·偏头痛·

偏头痛与睡眠障碍

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【摘要】 偏头痛和睡眠障碍均为临床常见疾病，二者存在复杂的双向关系，睡眠障碍可诱发偏头痛发作，偏头痛发作又可引起或加重睡眠障碍。偏头痛还与多种睡眠障碍长期共病。本文综述偏头痛与睡眠障碍的共病关系及其发病机制。

【关键词】 偏头痛； 睡眠障碍； 共病现象； 综述

Migraine and sleep disorders

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【Abstract】 Migraine and sleep disorders are common clinical diseases with complex bidirectional relationship, sleep disorders can induce migraine attacks, migraine attacks can also cause or aggravate sleep disorders. Migraine is also associated with a variety of sleep disorders for a long time. This review discusses the common neuroanatomical physiology and comorbidity mechanism between migraine and sleep disorders, providing better understanding of the diagnosis and therapy.

【Key words】 Migraine; Sleep disorders; Comorbidity; Review

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头痛和睡眠障碍均为临床常见疾病，二者关系密切且复杂。偏头痛作为常见的头痛类型，是与睡眠相关性最显著的原发性头痛之一。睡眠障碍可诱发偏头痛发作，偏头痛发作又可引起或加重睡眠障碍；此外，偏头痛还与多种睡眠障碍长期共病，二者相互作用，严重影响预后和生活质量。本文拟在偏头痛与睡眠障碍的解剖生理学基础上综述二者关系及其发病机制研究进展，以使临床进一步重视偏头痛与睡眠障碍，进行精准诊断与治疗，使更多患者获益。

一、偏头痛与睡眠障碍的共同解剖生理学基础

多个中枢神经系统结构区和功能区在头痛和睡眠障碍的调控中发挥重要作用，其中以丘脑、下丘脑和脑干尤为关键。丘脑是感觉系统的中继站，在头痛的发病机制中发挥至关重要的作用[1-3]。下丘脑与诸多涉及三叉神经血管和脊髓疼痛处理的结构有直接或间接联系[4-6]。下丘脑前腹侧区视交叉上核（SCN）参与中脑导水管周围灰质（PAG）和单胺类神经元的传入与传出[7-8]；下丘脑后部和室旁核区可被硬脑膜血管刺激激活，是偏头痛和丛集性头痛的潜在激活区域[9]；室旁核下行投射至上泌涎核，后者在偏头痛自主神经症状中起重要作用[10]；位于下丘脑尾侧部脑室周围灰质腹前轴的A11核认为是多巴胺能抑制性投射至脊髓后角的唯一来源[11-12]，电刺激此处神经核团可抑制三叉神经血管单元支配的硬脑膜和面部皮肤诱发的伤害感受性的传入，损伤此处神经核团则可促进伤害感受性的传入[13]。同时，下丘脑也是参与睡眠调节的关键解剖结构。下丘脑腹外侧视前区（VLPO）可能是睡眠的启动点，该区域神经元分泌γ-氨基丁酸（GABA）和甘丙肽（GAL）以促进困倦和睡眠[14-16]；视交叉上核是昼夜

