秦理想,田琰,陈秉政,等. 甲基苯丙胺诱发小胶质细胞炎症的机制及治疗研究进展［J］. 中国比较医学杂志, 2026, 36(19): 129-138.
Qin LX, Tian Y, Chen BZ, et al. Research progress on the mechanisms and treatment of methamphetamine-induced microglial inflammation［J］. Chin J Comp Med, 2026, 36(19): 129-138.
doi: 10.3969/j.issn.1671-7856.2026.19.013

甲基苯丙胺诱发小胶质细胞炎症的机制及治疗研究进展

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【摘要】 甲基苯丙胺(METH)属于苯丙胺类中枢兴奋剂,是一类以精神依赖为主的新型合成毒品,长期滥用可产生显著的神经毒性并形成药物依赖,已成为全球性的重大公共卫生问题。METH 可以激活小胶质细胞产生炎症反应,但作用机制尚未阐明。本文系统综述 METH 诱发小胶质细胞炎症的核心发生机制,重点阐述多巴胺-谷氨酸能紊乱、TLR4/NF-κB 经典炎症通路、sigma-1 受体调控在神经炎症中的关键作用;全面梳理褪黑素、姜黄素、天麻素、大麻二酚等天然药物,以及甜菜碱、二甲双胍等化学药物的抗炎干预效应与作用靶点;同时总结运动干预、重复经颅磁刺激、针灸等非药物治疗手段的研究进展。现有研究证实,靶向抑制小胶质细胞过度活化、阻断关键炎症信号通路、降低氧化应激水平并抑制炎症因子释放,可有效缓解 METH 诱发的神经炎症并改善神经损伤。本文旨在为进一步阐明 METH 诱发的神经炎症机制,以及药物、非药物干预的相关研究提供参考。

【关键词】 甲基苯丙胺;神经炎症;小胶质细胞;机制;治疗
【中图分类号】 R749.61;R338.2;R964　**【文献标识码】** A　**【文章编号】** 1671-7856 (2026) 19-0129-10

Research progress on the mechanisms and treatment of methamphetamine-induced microglial inflammation

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[**基金项目**]国家自然科学基金(82260336);云南省科技厅-昆明医科大学联合专项重点项目(202301AY070001-026);昆明医科大学-国家卫健委毒品依赖和戒治重点实验室开放性课题(KY202409)。
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【**Abstract**】 Methamphetamine, an amphetamine-type central nervous system stimulant, is a synthetic drug characterized primarily by strong psychological dependence. Long-term methamphetamine abuse causes severe neurotoxicity and dependence. Methamphetamine abuse has become a major global public health concern. Studies have shown that methamphetamine activates microglia and induces inflammatory responses, but the underlying mechanisms have not been fully elucidated. This paper systematically reviews the main mechanisms of methamphetamine-induced microglial inflammation, focusing on the pivotal roles of dopaminergic and glutamatergic dysregulation, the canonical Toll-like receptor 4/nuclear factor-κB inflammatory pathway, and sigma-1 receptor-mediated regulation of neuroinflammation. It comprehensively summarizes the anti-inflammatory effects and therapeutic targets of natural compounds, including melatonin, curcumin, gastrodin, and cannabidiol, as well as other agents such as betaine and metformin. Research advances in nonpharmacological interventions including exercise therapy, repetitive transcranial magnetic stimulation, and acupuncture are also reviewed. Targeted inhibition of excessive microglial activation, blockade of key inflammatory signaling pathways, and reduction of oxidative stress and inflammatory mediator release have been demonstrated to alleviate methamphetamine-induced neuroinflammation and nerve damage. This review aims to provide a reference for further research on the mechanisms of methamphetamine-triggered neuroinflammation, and related pharmacological and nonpharmacological interventions.

【**Keywords**】 methamphetamine; neuroinflammation; microglia; mechanism; therapy

Conflicts of Interest: The authors declare no conflict of interest.

