

综述

睡眠障碍后小胶质细胞活化相关信号通路的研究进展

舒治钧, 张全怡, 徐义鹏, 赵征宇*

成都中医药大学针灸推拿学院, 成都 610075

摘要: 睡眠是维持人类生命极其重要的生理状态, 睡眠障碍不仅会导致焦虑、抑郁情绪的产生, 还会通过诱发多系统疾病严重影响脑功能和身体健康。神经炎症反应是睡眠障碍后的关键病理过程, 可导致一系列神经系统疾病的发生。近年来, 小胶质细胞活化在神经炎症产生机制中所起的作用越来越受到重视, 已成为该领域的研究热点。睡眠障碍后中枢微环境的失衡, 导致小胶质细胞活化和极化状态改变, 从而触发神经炎症反应。小胶质细胞活化受多个信号通路和复杂分子机制的调控, 本文总结了睡眠障碍诱发神经炎症中小胶质细胞活化相关的5条信号通路: 嘌呤P2X7受体(P2X7 receptor, P2X7R)、p38MAPK、Toll样受体4 (Toll-like receptor 4, TLR4)/NF- κ B、JAK/STAT、 α 7-烟碱型乙酰胆碱受体(α 7 nicotinic acetylcholine receptor, α 7-nAChR)通路, 以期为睡眠障碍后续深入研究和临床治疗靶点选择提供参考。

关键词: 睡眠障碍; 神经炎症; 小胶质细胞; P2X7R; p38MAPK; TLR4/NF- κ B; JAK/STAT; α 7-nAChR

Research progress of signal pathways of microglia activation in sleep disorders

SHU Zhi-Jun, ZHANG Quan-Yi, XU Yi-Peng, ZHAO Zheng-Yu*

School of Acupuncture-moxibustion and Tuina, Chengdu University of Traditional Chinese Medicine, Chengdu 610075, China

Abstract: Sleep is an extremely important physiological state to maintain human life. Sleep disorders can not only cause anxiety and depression, but also induce multi-system diseases that seriously affect brain function and physical health. The neuroinflammation is a key pathological process after sleep disorders, which can induce a series of nervous system diseases. In recent years, the role of microglia activation in neuroinflammation has been paid more and more attention and become a research hotspot in this field. The imbalance of the central microenvironment after sleep disorders leads to changes in the activation and polarization of microglia, which triggers neuroinflammatory response. The activation and polarization of microglia in the sleep disorders are regulated by multiple signaling pathways and complex molecular mechanisms. This paper summarizes five signaling pathways of microglia activation in central inflammation induced by sleep disorders, including P2X7 receptor (P2X7R), p38MAPK, Toll-like receptor 4 (TLR4)/NF- κ B, JAK/STAT, and α 7 nicotinic acetylcholine receptor (α 7-nAChR) pathways, in order to provide reference for further research and clinical treatment targets selection of sleep disorders.

Key words: sleep disorders; neuroinflammation; microglia; P2X7R; p38MAPK; TLR4/NF- κ B; JAK/STAT; α 7-nAChR

睡眠障碍是指睡眠与觉醒正常节律性交替紊乱所表现出来的各种功能异常, 临床上主要表现为失眠、睡眠呼吸障碍、异态睡眠等。世界上 1/3 的人深受睡眠问题的困扰, 睡眠障碍会导致多系统损伤, 是高血压、帕金森病、阿尔茨海默病等多种疾病的

关键诱发或加重因素。研究表明神经炎症是睡眠障碍的主要病理特征之一^[1], 睡眠障碍后中枢微环境的改变诱导小胶质细胞的激活, 导致神经炎症反应的产生和加重, 而神经炎症进一步加速睡眠障碍的进程。虽然目前睡眠障碍后中枢神经炎症发生机制

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*Corresponding author. E-mail: zhaozhengyu@cdutcm.edu.cn

