文章编号:1003-2754(2025)10-0911-05 doi:10.19845/j.cnki.zfysjjbzz.2025.0168

神经病理性疼痛所致睡眠障碍的研究进展

成 帆[1,2], 李 戈[1,2], 毕艳兴[1,2], 李育宁[1,2], 崔文平[1,2], 高进贤[2]综述, 杨孝来[1,2]审校

摘 要: 神经病理性疼痛(NP)导致的睡眠障碍是一种难治疗的神经性疾病,严重影响患者的生活质量。研究发现NP相关脑区参与了睡眠障碍的调节,如丘脑、下丘脑、基底前脑等,二者在发病的中枢机制、外周机制和其他方面有密切联系,但相关研究尚不充分。本文对近年来NP导致睡眠障碍的主要发病机制、治疗药物进行综述,旨在为临床寻找疗效显著的药物提供参考。

关键词: 睡眠障碍; 神经病理性疼痛

中图分类号:R338.63 **文献标识码:**A

Research advances in sleep disorders caused by neuropathic pain *CHENG Fan, LI Ge, BI Yanxing, et al. (College of Pharmacy, Gansu University of Chinese Medicine, Lanzhou 730000, China)*

Abstract: Sleep disorders caused by neuropathic pain (NP) are a type of neurological disorder with difficulties in treatment, which greatly affects the quality of life of patients. Studies have shown that NP-related brain regions are involved in the regulation of sleep disorders, such as the thalamus, the hypothalamus, and the basal forebrain and the two diseases are closely associated with each other in terms of central and peripheral pathogeneses, but there is still a lack of sufficient research. This article reviews the main pathogenesis and therapeutic drugs for sleep disorders caused by NP in recent years, in order to provide a reference for the clinical search for effective drugs.

Key words: Sleep disorder; Neuropathic pain

神经病理性疼痛(neuropathic pain,NP)是一种常见的由神经功能障碍或病变引起的慢性疼痛,典型特征是中枢和外周神经系统的痛觉神经元超敏,其在世界范围内的发病率约为7.0%~8.0%,通常被归类为一种对生活质量有重大影响的慢性疼痛[1]。睡眠是维持人基本生理功能和保持健康的关键要素之一,人的一生中大约1/3的时间都是在睡眠中度过的[2]。根据脑电波的特征可将脑功能状态分为快速眼动睡眠(rapid eye movement sleep,REM)和非快速眼动睡眠(non-rapid eye movement sleep,NREM)两种生理状态,其中,REM睡眠被认为与情绪调节、创造性问题解决和情绪记忆巩固密切相关[3],NREM睡眠中大脑会产生标志性的纺锤波[4](sleep spindle),与代谢物的清除、认知学习及智力恢复有关。睡眠时,大脑状态在这两种主要睡眠状态之间周期性地交替,构成睡眠-觉醒周期[5]。睡眠-觉醒周期的紊乱会造成睡眠障碍(sleep disorder,SD),包括入睡困难、睡眠不足和睡眠质量低,这可能导致广泛的身体和精神问题,严重影响生活质量[6-8]。其中,NP患者的睡眠障碍患病率在50%~80%之间,包括睡眠质量降低和睡眠结构改变(REM、NREM、睡眠碎片化)。睡眠碎片化指的是睡眠时间缩短,睡眠和清醒状态之间频繁转换。有研究发现,NP患者在NREM睡眠的第一阶段花费更多的时间,并且经历了更多的睡眠碎片化,从睡眠到清醒的过渡也更频繁[9]。提示NP是导致睡眠障碍的一个重要因素,另一方面,睡眠障碍也会加重NP[10,11],两者在发病机制上密切相关[12,13]。本文将对近年来NP导致睡眠障碍的主要发病机制和治疗药物的相关研究进行详细阐述。

