·综述·

# 单核细胞趋化蛋白-1/C-C趋化蛋白受体2信号传导参与酒依赖致脑损害的机制进展

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【摘要】 酒依赖对大脑造成严重损害，与大脑萎缩、记忆力和注意力缺陷、交流障碍和身体残疾有关。单核细胞趋化蛋白-1(MCP-1)是调节单核细胞和小胶质细胞募集和活化的关键趋化因子之一，与其受体C-C趋化蛋白受体2(CCR2)参与各种神经炎性疾病。最近的证据表明，酒精增加了中枢神经系统中MCP-1/CCR2的活性，阻断MCP-1/CCR2可抑制大脑和脊髓中的神经炎症进而减轻酒精诱导的神经毒性。现对MCP-1/CCR2信号在酒精诱导的神经炎症和脑损伤中的作用进行综述。

【关键词】 酒依赖； 单核细胞趋化蛋白-1； C-C趋化蛋白受体2； 神经炎症； 综述

**Research progress in alcohol dependence leading to brain damage through MCP-1/CCR2 conduction**

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【Abstract】 Alcohol dependence causes profound damage to brain. Alcohol dependence is associated with brain shrinkage, memory and attention deficits, communication disorders and physical disabilities. Monocyte chemoattractant protein-1 (MCP-1) is one of the key chemokines that regulate the recruitment and activation of monocytes and microglia. Both MCP-1 and its receptor C-C chemokine receptor type 2 (CCR2) are involved in various neuro inflammatory disorders. Recent evidence indicates that alcohol exposure increased the activity of MCP-1/CCR2 in central nervous systems. MCP-1/CCR2 inhibition can alleviate alcohol neurotoxicity by reducing neuro inflammation in the brain and spinal cord. In this review, we discussed the role of MCP-1/CCR2 signaling in alcohol-induced neuro inflammation and brain damage.

【Key words】 Alcohol dependence； Monocyte chemoattractant protein-1； C-C chemokine receptor type 2； Neuro inflammation； Review

中枢神经系统特别容易受到酒精的影响，慢性酒精暴露引起神经元变性和认知缺陷[1]。然而，酒精引起中枢神经系统损伤的机制尚不清楚。研究表明神经炎症在酒依赖的发病机制中起重要作用，酒精引起的神经元死亡伴随着神经炎症[2]，提示神经炎症与酒精引起的中枢神经系统损伤有关。

单核细胞趋化蛋白-1(monocyte chemoattractant protein-1, MCP-1)是调节神经炎症的重要趋化因子，主要是单核细胞和记忆T细胞的有效趋化因子，MCP-1的生物学功能由其受体C-C趋化蛋白受体2(C-C chemokine receptor type 2, CCR2)介导[3]。CCR2可结合5种促炎趋化因子，而MCP-1是触发CCR2介导的信号转导途径中最有效的趋化因子[4]。MCP-1/CCR2与酒依赖有关，在酒依赖动物模型的不同脑区域中可发现MCP-1表达均增加，MCP-1水平的升高伴随着酒精消耗的增加[5]；MCP-1过表达的小鼠表现出海马突触传递的改变，进而推测人类酗酒者MCP-1表达的增加可能通过改变突触传递来影响认知[6]，而且与边缘系统相关的海马、杏仁核复合物和丘脑等脑区中存在MCP-1/CCR2结合位点，提示MCP-1/CCR2与认知功能相关[7]。这些数据一致表明MCP-1表达水平与酒精病理学之间的关联。本综述将讨论MCP-1/CCR2信号传导在分子水平、细胞水平和蛋白水平上介导的酒精诱导的神经炎症中的作用以及潜在机制。

