综述

氯胺酮及内源性大麻素系统在快速抗抑郁中的作用研究进展

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[摘要] 抑郁症是现代社会一类常见且严重的情感障碍疾病，其进展后期常伴随有自杀意念及自杀行为，给社会、家庭带来沉重负担。抗抑郁药物治疗对一部分重度抑郁症患者无明显疗效，这一类抑郁症又称为耐药性抑郁症 (treatment resistant depression，TRD)。有研究报道了氯胺酮的快速及长效的抗抑郁作用，对 TRD 亦有明显的治疗效果。大麻中的主要活性物质 Δ^9- 四氢大麻酚也可通过作用于脑内大麻素受体发挥快速抗抑郁作用，这 2 种中枢神经兴奋剂都具有明显的不良反应，属于严格管控的精神活性物质。该文结合近年来相关研究就氯胺酮及内源性大麻素系统快速抗抑郁作用作一综述。

[关键词] 氯胺酮；内源性大麻素系统；抑郁症；Δ^9- 四氢大麻酚；脑源性神经生长因子；哺乳动物雷帕霉素靶蛋白信号通路；N- 甲基 -D- 天冬氨酸受体
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Action of ketamine and endocannabinoid system in rapid anti-depression therapy

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[Abstract] Major depression disorder (MDD) is a common but serious affective disorder in modern society. Suicide idea and suicide behaviour induced by MDD during its later stage put a heavy burden on society and family. Anti-depression drugs lack efficiency in treating a portion of MDD patients. This is referred to as treatment resistant depression (TRD). A study reported the rapid onset and long lasting anti-depression effect of ketamine, which also come into effect in TRD patients. Δ^9-Tetrahydrocannabinol is the active substance of marijuana, which also exerts rapid anti-depression effect *via* targeting at brain cannabinoid receptors. The two central nerve system stimulants belonging to the tightly controlled psychoactive substances have obvious adverse effects. This article summarizes the action of ketamine and endocannabinoid system in rapid anti-depression therapy in recent researches.

[Key words] ketamine; endocannabinoid system; major depression disorder; Δ^9-tetrahydrocannabinol (Δ^9-THC); brain derived neurontrophic factor (BDNF); mammalian target of rapamycin (mTOR) pathway; N-methyl-D-aspartate (NMDA) receptor

抑郁症是一种全球范围内常见的慢性的致残性精神疾病，有报道[1]称其影响着全世界 16% 的人口。抑郁症潜在的病理生理机制复杂，约 1/3 的抑郁症患者对于抗抑郁药治疗无明显效果[2]。抑郁症患者对现有的抗抑郁药物如选择性 5- 羟色胺再摄取抑制剂（selective serotonin reuptake inhibitor，SSRI）表现出应答率低下（不足 50%），2/3 患者需要多次更换药物才能达到理想的治疗效果[3]。另外，即使对于药物治疗有效的患者，药物起效时间也需要 2 周左右[4]。安慰剂对照研究的大量证据表明，非竞争性 N- 甲基 -D- 天冬氨酸（N-methy-D-aspartic-acid，NMDA）受体拮抗剂氯胺酮对于抑郁症患者具有静脉注射后快速起效（1.5 ～ 2 h 起效）且持续时间较长（持续 7 ～ 10 d）的特点[5-8]；同时也对传统抗抑郁药物抵抗的耐药性抑郁症（treatment resistant depression，TRD）患者有良好效果。大量动物实验[9-15]也证明了氯胺酮的快速抗抑郁作用。而氯胺酮的致分离作用、致精神病作用及成瘾性限制了其临床应用[16]。动物实验[17-18]表明，与氯胺酮同属中枢神经兴奋剂的大麻，其主要活性成分 Δ^9– 四氢大麻酚（Δ^9-tetrahydrocannabinol，Δ^9-THC）通过作用于内源性大麻素受体亦可产生快速的抗抑郁作用。本文总结了近年来针对氯胺酮及内源性大麻素系统的抗抑郁机制研究，为研发新型快速抗抑郁药物提供参考。