1 神经病理性疼痛引起的睡眠障碍

最常见的NP动物模型有部分坐骨神经结扎(partial sciatic nerve injury,PSNL)模型、坐骨神经慢性缩窄性损伤(chronic constriction injury,CCI)模型和坐骨神经分支损伤(spared nerve injury,SNI)模型。研究发现各种NP动物模型均对动物REM、NREM睡眠和觉醒时间有不同程度的影响(见表1)。相对的,完全剥夺个体睡眠会增加健康参与者的疼痛敏感性,损害条件性疼痛调节,并促进疼痛的时间总和,形成持续性疼痛[14]。以上模型证实NP会导致睡眠障碍,同时睡眠障碍也会反过来作用于NP,加重症状。

2 神经病理性疼痛导致睡眠障碍的机制研究

NP的特征是感觉异常,例如机械异常性疼痛和热痛觉过敏,在疼痛状态下,伤害感受器遭受刺激,疼痛信号通过传入神经纤维传导至背根神经节(dorsal root ganglion,DRG),继续传向脊髓背角,到达背角后,疼痛信号横跨脊髓传导到对侧脊髓丘脑束,继续上行到达脑干、中脑、大脑皮质进行疼痛信号的分析与整合,进而产生痛觉,这一过程涉及多个脑区,主要与外周和中枢神经系统神经递质和离子通道的改变有关[23]。睡眠障碍的特征是睡眠-觉醒系统紊乱。

收稿日期:2025-06-30;**修订日期:**2025-09-10

基金项目:甘肃省自然科学基金项目(1208RJZA120)

作者单位:(1.甘肃中医药大学药学院,甘肃 兰州 730000;2.甘肃省人民医院药剂科,甘肃 兰州 730000)

通信作者:杨孝来,E-mail:yxl1668@vip.163.com

表 1　神经病理性疼痛动物模型对睡眠的影响

模型	作用结果	参考文献
PSNL	觉醒增加，NREM 睡眠减少	[15]
PSNL	PSNL 导致快速眼动睡眠和非快速眼动睡眠时间减少；非快速眼动睡眠的持续时间被打断，从而导致睡眠碎片化	[16]
PSNL	患有 PSNL 的小鼠表现出睡眠障碍，包括睡眠减少和睡眠碎片化增加	[17]
CCI	NREM 睡眠时间显著减少，觉醒时间增加	[18]
CCI	基底前脑的基底前核中胆碱能神经元在 NREM 睡眠期间逐渐活跃	[19]
CCI	REM 睡眠减少，NREM 睡眠增加。此外，睡眠纺锤体密度和纺锤体频率也有所增加	[20]
SNI	小鼠的觉醒时间增加，NREM 睡眠减少	[21]
SNI	神经性疼痛保留了传统的睡眠措施，但导致自发和诱发的觉醒能力提高	[22]

2.1　外周神经系统

神经损伤产生的痛觉刺激导致外周瞬时受体电位（transient receptor potential，TRP）伤害感受器的激活，伤害感受器末端释放 P 物质和降钙素基因相关肽，随后阳离子通道打开，导致去极化和动作电位沿传入感觉纤维传播到脊髓背角的突触。突触前囊泡释放兴奋性非肽递质和肽递质，产生痛觉。外周痛觉传入纤维存在于背根神经节、三叉神经节、迷走神经的结节神经节和中央轴突分支，所有这些神经节都与脊髓背角的神经元形成突触连接，研究发现在外周神经系统（peripheral nervous system，PNS）中主要涉及小直径 Aδ 纤维和 C 纤维，C 纤维神经病引起的热痛觉过敏，Aδ 纤维神经病引起的机械性异常痛。周围神经损伤能特异性降低与神经性痛觉相关的脊髓背角细胞的表达[24]，由周围神经损伤产生的疼痛也可能引起 REM 睡眠减少的睡眠障碍[25]。此外，异常的脊髓致敏活动导致周围神经损伤引起的疼痛相关基因如离子通道，受体和脊髓细胞间信号分子的不适应变化，也会引起睡眠障碍。