尚未完全明确,但已有大量证据表明,活化的小胶质细胞在其中发挥着重要作用,阐明小胶质细胞活化进程将是改善神经炎症反应的重点,因此本文将就睡眠障碍引起神经炎症中小胶质细胞活化机制进行阐述,以期后续相关研究以及潜在治疗靶点选择提供参考。

1 睡眠障碍诱发小胶质细胞活化,介导炎症反应

神经炎症被广泛认为是中枢神经系统的炎症,包括小胶质细胞激活和促炎细胞因子水平升高,是睡眠障碍后的关键病理过程,可导致继发性脑组织损伤和功能障碍^[2],近年来逐渐被视作疾病发展的主要驱动力。小胶质细胞作为中枢神经系统内的常驻免疫细胞,参与调控睡眠障碍的关键病理环节,其活化被认为是神经炎症的主要来源^[3]。此外睡眠障碍后小胶质细胞活化不仅会导致神经炎症的发生,还会增强其吞噬活性,介导突触修剪受损,增加大脑对其他形式损伤的易感性;同时影响小胶质细胞线粒体自噬功能,诱发神经元促凋亡和抗凋亡基因级联失衡等改变。在静息状态下,小胶质细胞发生特征性分支延伸,对中枢神经系统持续免疫扫描与监测,进而维持内环境稳态。当脑内组织感染或产生炎症时,小胶质细胞迅速激活,其形态呈阿米巴样^[4]。活化小胶质细胞主要有两种相反的状态:经典(M1)和替代(M2)型,发挥神经毒性和神经保护作用;两种表型之间存在着一系列连续的中间表型,小胶质细胞可从一种表型过渡到另一种表型,即M1/M2表型代表一系列激活模式而不是单独的细胞亚型,形成的表型分布根据神经退行性疾病的进展而改变^[5]。两种小胶质细胞表型之间的平衡介导着神经炎症的发生和发展。大量研究发现小胶质细胞的活化存在于睡眠障碍的病理过程,睡眠障碍情况下可释放一系列的细胞因子和趋化因子等,充分诱导M1型小胶质细胞激活,抑制M2型活化,促进海马、下丘脑、前额叶皮层等多个脑区IL-6、TNF- α 释放,加重神经炎症反应^[6]。本研究组前期的研究也证实睡眠障碍可诱导丘脑网状核小胶质细胞活化,并促进IL-1 β 和TNF- α 的释放,损伤中枢神经功能,引起认知缺陷^[7]。而腹腔注射小胶质细胞活化抑制剂米诺环素,可显著下调睡眠障碍后炎性细胞因子的释放,改善大鼠空间记忆功能^[8]。总之,睡眠障碍会引起中枢内环境稳态失衡,多因子

水平紊乱可通过多种途径诱导促炎性小胶质细胞激活,介导神经炎症反应,破坏神经元结构和功能,进一步加重睡眠障碍并诱发多种神经退行性疾病。

2 睡眠障碍后小胶质细胞活化相关信号通路

小胶质细胞活化是睡眠障碍后神经炎症反应产生的主要因素,睡眠障碍激活小胶质细胞途径和机制复杂多样,多种信号通路参与其中并发挥着重要作用,包括小胶质细胞嘌呤P2X7受体(P2X7 receptor, P2X7R)、p38MAPK、Toll样受体4(Toll-like receptor 4, TLR4)/NF- κ B、JAK/STAT、 α 7-烟碱型乙酰胆碱受体(α 7 nicotinic acetylcholine receptor, α 7-nAChR)通路等。