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节律的起搏点，通过内环境自我调节模式，如中心体温降低、外周体温升高、糖皮质激素释放和褪黑素分泌增加，诱导睡眠[17-19]；下丘脑外侧区及其邻近区域神经元主要分泌一组神经肽即下丘脑分泌素（也称食欲素），食欲素通过向结节乳头核组胺能神经元、蓝斑去甲肾上腺素能神经元、中缝背核5-羟色胺（5-HT）能神经元、中脑多巴胺能神经元和脑桥核胆碱能神经元发出投射，调节组胺、去甲肾上腺素、5-羟色胺、多巴胺和胆碱的分泌[20]，进而调控快速眼动睡眠期（REM）睡眠与非快速眼动睡眠期（NREM）睡眠以及睡眠与觉醒转换[21]。脑干是参与头痛和睡眠障碍发病机制的另一重要解剖结构。中脑导水管周围灰质和延髓头侧部腹内侧区神经元是内源性痛觉调节系统的主要部分，与脊髓和脊髓背角进行双向连接，主要调节脊髓和脊髓背角的痛觉信号转导[22-24]；延髓头侧部腹内侧区中缝大核是最大的5-羟色胺能神经核团，通过非5-羟色胺能ON细胞和OFF细胞对脊髓和脊髓背角的伤害性感受提供下行控制，ON细胞可促进疼痛，且觉醒时ON细胞激活数目增多，OFF细胞放电则可抑制伤害性感受的传入，且睡眠时OFF细胞激活数目增多[25-26]。脑干单胺能神经元主要包括蓝斑去甲肾上腺素能、中脑导水管周围灰质多巴胺能、中缝背核5-羟色胺能和结节乳头核组胺能神经元，这些神经元均投射至丘脑、下丘脑、基底前脑和大脑皮质，对维持觉醒发挥重要作用[27-28]。中脑导水管周围灰质腹外侧区（vlPAG）和脑桥被盖背外侧区神经元接受下丘脑外侧区食欲素能神经元和腹外侧视前区兴奋和抑制的传入，并与外侧背核和蓝斑神经元相互抑制快速眼动睡眠期睡眠[29-30]。上述研究结果表明偏头痛与睡眠障碍具有共同的解剖生理学基础[31]。

二、偏头痛和睡眠障碍的相关神经肽类

1.食欲素　食欲素是下丘脑分泌的一种兴奋性神经肽，包括食欲素A和食欲素B，主要参与昼夜节律和睡眠觉醒周期的调节。同时，食欲素能系统广泛投射至三叉神经伤害性感受相关脑区，如大脑皮质、扣带回皮质、中脑导水管周围灰质和脊髓背角等[32-33]，其中食欲素能神经元的传入经中脑导水管周围灰质投射至脑干三叉颈髓复合体（TCC），参与三叉神经伤害性感受的调节[34]；食欲素能神经轴突在脊髓各节段（颈髓至骶髓）均有分布，特别是疼痛调节相关区域，脊髓食欲素受体可以调节下丘脑外侧刺激产生的神经疼痛[5]。动物模型显示，电刺激正常雄性大鼠硬脑膜血管可诱发三叉神经尾核的激活，予以食欲素A1受体（OX1R）阻断药可以阻断食欲素A，抑制神经纤维对硬脑膜刺激的反应，说明食欲素A可通过激活OX1R抑制神经纤维对三叉神经尾核的硬脑膜电刺激反应[35]。亦有研究显示，慢性偏头痛患者脑脊液食欲素A水平升高可能是慢性疼痛的代偿反应，也可能是下丘脑对慢性疼痛的应激反应[36]。由此可见，食欲素参与伤害性感受和镇痛调节的过程[32]。

2.褪黑素　褪黑素是主要由松果体产生并受视交叉上核调节的神经激素，对调节昼夜节律具有至关重要的作用，包括睡眠启动和节律维持。褪黑素的分泌有昼夜节律，即在无光照环境下分泌增加、有光照环境下分泌减少，这一过程受下丘脑视交叉上核的调控[37]；同时，褪黑素还具有镇痛作用，其分泌紊乱可导致头痛。褪黑素与头痛相互作用的机制可能包括增强疼痛通路GABA能神经元的抑制作用，调节5-羟色胺信号转导，减少促炎性因子生成，抑制一氧化氮合成，促进抗氧化作用，以及诱导作用于阿片受体的细胞因子（褪黑素诱导的阿片受体）[38-40]。研究显示，慢性偏头痛合并失眠的患者除有睡眠时相延迟综合征（DSPS）外，还存在褪黑素水平的显著下降[41-42]；丛集性头痛患者表现为褪黑素分泌延迟和减少[43-44]；发作性睡病患者非特异性头痛患病率显著增加[45]。