2.2　中枢神经系统

2.2.1　丘脑　睡眠纺锤波是发生在 NREM 睡眠期间的 11~16 Hz 神经活动振荡，由丘脑产生，通过丘脑皮质震荡传递到皮质，有助于记忆巩固和对环境噪声的屏蔽，从而提高睡眠质量。在 SNI 大鼠模型中，睡眠纺锤体密度降低[26]，干扰丘脑皮质振荡，参与睡眠的调节。丘脑网状核（thalamic reticular nucleus，TRN）对 NP 所致的 SD 有不同的调节作用，TRN 是纺锤体的起搏器，通过向丘脑核提供强烈的 γ-氨基丁酸（γ aminobutyric acid，GABA）能抑制，从而引起丘脑皮质细胞的反弹爆发性放电，睡眠纺锤体的发生是由 sk2 通道介导的重复 TRN 爆发形成的，并有助于增强 NREM 巩固和唤醒阈值。表明 NP 通过影响睡眠纺锤波导致 SD，提示临床通过增加 NP 患者纺锤体密度可以有效地降低疼痛敏感性[26]，从而改善 SD。丘脑腹后外侧核（ventral posterolateral thalamic nucleus，VPL）是丘脑中最重要的体感核，丘脑室旁核（paraventricular thalamus，PVT）被认为是许多下行和上行通路的重要信号整合位点，从 PVT 到中央杏仁核（central amygdala，CeA）的神经回路对 NP 和 SD 均有影响作用，Liang 等[27]用雄性大鼠神经病理性疼痛模型确证了该神经回路对 NP 有促进作用。Zhao 等[28]确定了该回路对清醒主动和清醒促进的作用，发现该回路在急性应激条件下会进一步激活，并调节急性应激引起的高度清醒，从而造成 SD。丘脑痛是一种由丘脑损伤引起的 NP[29]，An 等[30]建立了一种将眼镜蛇毒液注射于单侧 VPL 的大鼠 TP 模型，并在造模成功后进行疼痛行为学测试，测得痛阈降低，可以认为 VPL 是丘脑中引起 NP 的主要核团。TRN 功能障碍与多种神经发育障碍的感觉异常、注意力缺陷和睡眠障碍有关。

2.2.2　下丘脑　睡眠周期由昼夜节律调节，昼夜节律由下丘脑的视交叉上核（suprachiasmatic nucleus，SCN）驱动。下丘脑可以控制睡眠的开始并调控疼痛，下丘脑外侧产生的促觉醒下丘脑泌素（Hcrt，也称为 orexin），orexin 是一种主要调节睡眠-觉醒周期的促觉醒神经递质[31]。通过单胺能/胆碱能（促醒）和 GABA 能（促眠）神经元回路之间的复杂相互作用，向大脑唤醒区域蓝斑、结节乳头核和基底前脑胆碱能系统等发送密集的投射。对睡眠-觉醒调节至关重要[32]。Chen 等[33]在雄性大鼠神经性疼痛实验模型中证实了增加 orexin 的表达，可以改善疼痛的行为表现。orexin 受体（orexin-1 和 orexin-2 受体）通过维持中枢唤醒系统中单胺能神经元的活性，参与稳定唤醒和抑制睡眠。Roehrs 等[34]用一种 orexin 拮抗剂评估其在神经性疼痛和睡眠中发挥的作用，orexin 拮抗剂与安慰剂相比增加了总睡眠时间，减少了入睡后的觉醒时间，且无夜间效应或相互作用，睡眠潜伏期和其他睡眠指标没有改变，改善了睡眠时间，并降低了疼痛敏感性。

2.2.3　基底前脑　基底前脑（basal forebrain，BF）是内源性睡眠通路的重要组成部分，可以促觉醒，在哺乳动物睡眠-觉醒调节中起着重要作用，其中的

阿片系统和多巴胺系统基因表达异常会引起NP[35]。Sun等[36]采用神经环路逆行示踪法确定了基底外侧杏仁核(basolateral amygdala,BLA)在调节REM睡眠中起作用[37],BLA中分叉的氨基丁酸能神经元可能参与情绪诱发的SD,而NP又是情绪诱发的关键原因,由此,可以推测NP可能因为引发不良情绪导致BLA氨基丁酸能神经元诱发SD。CeA中富含与疼痛相关神经可塑性核疼痛行为的重要兴奋性或抑制性调节剂的神经肽,通过BLA复合物间接地从丘脑和皮质区域接收疼痛相关信息,并通过脊柱-旁肱肌-杏仁核通路更直接地接收痛觉输入影响睡眠[38]。