一、分子水平

在人类酗酒者的大脑中可观察到MCP-1表达增加和小胶质细胞激活[8]。酒精激活小胶质细胞，

伴随促炎细胞因子活化和神经元死亡[9]，这为酒精诱导的神经炎症和神经毒性提供了间接证据。酒精直接刺激小胶质细胞的受体或间接通过次级刺激“引发”小胶质细胞，活化的小胶质细胞产生促炎型M1样表型，分泌MCP-1等促炎细胞因子引起神经毒性[10]。小胶质细胞作为环境损害的第一反应者，MCP-1可通过充当小胶质细胞的“引发”刺激物，降低其“阈值敏感性”激活小胶质细胞[11]。Feng等[12]报道光感受器细胞凋亡诱导MCP-1和CCR2的表达增加促进了小胶质细胞的活化。Dubový等[13]观察到，损伤后大鼠的导水管周围灰质(PAG)和延髓腹内侧髓质(RVM)的小胶质细胞活化，活化是由MCP-1/CCR2信号介导。与单独的神经元培养物相比，在神经元/小胶质细胞共培养物中，外源性MCP-1能够激活和刺激小胶质细胞产生细胞因子，引起更多的神经元死亡[14]。上述证据表明MCP-1/CCR2信号传导在酒精诱导的小胶质细胞激活中起重要作用。糖原合成酶激酶3β(Glycogen synthase kinase 3β，GSK-3β)、c-Jun氨基末端激酶(c-Jun N-terminal kinase，JNK)和Toll–样受体4(Toll-like receptor 4，TLR4)是小胶质细胞激活的关键调节因子[15]。MCP-1/CCR2通过GSK-3β、JNK和TLR4等分子途径激活小胶质细胞介导酒精的神经毒性。

1. GSK-3β与JNK：GSK-3β对中枢神经系统中神经元的发生、分化、迁移和存活起重要作用。GSK–3β通过激活Bax蛋白引起神经元死亡，神经元死亡是酒依赖患者行为缺陷的基础。因此GSK-3β表达水平、活性决定神经元对酒精的敏感性。在长期酒精暴露状态下，GSK-3β过度表达并参与小胶质细胞激活及促炎细胞因子的上调，介导酒精诱导的神经毒性[16]。MCP-1需要GSK-3β才能有效表达，阻断MCP-1/CCR2信号传导后可部分减轻酒精诱导的GSK-3β活化。JNKs参与中枢神经系统小胶质细胞激活，调节神经元死亡和神经炎症[17]。酒精暴露显著增强JNKs磷酸化，与野生型小鼠相比，阻断MCP-1/CCR2的小鼠酒精诱导的GSK-3β和JNKs活化显著减少，表明MCP-1/CCR2信号传导在酒精诱导的促炎和促凋亡途径的激活中起重要作用。活化的MCP-1/CCR2信号通过GSK-3β或JNKs调节促炎转录因子，这些转录因子刺激炎性细胞因子和包括MCP-1在内的趋化因子表达，引起神经炎症和神经元死亡。作为“小胶质细胞抑制剂”的米诺环素可通过阻断酒精诱导的MCP-1、GSK-3β和JNKs的活化，抑制小胶质细胞的激活[18]。支持了MCP-1、GSK-3β和JNKs之间通过相互作用介导酒精诱导神经炎症的观点。

2. TLR4：酒精作为TLR4的配体，直接或间接地激活TLR4并打开其下游效应物如JNKs[19]，同时活化的TLR4可激活GSK-3β。TLR4和GSK-3β在响应酒精暴露时存在相互影响，阻断TLR4可观察到酒精诱导的GSK-3β活化和小胶质细胞中MCP-1的上调均被抑制；阻断GSK-3β，可观察到酒精诱导的TLR4和MCP-1的上调也均受到抑制。因此，活化的GSK-3β进一步刺激TLR4和JNKs，导致促炎细胞因子MCP-1表达增加。释放的MCP-1与CCR2相互作用并进一步激活TLR4、GSK-3β和JNKs，这种正反馈回路进一步加剧了酒精诱导的神经炎症和神经毒性。

二、细胞水平

MCP-1或CCR2敲除小鼠对酒精诱导的小胶质细胞激活、GSK-3β和JNK的活化及细胞凋亡具有抵抗性。一方面，MCP-1可通过直接诱导神经元凋亡，在细胞水平上介导酒精诱导的中枢神经系统损害。Kalehua等[20]研究发现MCP-1存在活跃的脑区可观察到明显的细胞凋亡现象，而且这种细胞凋亡是发生在单核细胞募集之前，MCP-1可在体内、外直接诱导海马神经元凋亡。酒依赖患者脑组织中MCP-1的增加可通过介导半胱天冬酶(caspase)依赖性细胞凋亡级联，促进神经细胞死亡，引起神经元损伤，并且这可能是导致酒精相关神经元丢失和脑萎缩的机制之一[21]。另一方面，MCP-1可通过改变血脑屏障的紧密连接以及内皮细胞黏附分子表达等直接改变血脑屏障的通透性，从外周向中枢神经系统募集更多的单核细胞，进而通过增强细胞因子和趋化因子的产生放大炎性反应[22]，因此MCP-1通过介导神经炎症间接引起细胞凋亡，促进神经元死亡。