2.1 小胶质细胞P2X7R通路

P2X7R属于ATP离子门控通道,该通道允许Na⁺、Ca²⁺的流入以及K⁺流出,内外向离子通量是产生炎症的基础,P2X7R与炎症反应密切相关,介导NLRP3炎症小体激活和IL-1 β 释放^[9],成为免疫反应早期阶段的重要启动子,同时还参与睡眠调节^[10]。细胞外高ATP水平充当危险信号,直接激活质膜通道P2X7R,在瞬时刺激下,胞内K⁺浓度迅速降低,低K⁺水平作为NLRP3炎症小体激活的关键触发器^[11],增强NLRP3炎症小体与相关激酶蛋白7的相互作用,并将pro-caspase-1裂解为caspase-1,促使下游IL-1 β 的生成和成熟,进而介导中枢神经炎症反应。中枢神经系统中P2X7R广泛分布于小胶质细胞中,其蛋白表达水平随着睡眠周期的改变而改变^[12]。Xia等研究发现慢性睡眠剥夺小鼠前额叶皮层中ATP的细胞外浓度显著增加,激活神经胶质细胞表面P2X7R,刺激睡眠调节因子TNF- α 和IL-1 β 释放,增强神经炎症^[10]。本研究组的前期研究也发现失眠大鼠丘脑网状核中小胶质细胞上P2X7R表达增强,提示该受体参与了小胶质细胞的活化和失眠后细胞因子的调节^[13]。此外时钟基因Per1也部分参与了睡眠障碍的病理环节^[14]。睡眠障碍后小胶质细胞P2X7R高度激活,选择性上调小胶质细胞Per1 mRNA表达,刺激小胶质细胞时钟系统紊乱,并诱导小鼠海马区静息小胶质细胞向M1型转化和增殖^[15],促进炎症因子水平上调,抑制抗炎因子释放,当药理性阻断P2X7R后,小胶质细胞从M1型向M2型转化,有效减轻病理症状^[16]。

2.2 小胶质细胞p38MAPK通路

p38MAPK作为有丝分裂原活化蛋白激酶(mitogen-

activated protein kinases, MAPKs) 家族中调节炎症反应的重要蛋白激酶之一, 在应激、病原体的刺激下磷酸化激活, 经多级激酶的级联反应将细胞外信号传递至细胞核, 调控底物如炎症因子、凋亡蛋白的表达, 介导细胞产生各种生物学反应^[17]。实验发现在炎症反应下, 高比例的免疫反应基因和 p38MAPK 信号通路基因的表达伴随着小胶质细胞的慢性激活, 这提示 p38MAPK 在小胶质细胞中过度表达^[18]。Fan 等研究发现睡眠剥夺可诱发小鼠海马小胶质细胞激活和 p38MAPK 磷酸化表达, 显著升高海马区 NLRP3 炎症小体和炎症因子 IL-1 β 、IL-18 水平, 而睡眠恢复后能有效抑制 p38MAPK 信号通路的激活^[19]。使用 p38MAPK 信号通路抑制剂 SB203580 阻断了睡眠障碍后小胶质细胞活化和神经炎症反应^[19]。此外, IL-17 作为激活 p38MAPK 信号通路的重要炎症细胞因子之一也参与了睡眠障碍后病理过程。Cui 等研究发现快速眼动睡眠剥夺诱导海马中 IL-17 的高表达, 通过与海马神经祖细胞的 IL-17RA 和 IL-17RC 结合激活 p38MAPK 信号通路, 并抑制海马齿状回的细胞增殖^[20]。且有文献报道, 睡眠剥夺组大鼠躯体感觉皮层 IL-1 β 和 p38MAPK 磷酸化表达增加, 而高表达的 IL-1 β 通过 p38MAPK 反过来抑制睡眠, 使得中枢炎症反应通过反馈环路不断放大, 引起神经元结构和功能的损伤, 持续诱发神经毒性作用, 导致认知功能障碍^[21]。