2.2.4 脊髓 脊髓背侧致敏被认为在疼痛超敏反应中起重要的作用。与该疾病相关的中枢神经系统(central nervous system,CNS)由乙酰胆碱、去甲肾上腺素、多巴胺、血清素、组胺、orexin和黑色素集中激素神经元组成[39]。其中,5-羟色胺、去甲肾上腺素、组胺、下丘脑素、乙酰胆碱、多巴胺、谷氨酸、氨基丁酸,主要通过促觉醒作用诱发SD,谷氨酸是主要的兴奋性神经递质,可以促进中枢神经系统的快速兴奋性突触传递,近年研究发现:NP对与睡眠相关的各种神经元活动有关键影响,P2X7受体(P2X7R)在小胶质细胞中广泛表达,在疼痛和睡眠-觉醒周期的神经元中均有活动[18]。多巴胺(dopamine,DA)是一种主要的儿茶酚胺,产生于中脑黑质(substantia nigra,SN)和腹侧被盖区(ventral tegmental area,VTA),来自SN和VTA的DA能神经元投射到纹状体、边缘和皮质区域,Wawrzczak-Bargiela等[35]人用CCI模型诱导的NP小鼠模型,发现伴随着纹状体/伏隔核中涉及多巴胺能和阿片能信号的分子的主要转录失调,证明多巴胺能系统和阿片系统参与了疼痛的调节。GABA是痛觉信息处理和疼痛调节的抑制性神经递质,GABA的三种亚型$GABA_A$、$GABA_B$、$GABA_C$不同程度地参与调节睡眠和觉醒,$GABA_A$受体是一种五聚体,由多个亚基($\alpha_{1\text{-}}\alpha_6$、$\beta_{1\text{-}}\beta_3$、$\gamma_{1\text{-}}\gamma_3$、$\pi_1$、$\varepsilon_1$、$\delta_1$和$\theta_1$)组成,具有绝对氯离子通道和多种变构结合位点,通过这些位点可以调节快速抑制性突触神经传递,参与疼痛的传递。脊髓小胶质细胞位于CNS中,NP药物滥用者激活的小胶质细胞数量显著增加[40],从而诱发睡眠疾病。

此外,Demarco等[41]提出导水管周围灰质等大脑区域可以调节睡眠阶段和痛觉,可能是由于中缝核参与下行疼痛控制系统和负责睡眠和清醒之间转换的上行网状激活系统(ascending reticular activating system,ARAS)。

2.3 免疫学机制

SD会通过激活免疫系统导致睡眠质量下降和神经痛发生[42]。主要共同原因是细胞因子水平升高和免疫细胞浸润到中枢神经中。小胶质细胞的激活和促炎细胞因子的升高与疼痛和睡眠调节相关[43],促炎细胞因子包括肿瘤坏死因子-α(tumor necrosis factor,TNF-α)[44],各种白细胞介素(interleukin,IL),包括IL-10[45,46]、IL-1β[1,46]、IL-6[47,48]和IL-17[46,49],活化的小胶质细胞可以释放促炎细胞因子,TNF-α和IL水平升高加重小鼠的疼痛感,引起睡眠障碍。对小胶质细胞的操作可能会改善大脑中受损的昼夜节律,并改善疼痛引起的睡眠异常。富集分析发现在GSE5281和GSE40562中$CD8^+$细胞构成了浸润免疫细胞的最高比例,这表明这些细胞可能在睡眠障碍的发展中发挥作用[50]。脊髓来源的浸润性巨噬细胞参与了疼痛信号的加工或调节[51,52],或许可以通过相应的免疫细胞浸润干预治疗该疾病。