三、蛋白水平

1. MCP-1参与内质网应激：最近提出内质网应激是酒精诱导中枢神经系统损害的重要机制。Kim等[23]表明CCR2抑制剂可下调MCP-1并减轻内质网应激。MCP-1/CCR2可通过触发心肌细胞和破骨细胞中单核细胞趋化蛋白–1诱导蛋白–1(MCPIP)的表达，诱导内质网应激，促进自噬，进而破坏细胞内钙稳态并激活转录因子和NF-κB炎症通路导致促炎因子的过度产生，加重神经毒性[24]。MCPIP1是一种转录激活因子，位于CCR2的下游，参与调节MCP-1的表达。酒精可显著增加MCPIP1水平，这与内质网应激增强有关，提示MCP-1/CCR2信号传导参与酒精诱导的内质网应激。敲除MCP-1/CCR2

小鼠显著降低或阻断酒精诱导的未折叠蛋白反应(UPR)的水平,并且敲除CCR2更有效。因此,酒精诱导的MCP-1上调可通过引起内质网应激,加剧中枢神经系统的损害。

2. MCP-1参与氧化应激:对氧化代谢动物模型(TD)的研究表明,阻断MCP-1显著抑制了氧化代谢诱导的小胶质细胞激活和神经元变性,并且活性氧(ROS)在氧化代谢诱导的MCP-1的表达及神经元死亡中起关键作用[25]。酒精损害神经元导致ROS水平增加,抗氧化剂水平降低,并促进神经元产生和分泌MCP-1,其募集并激活小胶质细胞,活化的小胶质细胞释放肿瘤坏死因子(TNF-α)和ROS,加剧神经炎症和氧化应激,进一步引起神经元细胞死亡。因此,在与氧化应激相关的神经变性过程中MCP-1可能是神经元/小胶质细胞相互作用的关键介质[26]。

综上所述,MCP-1/CCR2信号传导在分子水平、细胞水平和蛋白水平上介导了酒精诱导的中枢神经系统神经炎症和神经毒性。因此,通过给予选择性抑制剂或遗传操作抑制MCP-1/CCR2信号可改善酒精诱导的中枢神经系统损伤。这些发现将MCP-1/CCR2信号传导确定为治疗的潜在目标,但是由于临床依据尚不确切,因此未来仍需要继续探究MCP-1/CCR2信号在酒精诱导的神经炎症和脑损伤中的机制,进一步明确抗MCP-1/CCR2的治疗概念,为酒依赖的治疗提供新途径。

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· 综述 ·

# 银杏萜类内酯治疗认知障碍机制研究进展

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【摘要】 认知障碍是一种获得性、进行性的智能障碍表现，其认知功能损伤包括学习、记忆、视空间等多方面能力异常，导致患者出现进行性记忆力下降、日常生活能力下降、精神行为异常等临床表现。认知障碍的病因复杂，包括阿尔茨海默病和血管性痴呆等。因此，针对多靶点的治疗是改善认知障碍药物疗效的关键，也是近年研究的热点和难点。银杏萜类内酯具有多靶点、多途径治疗特点，现以银杏萜类内酯主要成分，即银杏内酯A、B、C及白果内酯为切入点，从其抗氧化应激、抗炎性反应、抗凋亡等方面，对其治疗认知障碍作用机制进行探讨。

【关键词】 阿尔茨海默病；　痴呆，血管性；　银杏内酯类；　白果内酯；　综述

**Effective mechanism of ginkgobiloba against dementia: a review of current literature**　*Yan Yi, Ma Li*

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【**Abstract**】 Cognitive impairment is characterized as an acquired and progressive manifestation of intellectual impairment. Cognitive impairment includes learning, memory, visual space and other abnormal abilities, leading to progressive memory decline, daily living ability decline, mental and behavioral abnormalities and other clinical manifestations. The pathological mechanism of cognitive impairment is complex, including Alzheimer disease and vascular dementia. Currently, the treatment of multiple targets is the key to improve the efficacy of pharmacotherapy, and it is also possesses the most significant position in recent years. Ginkgobiloba has multi-target and multi-channel treatment characteristics. In this review, we will use the main components of ginkgo biloba lactone, namely ginkgolides A, B, C and bilobalide as the entry point, from its

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