甲基苯丙胺(methamphetamine,METH)是一种合成兴奋剂,其诱发的小胶质细胞炎症反应表现为促炎、抗炎标志物同步变化的混合炎症状态[1]。大量研究证实,METH 可诱发小胶质细胞 M1 激活,促使肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)、白细胞介素(interleukin,IL)-1β、IL-6 等炎症因子表达与释放水平升高,进而介导神经退行性损伤[2]。然而,其确切分子机制、关键信号通路调控网络以及有效干预靶点仍未完全阐明,临床上仍缺乏靶向性强、安全性高的干预与治疗手段。基于此,本文围绕 METH 诱发小胶质细胞炎症的发生机制、关键信号转导通路、药物干预与非药物治疗的研究进展进行系统综述,旨在明晰 METH 相关神经炎症的调控规律,为深入揭示 METH 神经毒性机制、开发靶向抗炎与成瘾戒断治疗策略、推动临床转化应用提供理论依据与研究参考。

1 METH 诱发小胶质细胞产生炎症

神经炎症最初被定义为需同时满足 4 个炎症特征:促炎性细胞因子释放、神经胶质细胞激活、继发性细胞死亡和免疫细胞浸润。目前已经放宽至满足一个炎症特征即可判定为神经炎症[3]。METH 具有神经毒性并可诱发神经退行性病变[4],表现为能诱发小胶质细胞激活产生神经炎症[5],且伴随强烈的精神症状及体征[6-8]。研究发现青少年时期接触 METH 诱发的神经炎症会持续到成年阶段[9]。此外,METH 还可与人类免疫缺陷病毒协同作用,显著加剧神经炎症[10]。小胶质细胞是大脑中主要的常驻免疫细胞,在神经炎症进展中发挥着重要作用,其特点是胶质细胞特异性蛋白表达量增加、细胞体过度增大,有时也会发生细胞增殖和迁移[11]。研究发现,METH 滥用人群血液中炎症因子 IL-18、IL-6 及 TNF-α 明显增加[12,13],METH 给药后导致大鼠脑组织和血清中炎症因子表达均增加,并诱发大鼠认知缺陷[14]。有学者在体外小胶质细胞株、小鼠及人尸检脑组织样本中证实,METH 可诱发小胶质细胞活化、上调炎症因子表达,该效应与 Toll 样受体 4(Toll-like receptor 4, TLR4)通路有关[15];抑制 METH 引起的神经炎症在减轻 METH 诱发的认知

障碍和神经退行性病变方面展现出较好前景[16]，为改善 METH 使用障碍(methamphetamine use disorder, MUD)提供了潜在治疗策略。值得一提的是，低剂量 METH 存在双向效应，短期低剂量 METH 干预小鼠的相关实验可能得到相反结论[17]。

2　METH 诱导小胶质细胞发生炎症的机制研究

2.1　多巴胺(dopamine, DA)及谷氨酸(glutamate, Glu)能途径在 METH 诱发小胶质细胞炎症中的作用

METH 可穿过血脑屏障(blood brain barrier, BBB)并诱发 TNF-α 表达增加[18,19]，其机制为诱发 DA、5-羟色胺和去甲肾上腺素的释放，引起 DA 耗竭[20]。此外，释放的 DA 被氧化生成毒性醌类物质，通过氧化应激、线粒体功能障碍，伴随过氧化物自由基和过氧化氢生成，导致突触前膜损伤；线粒体能量代谢的损伤增加了神经炎症反应[21]。已有研究证明，METH 通过促进 DA 和 Glu 过表达进而诱发神经炎症[22,23]，代谢型 Glu 受体 3 的激活能够减弱药物寻求行为和/或改善认知功能[24]；但 Glu 积累可过度激活 Ca^{2+} 内流相关的多条下游信号转导通路，细胞中 Ca^{2+} 超载会激活蛋白激酶、磷酸酶以及一氧化氮合酶，并促进 NO 产生。过量的 NO 可诱发内质网(endoplasmic reticulum, ER)应激并最终导致 METH 引起神经毒性[25]。细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)是一种代表性激酶，在调节 DA 和 Glu 介导的神经元损伤过程中具有重要作用[26]。另有研究证明，METH 可抑制细胞内吞作用[27]，增加某些大脑区域中 ERK 磷酸化的激活[28]，激活后，ERK 会引起环磷酸腺苷反应元件结合蛋白(cAMP response element-binding protein, CREB)磷酸化，并增加 N-甲基-D-天冬氨酸受体 2B 亚基、磷酸化 ERK、磷酸化 CREB 和脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)的释放[29]，该过程是推动神经系统炎症发生的重要环节。