3 神经性疼痛导致睡眠障碍的药物治疗

SD是主要疾病,NP是次要疾病,理想的药物应该是对两种疾病均有治疗作用。NP的主要治疗药物为三环抗抑郁药阿米替林、抗惊厥药加巴喷丁和普瑞巴林、5-羟色胺去甲肾上腺素再摄取抑制剂(度洛西汀和文拉法辛)[53],阿米替林可调节大脑中血清素能传递,对慢性神经性疼痛引起的睡眠障碍有效[15],表明阿米替林能改善慢性疼痛患者的睡眠质量和睡眠量。然而,加巴喷丁、普瑞巴林通过抑制神经元电压门控钙通道电流起作用,Davari等[54]用加巴喷丁、普瑞巴林与安慰剂组比较,发现两者均对NP有显著效果,对SD也有改善治疗效果,但常伴随嗜睡、头晕、恶心、呕吐的副作用[55],并且有滥用和成瘾的可能性[56],患者常因此而被迫停止药物治疗,5-HT2A受体拮抗与疼痛无关,但与睡眠改善密切相关[15]。SD的主要治疗药物为地西泮和褪黑素,地西泮由于副作用多,现已少用。褪黑素通过调节身体某些生理功能的昼夜节律,从而促进睡眠[57]。近年来,有大量研究表明褪黑素在NP的缓解和治疗中发挥重要作用[58-63]。同时,Kim等[64]发现迷迭香可以降低促觉醒脑区的神经元活动,同时增加促睡眠脑区的神经元活动,从而发挥催眠作用,可能成为潜在药物。

4 小 结

NP引起的SD常表现为NREM减少,觉醒增加,可能会加重疲劳的感觉、影响情绪、认知功能、损害组织和相关脑区,严重者可能会形成焦虑、抑郁、狂躁的病理状态。疼痛与睡眠的调节在相关脑区、神经递质、神经回路、免疫因子细胞方面有共同机制联系,这为研究神经病理性疼痛导致的睡眠障碍提供了方向。目前可选择的治疗药物有限,主要是依据药物对NP和SD的兼备治疗作用,但是此类药物往往不是该疾病的特异治疗药物,对两病之间机制的研究,有利于开发出NP所致SD的特异性药物,这也是临床开发新药的目标。

利益冲突声明：所有作者均声明不存在利益冲突。

作者贡献声明：成帆负责论文设计、撰写论文、绘制表格、论文修改；李戈、毕艳兴、李育宁、崔文平负责文献收集；高进贤负责拟定写作思路；杨孝来负责指导撰写论文并最后定稿。

［参考文献］

[1] Oliva CA, Stehberg J, Barra R, et al. Neuropathic pain induces interleukin-1β sensitive bimodal glycinergic activity in the central amygdala[J]. Int J Mol Sci, 2022, 23(13): 7356.

[2] Cao J, Herman AB, West GB, et al. Unraveling why we sleep: Quantitative analysis reveals abrupt transition from neural reorganization to repair in early development[J]. Sci Adv, 2020, 6(38): eaba0398.

[3] 金　鑫, 陈　坤, 徐云霞, 等. 惯性睡眠-觉醒模式与急性缺血性脑卒中短期预后关系的研究[J]. 中风与神经疾病杂志, 2024, 41(9): 799-805.

[4] Fernandez LMJ, Lüthi A. Sleep spindles: Mechanisms and functions[J]. Physiol Rev, 2020, 100(2): 805-868.

[5] Park SH, Weber F. Neural and homeostatic regulation of REM sleep [J]. Front Psychol, 2020, 11: 1662.

[6] Lin Y, Hu Y, Guo J, et al. Association between sleep and multimorbidity in Chinese elderly: Results from the Chinese longitudinal healthy longevity survey (CLHLS)[J]. Sleep Med, 2022, 98: 1-8.

[7] Nguyen VV, Zainal NH, Newman MG. Why sleep is key: Poor sleep quality is a mechanism for the bidirectional relationship between major depressive disorder and generalized anxiety disorder across 18 years[J]. J Anxiety Disord, 2022, 90: 102601.

[8] Shi W, Chen C, Cui Q, et al. Sleep disturbance exacerbates the cardiac conduction abnormalities induced by persistent heavy ambient fine particulate matter pollution: A multi-center cross-sectional study[J]. Sci Total Environ, 2022, 838: 156472.

[9] Mathias JL, Cant ML, Burke AJ. Sleep disturbances and sleep disorders in adults living with chronic pain: A meta-analysis[J]. Sleep Med, 2018, 52: 198-210.