2.3 小胶质细胞TLR4/NF- κ B通路

TLR4 是模式识别受体家族中的重要成员之一, 在中枢神经系统小胶质细胞中高表达^[22], 可特异性识别内外源性配体, 激活 NF- κ B 和其他转录因子, 诱导免疫反应, 其表达水平随着病原体或其他促炎刺激的存在而增加, TLR4 作为小胶质细胞信号传导和促炎反应的最佳特征参与机体免疫应答过程^[23]。NF- κ B 是小胶质细胞中调控炎症反应的关键转录因子, 控制编码促炎细胞因子的基因表达, 负责小胶质细胞 M1/M2 型极化^[24]。Qiu 等研究表明睡眠剥夺会诱导机体大量释放高迁移率族蛋白 B1, 该促炎细胞因子导致 TLR4/NF- κ B p65 表达上调, 激活小鼠海马小胶质细胞, 促进下游炎症细胞因子 IL-1 β 和 TNF- α 的释放, 导致睡眠障碍后认知损伤^[25]。Dai 等采用双重免疫荧光标记的方法标记慢性睡眠剥夺大鼠海马区中小胶质细胞和 TLR4 的共表达, 发现 TLR4⁺ 和 Iba1⁺ 高度相关, 即慢性睡眠剥夺激活了 TLR4 信号通路, 该通路强烈诱导了小胶

质细胞 M1 型极化, 并增加了海马区 NLRP3、ASC、caspase-1、IL-1 β 的蛋白表达水平, 加重慢性疼痛大鼠的疼痛行为^[26]。另外, 睡眠障碍还可通过 TLR4-MyD88 级联反应激活小胶质细胞^[27], 并不同程度地调节炎症因子的表达, 诱导神经炎症反应, 加重实验性大鼠的脑损伤和神经功能障碍, 而使用 TLR4 信号通路抑制剂治疗显著减轻了睡眠障碍引起的神经炎症和病理改变。

2.4 小胶质细胞JAK/STAT通路

JAK/STAT 是一条受多细胞因子调节的信号通路, 其功能失调可诱导小胶质细胞激活和极化为致病表型, 对神经炎症性疾病具有病理意义。该通路的作用机制如下^[28]: 1) 细胞因子与细胞表面受体结合, 诱导受体二聚化形成, 激活与受体相关联的 JAK 激酶; 2) JAK 激酶促使特异性受体的酪氨酸结合位点磷酸化, 相应的 STAT 因子激活; 3) 激活后 STAT 蛋白与受体上酪氨酸残基结合, 形成二聚体游离并转移到细胞核与特定的 DNA 元素结合, 实现对靶基因的调控。睡眠障碍时机体内 IL-1 β 、IL-6 等促炎因子水平增加, JAK/STAT 信号通路在睡眠障碍患者中被显著激活^[29], 同时可通过 IL-6 与小胶质细胞 gp130 受体结合来进行调节^[30]。动物研究中发现睡眠剥夺可促进果蝇体内神经胶质细胞标志物水平增加, 激活 JAK/STAT 信号通路, 加重神经炎症反应, 介导神经元的稳态改变^[31]。Zhang 等通过建立睡眠剥夺模型大鼠, 探索睡眠剥夺对大鼠海马 JAK/STAT 通路及炎症的影响, 发现睡眠剥夺促进海马中 IL-6 和受体 (IL-6R) 表达增加, 并使得 JAK2/STAT3 信号通路中的关键蛋白 p-JAK2 和 p-STAT3 表达显著上调, JAK2 和 STAT3 蛋白的磷酸化表明其蛋白功能活化, 提示睡眠剥夺诱导了 JAK2/STAT3 信号通路的激活^[32]。故有文献探讨靶向 JAK/STAT 通路作为神经炎症和神经退行性疾病保护性疗法的可行性^[33]。

2.5 小胶质细胞 α 7-nAChR通路

α 7-nAChR 是一种介导突触间快速信号传递的配体门控离子通道蛋白, 对钙离子有较高的通透性, α 7-nAChR 作为胆碱能神经系统和免疫系统中广泛分布的分子之一, 介导着机体的免疫炎症反应^[34]。研究发现 α 7-nAChR 在小胶质细胞表面存在不同密度的表达, 刺激 α 7-nAChR 可调节小胶质细胞的活化状态并介导表型改变, 受体的激活促进 M1 型小胶质细胞向 M2 型转化, 并支配下游信号分子的表