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1 NMDA 受体拮抗剂介导的机制

氯胺酮是 NMDA 受体非竞争性拮抗剂。NMDA 受体为促离子型谷氨酸受体，在中枢神经系统分布广泛。NMDA 受体为异四聚体，其亚单位包含 GluN1、GluN2A、GluN2B、GluN2C、GluN2D、GluN3A、GluN3B[19]。常见的 NMDA 受体由 2 个 GluN1 及 2 个 GluN2 亚基构成，也可由 2 个 GluN2 及 2 个 GluN3 亚基构成[20]。Trullas 等[21]首次报道了非竞争性 NMDA 受体拮抗剂 MK-801 与竞争性 NMDA 受体拮抗剂 AP-7 改善了小鼠在强迫游泳实验中的行为绝望表现。

1.1 去抑制假说

针对前额叶的研究认为，氯胺酮可作用于 γ- 氨基丁酸（γ-aminobutyric acid，GABA）能中间神经元，通过抑制中间神经元 GABA 的释放，从而减轻对突触前神经元的抑制作用，增加突触前神经元释放谷氨酸，激活突触后神经元上的 α- 氨基 -3- 羟基 -5- 甲基 -4- 异噁唑丙酸（α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid，AMPA）受体，增加脑源性神经生长因子（brain derived neurontrophic factor，BDNF）的表达及释放，激活哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）信号通路，增强突触活性[22]。

1.2 直接抑制假说

免疫组织化学与电生理技术明确了在突触后膜区域外的轴突膜上也表达 NMDA 受体[23]，且此处 NMDA 受体为 GluN2B 参与构成的异四聚体[19-20]。在一次突触前膜谷氨酸释放后，大部分谷氨酸由星形胶质细胞表达的谷氨酸转运体重吸收进入谷氨酸—谷氨酰胺循环；在各种压力应激作用下，星形胶质细胞表达谷氨酸转运体下调，未被有效吸收的谷氨酸会进入突触外膜区域，过度激活该部位的 NMDA 受体，从而关闭了环磷酸腺苷效应元件结合蛋白（cAMP-response element binding protein，CREB）（CREB-BDNF）—脑源性神经生长因子信号通路[24-25]。直接抑制假说认为，氯胺酮可拮抗该处 NMDA 受体，重新开启 CREB-BDNF 信号通路，促进 BDNF 的表达，从而使被抑制的 mTOR 信号恢复活性[26-29]。动物研究[26-29]表明选择性 GluN2B 拮抗剂也可通过与直接抑制假说相似的作用机制起到快速的抗抑郁作用，进一步支持了该假说。

1.3 氯胺酮代谢产物

Zanos 等[13]报道，2R,6R- 羟基去甲氯胺酮（2R,6R-hydroxynorketamine，2R,6R-HNK）作为氯胺酮的代谢产物，亦具有抗抑郁作用；其发挥抗抑郁作用的机制是 NMDA 受体非依赖性的，主要通过作用于另一类促离子型谷氨酸受体 AMPA 受体发挥作用。通过作用于 AMPA 受体，促进 BDNF 的释放，活化 mTOR 信号，增强突触活性。2R,6R-HNK 没有氯胺酮的致瘾性等不良反应，一度成为研究热点。曾有学说提出氯胺酮的快速抗抑郁作用是由氯胺酮本身发挥的，而 2R,6R-HNK 介导了一次注射后较长时间的持续作用。但也有研究[30]对 2R,6R-HNK 的抗抑郁作用提出质疑。2R,6R-HNK 的抗抑郁机制还需进一步研究。

2 内源性大麻素系统介导的抗抑郁作用

2.1 内源性大麻素系统

脑内存在内源性大麻素系统（endocannabinoid system，ECS），包括大麻素受体（cannabinoid receptor 1/2，CB1/2）及其配体 N- 花生四烯酰乙醇胺（nandamide，AEA）和 2- 花生酰甘油（2-arachidonoyl-glycerol，2-AG），以及相关酶类，如脂肪酸酰胺水解酶（fatty acid amide hydrolase，FAAH；与 AEA 降解相关）、单酰甘油脂肪酶（monoacylglycerol lipase，MAGL；与 2-AG 降解相关）等。与经典递质释放不同，内源性大麻素物质并非存储于突触囊泡中，而是细胞膜的脂类成分，当细胞接受刺激后由相关的酶作用于细胞膜上的前体物质，即时合成 AEA 及 2-AG。ECS 另一个特点是 AEA 及 2-AG 由突触后膜释放后作用于突触前膜相关受体[31]。AEA、FAAH 与 CB1 受体在调节应激、恐惧与奖赏环路的相关脑区（诸如基底外侧杏仁核、海马、内侧前额叶、伏隔核）都有表达[32]。动物实验[33-38]表明，激活内源性大麻素系统具有抗焦虑、抗抑郁作用，而 Δ^9-THC 可有效激活 ECS。