[10] Krause AJ, Prather AA, Wager TD, et al. The pain of sleep loss: A brain characterization in humans[J]. J Neurosci, 2019, 39(12): 2291-2300.

[11] Pinto SM, Cheung JPY, Samartzis D, et al. Are morphometric and biomechanical characteristics of lumbar multifidus related to pain intensity or disability in people with chronic low back pain after considering psychological factors or insomnia?[J]. Front Psychiatry, 2022, 13: 809891.

[12] Borgonetti V, Galeotti N. Rosmarinic acid reduces microglia senescence: a novel therapeutic approach for the management of neuropathic pain symptoms[J]. Biomedicines, 2022, 10(7): 1468.

[13] 孙　杰, 郑永博, 李　赓, 等. 内嗅皮质在疼痛感知与睡眠障碍间的中介效应分析[J]. 中国疼痛医学杂志, 2023, 29(2): 101-106.

[14] Staffe AT, Bech MW, Clemmensen SLK, et al. Total sleep deprivation increases pain sensitivity, impairs conditioned pain modulation and facilitates temporal summation of pain in healthy participants[J]. PLoS One, 2019, 14(12): e0225849.

[15] Tesfaye S, Sloan G, Petrie J, et al. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): A multicentre, double-blind, randomised crossover trial[J]. Lancet, 2022, 400(10353): 680-690.

[16] Ito H, Tsuneki H, Sasaoka T, et al. Suvorexant and mirtazapine improve chronic pain-related changes in parameters of sleep and voluntary physical performance in mice with sciatic nerve ligation [J]. PLoS One, 2022, 17(2): e0264386.

[17] Ito H, Navratilova E, Vagnerova B, et al. Chronic pain recruits hypothalamic dynorphin/kappa opioid receptor signalling to promote wakefulness and vigilance[J]. Brain, 2023, 146(3): 1186-1199.

[18] Li T, Gao Y, He M, et al. P2X7 receptor-activated microglia in cortex is critical for sleep disorder under neuropathic pain [J]. Front Neurosci, 2023, 17: 1095718.

[19] Zhou H, Li M, Zhao R, et al. A sleep-active basalocortical pathway crucial for generation and maintenance of chronic pain [J]. Nat Neurosci, 2023, 26(3): 458-469.

[20] Soltani A, Bahrami F, Bahari Z, et al. The effects of Valerian on sleep spindles in a model of neuropathic pain [J]. Sleep Sci, 2021, 14(Spec 2): 133-139.

[21] Ito H, Takemura Y, Aoki Y, et al. Analysis of the effects of a tricyclic antidepressant on secondary sleep disturbance induced by chronic pain in a preclinical model[J]. PLoS One, 2020, 15(12): e0243325.

[22] Cardis R, Lecci S, Fernandez LM, et al. Cortico-autonomic local arousals and heightened somatosensory arousability during NREMS of mice in neuropathic pain[J]. eLife, 2021, 10: e65835.

[23] Katagiri A, Kato T. Multi-dimensional role of the parabrachial nucleus in regulating pain-related affective disturbances in trigeminal neuropathic pain[J]. J Oral Sci, 2020, 62(2): 160-164.

[24] Li YZ, Zhu YB, Ge AN, et al. Reduced expression of APLP2 in spinal GABAergic inhibitory neurons contributed to nerve injury-induced microglial activation and pain sensitization [J]. Neuropharmacology, 2023, 224: 109334.

[25] Boentert M. Sleep disorders in patients with neuromuscular diseases[J]. Somnologie (Berl), 2023, 27(1): 64-73.

[26] Caravan B, Hu L, Veyg D, et al. Sleep spindles as a diagnostic and therapeutic target for chronic pain[J]. Mol Pain, 2020, 16: 1744806920902350.

[27] Liang SH, Zhao WJ, Yin JB, et al. A neural circuit from thalamic paraventricular nucleus to central amygdala for the facilitation of neuropathic pain[J]. J Neurosci, 2020, 40(41): 7837-7854.

[28] Zhao J, Liu C, Zhang F, et al. A paraventricular thalamus to central amygdala neural circuit modulates acute stress-induced heightened wakefulness[J]. Cell Rep, 2022, 41(11): 111824.