2.2　TLR/NF-κB 信号通路在 METH 诱发的小胶质细胞炎症中的作用

TLR4 是一种可以激活髓样分化因子 88(myeloid differentiation primary response 88, MyD88)依赖性和 MyD88 非依赖性途径的受体，METH 介导神经炎症与小胶质细胞活化及 TLR4 有关[30]。在 MyD88 依赖性途径中，MyD88 激活 TNF-α 受体相关因子 6、IL-1 受体相关激酶，进而诱发核因子 κB(nuclear factor-κB, NF-κB)活化[31]。MyD88 非依赖性途径通过激活 TRIF 相关衔接分子和干扰素调节因子 3，促使 γ-干扰素发挥作用[32]；此过程也同样可激活 NF-κB，但其激活时相晚于 MyD88 依赖性途径[33]。此外，采用 TAK-242(TLR4 的特定抑制剂)或小干扰 RNA 分别抑制 TLR4 功能、下调 TLR4 表达，对 METH 诱发胶质细胞产生的炎症有明显的减轻作用[34]，进一步证实 TLR4 信号通路对 METH 介导的神经炎症具有重要的调控作用。

2.3　σ_1 受体(sigma-1 receptor, Sig-1R)在 METH 诱发的小胶质细胞炎症中的作用

Sig-1R 是一种 ER 伴侣蛋白，在大脑中广泛表达且对 METH 具有高亲和力[35]。Sig-1R 与 METH 引起的神经毒性和炎症反应密切相关，可通过调节钙稳态、活性氧(reactive oxygen species, ROS)生成、ER 和线粒体功能等多种机制参与神经炎症过程[36,37]。研究表明，Sig-1R 主要通过激活丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)和磷脂酰肌醇 3-激酶/蛋白激酶 B 信号通路[38]，而 MAPK 通路与 NF-κB 炎症通路之间存在紧密交叉调控关系[39-41]。此外，采用 Sig-1R 拮抗剂 SN79 预处理，可减少 METH 诱导的分化簇 68、离子钙结合衔接分子 1 及促炎性细胞因子家族成员的 mRNA 水平上调，提示 Sig-1R 干预能够抑制小胶质细胞活化，减轻 METH 相关的神经炎症[42]。

3　药物治疗 METH 诱发小胶质细胞炎症的研究进展

3.1　褪黑素可减弱 METH 诱发的神经炎症

褪黑素(melatonin, Mel)是松果体的主要分泌产物，可作为成瘾相关的生物标志物[43]，Mel 预处理能够缓解 METH 诱导的大鼠小胶质细胞系的毒性，抑制 ROS 和活性氮的生成，并下调炎症因子 IL-1β、IL-6 及 TNF-α 的表达[44]。Mel 预处理神经胶质瘤细胞系可有效激活核因子 E2 相

关因子,逆转 METH 诱导的 NF-κB 活化。Mel 可上调血红素氧合酶 1、醌氧化还原酶 1、γ-谷氨酰半胱氨酸连接酶催化亚基的表达,提高超氧化物歧化酶的抗氧化活性;同时可抑制 NF-κB 抑制蛋白 α 降解与 p65 亚基核转位,降低一氧化氮合酶表达、减少 NO 生成,进而减轻神经炎症[45,46]。此外,Mel 可保护 METH 损伤大鼠的 BBB 完整性,发挥与体外实验相似的抗炎作用[47,48]。Mel 还可通过抑制 TLR4/MyD88/NF-κB 信号通路,进而抑制神经炎症并改善 METH 诱导的认知障碍[49]。综上,Mel 可通过保护 BBB 完整性、抑制氧化应激、下调炎症因子表达等多条途径,减轻 METH 诱发的神经炎症。

3.2 姜黄素减弱 METH 诱发的神经炎症

姜黄素(curcumin, Cur)可改善药物滥用介导的神经毒性,涉及多重调控机制,包括调节炎症细胞因子、维持离子稳态、表观遗传调控、增强抗氧化能力、激活 CREB 以及调控 BDNF 信号传导途径[50]。Cur 还可减轻脑水肿与神经元损伤,抑制各脑区的 BBB 泄漏,提升脑内 BDNF 和 DA 水平,从而减轻 METH 诱导的神经毒性[51]。Cur 可通过抑制细胞凋亡、氧化应激及炎症反应发挥神经保护效应,该效应可能依赖 CREB-BDNF 信号通路[52]。Cur 可显著抑制 METH 诱导的小胶质细胞活化,上调超氧化物歧化酶、谷胱甘肽过氧化物酶水平,降低 TNF-α 与丙二醛含量,并显著改善 METH 给药引起的大鼠空间记忆障碍[53]。此外,胡椒碱和 Cur 纳米颗粒具有剂量依赖性的协同作用,可显著降低 METH 引起的小鼠大脑神经毒性、氧化应激及空间记忆障碍。综上,Cur 可单独用药或与其他药物联用发挥抗炎及神经保护作用,其作用机制涵盖保护 BBB 完整性、抑制小胶质细胞活化、上调 BDNF 表达、抗氧化应激及调控炎症因子分泌等多个方面。

