通过CB2受体调控神经炎症以及情绪认知能力的作用机制可能是抑制CB2受体,而非激活[85]。综上所述,运动通过调节ECS,抑制神经炎症,促进神经发生,改善突触传递效能,发挥抗抑郁作用,但仍有以下问题尚未阐明。(1)运动诱导的eCBs来源尚未可知,其产生的机制未能阐明。(2)运动与药物干预对抑郁模型中ECS的影响相互矛盾,CB2受体激动剂具有抗抑郁作用,而运动调节情绪与CB2受体受到抑制有关。(3)不同运动类型对ECS的影响相互矛盾。运动抗抑郁已经成为共识,虽然不同运动方式对抑郁情绪均有改善作用,但不同类型的运动对ECS的影响不尽相同,一次性急性运动后外周eCBs水平升高,但长期中等运动后出现下调[86],未来的研究需进一步探索不同类型运动方式对中枢和外周ECS的调控,以更好地理解其抗抑郁效果。

5 总结和展望

综上所述,基于ECS的抑郁症病理机制研究,虽然仍存在许多挑战和未解之谜,但已经取得了显著进展:ECS通过调节小胶质细胞和NLRP3炎症小体的激活,以及调节促炎因子释放,调控抑郁情绪诱导的神经炎症;ECS通过调节ACTH和GC水平,改善负面情绪诱导的HPA轴稳态失衡;ECS与BDNF协同调节海马神经发生,发挥突触传递调节和神经保护等作用,改善抑郁情绪。氯胺酮被认为是最有潜力的新型抗抑郁药物,通过多靶点直接增强ECS可能是其抗抑郁的重要机制之一;CB1受体可能是介导高刺激频率rTMS治疗的重要靶点;运动通过调节ECS,抑制神经炎症,促进神经发生,改善突触传递效能,发挥抗抑郁作用。未来的研究可以从以下几个方面进行深入探索:进一步阐明ECS与多系统(如肠道菌群)之间的相互作用机制,探究ECS在

不同脑区的作用差异,开发靶向ECS的抗抑郁药物,并探索非药物疗法调控ECS防治抑郁症的可能机制,共同推动抑郁症发病机制的研究和治疗方法的创新。此外,抑郁症的发生发展还涉及遗传和表观遗传异常假说和社会心理学假说,但ECS是否参与以上两种病理机制尚不清晰,值得未来进一步深入研究。

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