[29] Cai Q, Guo Q, Li Z, et al. Minimally invasive evacuation of spontaneous supratentorial intracerebral hemorrhage by transcranial neuroendoscopic approach [J]. Neuropsychiatr Dis Treat, 2019, 15: 919-925.

[30] An JX, Shi WR, Zhang JF, et al. A new rat model of thalamic pain produced by administration of cobra venom to the unilateral ventral posterolateral nucleus[J]. Pain Physician, 2019, 22(6): E635-E647.

[31] Berhe DF, Gebre AK, Assefa BT. Orexins role in neurodegenerative diseases: From pathogenesis to treatment[J]. Pharmacol Biochem Behav, 2020, 194: 172929.

[32] Li SB, Damonte VM, Chen C, et al. Hyperexcitable arousal circuits drive sleep instability during aging[J]. Science, 2022, 375 (6583): eabh3021.

[33] Chen H, Ma D, Zhang H, et al. Antinociceptive effects of oleuropein in experimental models of neuropathic pain in male rats[J].

Korean J Pain, 2021, 34(1): 35-46.
[34] Roehrs T, Withrow D, Koshorek G, et al. Sleep and pain in humans with fibromyalgia and comorbid insomnia: double-blind, crossover study of suvorexant 20 Mg versus placebo[J]. J Clin Sleep Med, 2020, 16(3): 415-421.
[35] Wawrzczak-Bargieła A, Ziółkowska B, Piotrowska A, et al. Neuropathic pain dysregulates gene expression of the forebrain opioid and dopamine systems[J]. Neurotox Res,2020, 37(4): 800-814.
[36] Sun Y, Blanco-Centurion C, Zou B, et al. Amygdala GABA neurons project to vlPAG and mPFC[J]. IBRO Rep, 2019, 6: 132-136.
[37] Machida M, Sweeten BLW, Adkins AM, et al. Basolateral amygdala regulates EEG Theta-activity during rapid eye movement sleep[J]. Neuroscience, 2021, 468: 176-185.
[38] Kato F, Sugimura YK, Takahashi Y. Pain-associated neural plasticity in the parabrachial to central amygdala circuit: pain changes the brain, and the brain changes the pain[J]. Adv Exp Med Biol, 2018, 1099: 157-166.
[39] Jones BE. Arousal and sleep circuits[J]. Neuropsychopharmacology, 2020, 45(1): 6-20.
[40] Kohno M, Link J, Dennis LE, et al. Neuroinflammation in addiction: a review of neuroimaging studies and potential immunotherapies[J]. Pharmacol Biochem Behav, 2019, 179: 34-42.
[41] Demarco GJ, Baghdoyan HA, Lydic R. Differential cholinergic activation of G proteins in rat and mouse brainstem: relevance for sleep and nociception[J]. J Comp Neurol, 2003, 457(2): 175-184.
[42] Mercan A, Uzun ST, Keles S, et al. Immunological mechanism of postherpetic neuralgia and effect of pregabalin treatment on the mechanism: a prospective single-arm observational study[J]. Korean J Pain, 2021, 34(4): 463-470.
[43] Choudhury ME, Miyanishi K, Takeda H, et al. Phagocytic elimination of synapses by microglia during sleep[J]. Glia, 2020, 68(1): 44-59.
[44] Zhao D, Han DF, Wang SS, et al. Roles of tumor necrosis factor-α and interleukin-6 in regulating bone cancer pain *via* TRPA1 signal pathway and beneficial effects of inhibition of neuro-inflammation and TRPA1[J]. Mol Pain,2019,15: 1744806919857981.
[45] Durante M, Squillace S, Lauro F, et al. Adenosine A3 agonists reverse neuropathic pain via T cell-mediated production of IL-10[J]. J Clin Invest, 2021, 131(7): e139299.
[46] Yi M, Zhao W, Fei Q, et al. Causal analysis between altered levels of interleukins and obstructive sleep apnea[J]. Front Immunol, 2022, 13: 888644.