达, 实现对炎症反应的调控^[35]。中枢胆碱能神经元在睡眠开始和维持中起重要作用, 它们的退化被认为会导致睡眠中断^[36]。有研究报道了睡眠重要脑区 nAChR 的变化, 在 Rett 综合征睡眠障碍小鼠模型中发现脑干神经元 $\alpha 7$ -nAChR 表达减少^[37]。Xue 等的研究阐述了胶质细胞 $\alpha 7$ -nAChR 在睡眠剥夺中的作用机制^[38], 慢性睡眠剥夺小鼠海马体小胶质细胞激活伴随着 $\alpha 7$ -nAChR 下调和下游 PI3K/AKT/GSK-3 β 激活减少, 促炎因子 IFN- γ 、MCP-1 增加, 抗炎因子 CD206、TGF- β 减少, 海马转录物 Nrf2 和抗氧化酶 HO-1 的活性降低。施用 $\alpha 7$ -nAChR 激动剂可诱导 PI3K/AKT/GSK-3 β 活化, 并逆转炎症因子

的变化。同时腹膜内注射 $\alpha 7$ -nAChR 激动剂还能有效改善阻塞性睡眠呼吸暂停后炎症反应所引起的认知功能障碍^[39]。因此小胶质细胞 $\alpha 7$ -nAChR 可作为缓解睡眠障碍后的神经炎症和病理进程的有效靶点之一。

3 小结与展望

随着现代科学研究的不断深入, 目前认为睡眠障碍可通过多条信号通路激活小胶质细胞, 介导神经炎症反应, 其作用过程纷繁复杂且调控机制精细多样, 根据对文献的梳理, 本文总结了其中 5 条小胶质细胞活化通路 (图 1), 此外尚可能存在其他通