3.3 天麻素减弱 METH 诱发的神经炎症

天麻(*Gastrodia elata* Blume, Gas)为兰科植物天麻的干燥块茎,其主要有效成分天麻素(对羟基苯甲醇-β-D 葡萄吡喃糖苷)具有改善认知、增强免疫、镇静催眠、抗癫痫、镇痛、神经保护、抗氧化及抗炎等作用。Gas 可降低 METH 诱发的大鼠星形胶质细胞与神经元损伤、增强炎症因子 IL-6、TNF-α 的表达[54]。朱婷娜等[55,56]研究证实,不同剂量 Gas(10 mg/kg、30 mg/kg 和 100 mg/kg)干预可显著抑制 METH 诱发的小胶质细胞活化,其中 30 mg/kg、100 mg/kg 剂量的抑制效果更为显著,Gas 能够剂量依赖性降低 METH 依赖大鼠的条件位置偏爱(conditioned place preference,CPP)效应,改善 METH 成瘾相关行为,该效应与 TLR4/MyD88/NF-κB 信号通路密切相关。此外,Gas 减轻 METH 诱导的小胶质细胞介导的神经炎症,还可能与 Akt、MAPK 等信号传导通路有关[57]。综上,Gas 可通过抑制小胶质细胞活化、抗氧化应激、抑制炎症因子释放等途径发挥抗炎与神经保护作用。

3.4 大麻二酚减弱 METH 诱发的神经炎症

大麻二酚(cannabidiol, CBD)是一种非精神活性大麻素,具有强大的抗炎和免疫抑制特性。CBD 显著降低了 METH 给药引起的 IL-1β、IL-6、IL-10 及 TNF-α 等炎症因子升高,发挥抗炎及免疫抑制效应[58]。已有研究证明,METH 可诱导小鼠刻板行为、空间记忆障碍、瞬时受体电位香草酸亚型 1 激活、Ca^{2+}超载、细胞凋亡和氧化应激,而 CBD 预处理可减轻 METH 给药小鼠的上述损伤表现[59]。此外,CBD 可抑制 METH 奖励记忆的获取和表达,显著降低 METH 诱发的 CPP 效应[60,61],该作用机制可能与多巴胺受体 D1(dopamine D1 receptor,D1R)[62]、D2R[63,64]、腺苷 A1 受体[65]及 Sig-1R/AKT/GSK-3β/CREB 信号通路[66]相关。有研究构建内源竞争 RNA 网络,揭示了 CBD 治疗 METH 诱发的 CPP 恢复和行为敏化的潜在机制[67];亦有研究表明,CBD 可抑制快速眼动睡眠剥夺,减轻 METH 诱发的 CPP 效应[68]。CBD 还可通过调节甲基 CpG 结合蛋白 2 和 DRD1 介导的 Ca^{2+} 信号通路磷酸化,减轻 METH 诱发的神经毒性[69]。与此同时,CBD 可调控 DRD1-MECP2-BDNF-TRKB 信号通路,抑制 METH 诱导的 DA 释放,进而减轻神经炎症[70]。另有研究证明,CBD 可作用于 TLR4/NF-κB 信号通路,对 METH 导致的神经功能减退、神经炎症及线粒体功能障碍起到干预效果[71]。综上,CBD 可通过调节 DA 受体、抑制小胶质细胞活化、上调 BDNF 表达、抗氧化、改善 Ca^{2+}超载等多个途径发挥其抗炎与神经保护作用。

METH 诱导小胶质细胞介导的神经炎症是一

个非常复杂的过程,多种兼具抗炎、抗氧化、抗凋亡活性的中草药能够通过不同信号通路缓解 METH 诱发的神经炎症。抗炎药物的作用机理同样错综复杂,针对 METH 成瘾戒断,已有综述总结了部分具有治疗潜力的药物[72]。开展此类药物的临床试验及疗效评价,将是未来重要的研究方向。