[47] Serizawa K, Tomizawa-Shinohara H, Miyake S, et al. Interleukin-6: evolving role in the management of neuropathic pain in neuroimmunological disorders[J]. Inflamm Regen, 2021, 41(1): 34.
[48] Baril AA, Beiser AS, Redline S, et al. Interleukin-6 interacts with sleep apnea severity when predicting incident Alzheimer's disease dementia[J]. J Alzheimers Dis, 2021, 79(4): 1451-1457.
[49] 王 琳, 朱博驰, 王 敏, 等. GSK-3β信号调控CX3CL1/CX3CR1参与大鼠偏头痛过程的机制研究[J]. 中风与神经疾病杂志, 2024, 41(12): 1113-1117.
[50] Liang L, Yan J, Huang X, et al. Identification of molecular signatures associated with sleep disorder and Alzheimer's disease[J]. Front Psychiatry, 2022, 13: 925012.
[51] Zigmond RE, Echevarria FD. Macrophage biology in the peripheral nervous system after injury[J]. Prog Neurobiol, 2019, 173: 102-121.
[52] Silva CEA, Guimarães RM, Cunha TM. Sensory neuron-associated macrophages as novel modulators of neuropathic pain[J]. Pain Rep, 2021, 6(1): e873.
[53] Moisset X, Bouhassira D, Attal N. French guidelines for neuropathic pain: An update and commentary[J]. Rev Neurol (Paris), 2021, 177(7): 834-837.
[54] Davari M, Amani B, Amani B, et al. Pregabalin and gabapentin in neuropathic pain management after spinal cord injury: a systematic review and meta-analysis[J]. Korean J Pain, 2020, 33(1): 3-12.
[55] Giménez-Campos MS, Pimenta-Fermisson-Ramos P, Díaz-Cambronero JI, et al. A systematic review and meta-analysis of the effectiveness and adverse events of gabapentin and pregabalin for sciatica pain[J]. Atención Primaria, 2022, 54(1): 102144.
[56] Molero Y, Larsson H, D'Onofrio BM, et al. Associations between gabapentinoids and suicidal behaviour, unintentional overdoses, injuries, road traffic incidents, and violent crime: population based cohort study in Sweden[J]. BMJ, 2019, 365: l2147.
[57] Sun SY, Chen GH. Treatment of circadian rhythm sleep-wake disorders[J]. Curr Neuropharmacol, 2022, 20(6): 1022-1034.
[58] Busa P, Kuthati Y, Huang N, et al. New advances on pathophysiology of diabetes neuropathy and pain management: potential role of melatonin and DPP-4 inhibitors[J]. Front Pharmacol, 2022, 13: 864088.
[59] Gilron I, Tu D, Holden RR, et al. Melatonin for neuropathic pain: protocol for a double-blind, randomized controlled trial[J]. JMIR Res Protoc, 2022, 11(9): e40025.
[60] Mokhtari T, Yue LP, Hu L. Exogenous melatonin alleviates neuropathic pain-induced affective disorders by suppressing NF-κB/NLRP3 pathway and apoptosis[J]. Sci Rep, 2023, 13(1): 2111.
[61] Altiparmak B, Cil H, Celebi N. Effect of melatonin on the daytime sleepiness side-effect of gabapentin in adults patients with neuropathic pain[J]. Braz J Anesthesiol, 2019, 69(2): 137-143.
[62] Kuthati Y, Goutham Davuluri VN, Yang CP, et al. Melatonin MT2 receptor agonist IIK-7 produces antinociception by modulation of ROS and suppression of spinal microglial activation in neuropathic pain rats[J]. J Pain Res, 2019, 12: 2473-2485.
[63] Kuthati Y, Lin SH, Chen IJ, et al. Melatonin and their analogs as a potential use in the management of Neuropathic pain[J]. J Formos Med Assoc, 2019, 118(8): 1177-1186.
[64] Kim TH, Bormate KJ, Custodio RJP, et al. Involvement of the adenosine A_1 receptor in the hypnotic effect of rosmarinic acid[J]. Biomed Pharmacother, 2022, 146: 112483.

引证本文:成 帆,李 戈,毕艳兴,等. 神经病理性疼痛所致睡眠障碍的研究进展[J]. 中风与神经疾病杂志,2025,42(10):911-915.