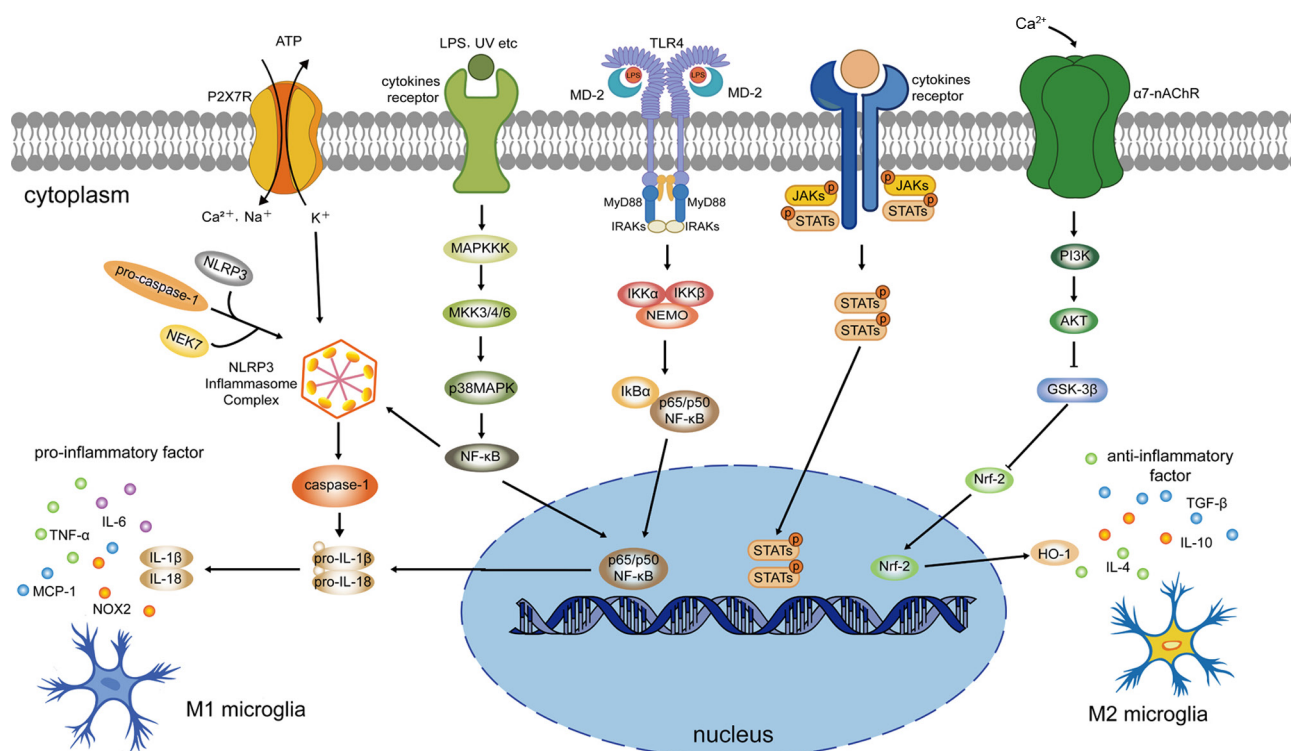


图 1. 睡眠障碍后小胶质细胞活化信号通路

Fig. 1. Microglial activation signal pathways in sleep disorders. Sleep disorders induce the imbalance of the central microenvironment, and release a range of chemokines, cytokines and so on, which activate the P2X7R, TLR4/NF- κ B, JAK/STAT, p38MAPK signal pathways, and inhibit the $\alpha 7$ -nAChR signal pathway in microglia. The activation of P2X7R is associated with the release of K⁺ from the cell, which causes NLRP3 inflammasome assembly. Activated inflammasome cleaves pro-caspase-1 into caspase-1, which causes maturation of IL-1 β and IL-18. Activated cytokines receptor induces the cellular responses of a three-step MAPK pathway (MAPKKK, MAPKK, MAPK) that lead to p38MAPK activation. Activated TLR4 associates with MyD88 to induce the autophosphorylation of IRAK, which activates a major pro-inflammatory pathway, IKK/I κ B/NF- κ B signaling pathways, thus the pro-inflammatory genes transcribe. Activated JAK induces the phosphorylation of STATs, and STATs induce the expression of pro-inflammatory mediators. The down-regulation of $\alpha 7$ -nAChR reduces activation of downstream PI3K/AKT/GSK-3 β , which occurs with increases of pro-inflammatory factors and decreases of anti-inflammatory factors. MAPK: mitogen-activated protein kinase; MyD88: myeloid differentiation primary response 88; IRAK: interleukin-1 receptor-associated kinase; JAK: janus kinase; STAT: signal transducer and activator of transcription; GSK-3 β : glycogen synthase kinase-3 β ; TLR4: Toll-like receptor 4; LPS: lipopolysaccharide; UV: ultraviolet; MD-2: myeloid differentiation protein-2.

路,靶向小胶质细胞活化信号通路对睡眠障碍具有治疗意义。目前有研究发现小胶质细胞在其他疾病中存在着一些在睡眠障碍中尚未被研究的活化通路,如阿尔茨海默病中 P2RY12 途径^[40]、血管痴呆中 Sirt1/PGC-1 α 途径^[41]等,此为睡眠障碍领域目前存在的局限之处,可为睡眠障碍信号通路后续研究提供启发。目前睡眠障碍后小胶质细胞激活途径的研究基本上都是单一信号通路的探索,但信号通路间是否存在复杂联系,以及其具体的交互调节机制等问题仍未阐明,故后续研究亦可针对各信号通路之间的交互作用进行探究。此外小胶质细胞在损伤环境中处于动态变化,M1/M2 型的表达发生了不同程度的改变,不同因素诱导其 M1/M2 型转化,但睡眠障碍情况下具体 M1/M2 型小胶质细胞间表型转化机制以及两者比例如何改变目前鲜有报道,因此后续研究可把握住小胶质细胞表型转化这个重点,在促炎和抗炎之间找到平衡,通过调节小胶质细胞的炎症反应实现对睡眠障碍后神经炎症的调整,为临床诊治因神经炎症反应导致的神经系统疾病提供新思路。

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