4　非药物治疗减弱 METH 诱发的神经炎症

4.1　运动对 METH 诱发神经炎症的治疗作用

运动干预和减少 METH 滥用之间存在潜在关联[73]。METH 给药导致小鼠自主活动增加并产生 CPP 效应[74];而体育锻炼对 METH 诱发的神经炎症和神经发生损伤具有保护作用[75],还能够提升女性 METH 使用者的脑网络可塑性[76]。运动可以通过阻止 BBB 破坏,改善海马微环境紊乱并抑制炎症因子升高,进而减轻 METH 诱发的神经毒性[77]。跑步干预逆转了小鼠纹状体、海马和血清中急性 METH 引起的促炎细胞因子的增加,改善了小鼠抑郁焦虑行为,表明跑步的抗焦虑作用可通过减少小胶质激活、调节炎症反应实现[78]。此外,急性有氧运动对 MUD 患者情绪记忆的特定阶段有显著影响[79],特别是在增强编码能力方面[80];长期中强度运动可下调皮质、海马中 IL-1β、纹状体 IL-6,以及大脑皮质、海马、纹状体 TNF-α 水平,而低强度运动干预效果相对有限,提示运动强度是调控 METH 小鼠药物依赖行为及脑内炎症反应的重要因素[81,82]。强迫运动可作为非药物的神经保护剂,减轻 METH 慢性暴露导致的大鼠认知能力下降,逆转丙二醛、TNF-α、IL-1β 升高以及超氧化物歧化酶、谷胱甘肽过氧化物酶和谷胱甘肽还原酶活性降低,该保护效应可能与 p-CREB/BDNF 信号通路有关[83]。适当的运动还可调控 NRF2 信号通路,发挥内源性抗氧化作用,减轻 METH 诱导神经炎症引起的各类损伤[84]。脑转录组分析提示运动可改善 METH 导致的小鼠学习和记忆功能障碍[85];代谢组学结果同样证实,运动干预与 METH 模型小鼠焦虑样行为的缓解、认知功能的改善密切相关[86]。由此可见,适宜强度的运动干预可通过保护 BBB 完整性、抑制小胶质细胞异常活化、降低氧化应激水平,进而发挥抗炎作用,最终缓解 METH 所致的神经毒性。

4.2　经颅磁刺激减弱 METH 诱发的神经炎症

MUD 患者存在特征性的脑电图微状态模式[87],重复经颅磁刺激(repetitive transcranial magnetic stimulation, rTMS)是一种无痛、无创的绿色物理疗法,已应用于抑郁症、焦虑症、精神分裂症、帕金森病等神经精神疾病的临床治疗,该疗法也被用于 MUD 患者的干预研究[88]。低频 rTMS 可下调大鼠背外侧纹状体中 γ-氨基丁酸 B 型受体亚基 1 的表达,同时阻断 METH 诱导 SD 大鼠产生 CPP 效应[89];高频 rTMS 作用于前额皮质,能够改善 MUD 患者的情绪与注意力水平[90];间歇性 rTMS 爆发刺激对 METH 成瘾人群的执行功能具有较好的治疗效果[91]。此外,经颅直流电刺激可缓解 METH 诱导的神经炎症;经颅聚焦超声在降低 METH 渴求、减少药物使用方面同样具备应用潜力。综上,不同频率 rTMS 及其他物理干预方式可发挥抗炎作用,减轻 METH 的神经毒性。

4.3　针灸减弱 METH 诱发的神经炎症

针灸疗法在我国已有 2000 多年历史,可用于治疗多种功能性疾病,包括药物滥用相关病症[92]。研究发现,针灸可通过激活代谢型 Glu 受体 2/3,抑制伏隔核的 DA 释放,缓解 METH 诱导的精神运动兴奋及奖赏相关情绪反应[93,94]。低频电针可显著缓解抑郁样行为和认知障碍,这可能与抑制小胶质细胞激活和恢复 BBB 完整性有关[95]。此外,针灸和中草药联合干预可获得更佳的疗效[96]。研究显示,经皮穴位电刺激有效改善 MUD 患者的抑郁、焦虑和睡眠质量,降低戒断期药物渴求[97]。综上所述,针灸可通过抑制小胶质细胞活化、保护 BBB 完整性、抑制 DA 过度释放等途径发挥抗炎作用,减轻 METH 介导的神经毒性。

5　小结

METH 滥用能够诱发小胶质细胞介导的神经炎症,而神经炎症在机体中又存在双重生物学效应:低剂量 METH 诱导的炎症可作为机体适应性的防御反应,发挥一定保护作用;高剂量 METH 诱发的炎症会引发机体炎症性细胞死亡,进一步

加重 METH 神经毒性。因此,深入探究 METH 神经毒性与炎症之间的相互作用,明确各类炎症调控通路与关键靶蛋白,围绕炎症核心靶点开展靶向药物筛选与研发,能够为临床防控 METH 滥用、治疗成瘾提供全新思路与治疗策略。

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〔收稿日期〕2026-04-09