2.2 ECS 参与应激调节

众多研究[39-40]表明，ECS 参与调节下丘脑—垂体—肾上腺素（hypothalamic − pituitary − adrenal，HPA）轴并有利于应激后恢复。CB1 受体在海马高度表达[41]，且主要表达于 GABA 能中间神经元[42]。海马是最易受应激刺激影响的脑区，是参与脑情感环路组成的重要区域[43]。海马负性调节 HPA 轴，HPA 轴的过度激活产生大量皮质醇，损害海马的正常功能[44]。药理学及遗传学研究[45-46]证明，ECS 参与调节海马在情感环路中所起的作用。抑制海马 ECS 信号系统足以引起抑郁样症状[47-50]。针对抑郁样动物

模型的研究[51]也表明，抑制 ECS 通路会增加强迫游泳及悬尾试验中的行为绝望时间。相反，激活 ECS 通路有抗焦虑及抗抑郁作用。在社交孤立模型动物中，激活海马齿状回 CB1 受体可产生抗抑郁作用[52]。

2.3 ECS 与 BDNF 的表达

BDNF 在突触活性、神经存活及神经生长机制中具有重要作用[53]。在临床研究及动物实验[54]中均发现 BDNF 在海马、前额叶、杏仁核等脑区表达下降。研究表明，BDNF 与 ECS 相关[55-56]，抑制 CB1 受体活性可降低 BDNF 在海马的表达[57-58]。有大量研究[57-60]证明 CB1 受体激活后可促进 BDNF 的表达并起到神经保护作用。海马 *CB1* 基因敲除动物表现出抑郁样行为并明显伴有 BDNF 表达的下降[61]。

3 氯胺酮与 Δ^9-THC 的共同下游信号通路

氯胺酮及 Δ^9-THC 都具有促进 BDNF 表达及释放的作用。BDNF 对于突触可塑性来说是必需的，在抗抑郁机制中发挥重要作用，其受体为原肌球蛋白相关激酶 B（tropomysin related kinase B，TrkB）。BDNF 与其受体 TrkB 作用后，激活的下游信号包括磷脂酰肌醇 3- 激酶 / 蛋白激酶 B（PI3K/Akt）通路、细胞外信号相关激酶 / 丝裂原活化蛋白激酶（ERK/MAPK）通路和磷脂酶 C-γ/Ca^{2+}（PLCγ/Ca^{2+}）通路[62]。而 Akt 和 ERK 是 mTOR 信号通路的上游激活因子。大量研究[63-64]证明 mTOR 信号通路在调控突触结构和功能方面发挥着重要作用。比如，该通路的活化可明显促进新棘突数量及突触功能蛋白的合成。预先给予 mTOR 抑制剂雷帕霉素可明显减弱氯胺酮及 Δ^9-THC 的抗抑郁作用。而在针对许多经典抗抑郁药的研究[65]中并未发现经典抗抑郁药有快速激活 mTOR 信号通路的作用。这为新型抗抑郁药研发提供了一个新的思路。

4 总结与展望

目前精神科临床工作中针对 TRD 患者无明显的特效药物，改良电抽搐治疗（modified electra convulsive therapy，MECT）仍是最为有效的临床治疗手段。开发具有快速起效的抗抑郁药物仍任重道远。随着氯胺酮快速抗抑郁作用的发现，另一种中枢兴奋剂大麻也被发现在抗抑郁方面具有与氯胺酮相似的作用。这为抗抑郁药的研发提供了新的作用靶点，但在临床应用方面仍然存在争议，如氯胺酮的给药方式、剂量及使用频率等[66-70]。现代社会压力巨大，因焦虑、抑郁问题就诊于精神科门诊的患者与日俱增；而近期毒品大麻在西方某些国家的合法化所带来的大麻无害论甚嚣尘上，易对人们产生误导。在我国，氯胺酮及大麻属于严格管控的精神类药品，具有明显的成瘾性，且目前仍然缺乏对以缓解抑郁为目的长期使用这 2 种物质引起的脑适应性改变的研究。因此，将中枢兴奋剂当作抗抑郁药物使用在目前来看是盲目的，还需要进行深入的临床及基础研究。

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