3.腺苷　腺苷是内源性促睡眠因子，主要参与能量代谢和睡眠整合等，在头痛和睡眠障碍的病理生理学机制中发挥重要作用。腺苷作用于中枢神经系统A1和A2a受体，刺激A1受体具有抗伤害性感受作用[46-47]，刺激A2a受体则可引起疼痛[48]。咖啡因是偏头痛急性期的治疗药物，作为腺苷受体阻断药，通过拮抗A1和A2a受体以阻止睡眠[49-50]。Hohoff等[51]的全基因组关联分析（GWAS）进一步强调腺苷在头痛中的作用，A2a受体多态性与偏头痛先兆有关，发作期血浆腺苷水平增加，可在易感个体中引起偏头痛。因此，腺苷对睡眠和偏头痛的影响取决于作用部位及其特定受体的表达。

4.5-羟色胺　5-羟色胺作为上行激活系统的重要组成部分，在维持觉醒和警觉状态中发挥重要作用，但在某些情况下也可增加睡眠。例如在轻度应激状态下，中缝背核5-羟色胺能神经元激活，可以减轻焦虑，增加非快速眼动睡眠期睡眠[52]，因此认为，5-羟色胺既是促觉醒又是促非快速眼动睡眠期睡眠

的递质[53]。同时,5-羟色胺还可通过激活痛觉通路上不同部位的亚型受体而发挥镇痛和致痛作用[54]。在周围神经系统,位于初级感觉神经末梢的5-羟色胺受体通过参与疼痛信号转导而产生痛觉[55],推测5-羟色胺在周围神经系统中可以致痛。下行的5-羟色胺能神经元主要通过激活抑制性中间神经元而发挥镇痛作用,如Aβ纤维可以减轻C纤维和Aδ纤维传入的触痛,从而减少伤害性感受的传入[56]和GABA能抑制性中间神经元的兴奋性增强,抑制脊髓背角5-羟色胺受体的表达,影响疼痛信号的转导而产生镇痛作用[57]。因此,5-羟色胺在中枢神经系统参与镇痛,对伤害性感受信号的转导和调节发挥重要作用[3,58]。业已证实5-羟色胺在偏头痛的病理生理学机制中发挥重要作用[59-60],偏头痛发作时血浆5-羟色胺水平降低[60],而5-羟色胺受体激动药是偏头痛急性期的特异性治疗药物,目前已广泛应用于临床。

三、偏头痛与睡眠障碍

1.偏头痛与失眠 研究显示,偏头痛患者的睡眠质量较正常人差。Kim等[61]发现,偏头痛患者失眠发生率高于无偏头痛患者(25.9%对15.1%,$P=0.001$);Buse等[62]亦发现,偏头痛患者失眠的风险增加;而与健康对照者相比,失眠患者罹患偏头痛和非偏头痛性头痛的风险更高[63]。基于北特伦德拉格健康研究(HUNT-2和HUNT-3)的前瞻性研究显示,偏头痛与失眠之间的关系是双向的,与无头痛且不失眠的受试者相比,无头痛的失眠患者11年内罹患偏头痛的风险更高($P=0.020$);同样,与无偏头痛的受试者相比,伴偏头痛的受试者11年内发生失眠的风险更高($P=0.020$)[64]。失眠与偏头痛的强度、发作频率有关[62,65-66],失眠是偏头痛的危险因素,且偏头痛患者失眠的风险亦增加。偏头痛与失眠关系的病理生理学机制尚不清楚,下丘脑和脑干功能障碍可能是偏头痛和失眠的共同机制,这些结构参与睡眠觉醒和疼痛的调节。

2.偏头痛与睡眠节律障碍 睡眠觉醒昼夜节律障碍是慢性或复发性睡眠节律障碍。研究显示,偏头痛发作与昼夜节律变化相关[67],常发生于清晨,其高峰发作时间为0:00~6:00[68]。一项来自挪威的针对需两班制或三班制工作的护理人员的横断面研究结果显示,有倒班制障碍者频繁头痛($OR=2.040$, 95%CI: 1.620 ~ 2.590; $P<0.005$)、偏头痛($OR=1.600$,95%CI:1.210~2.120;$P=0.001$)和慢性头痛($OR=2.450$,95%CI:1.250~2.480;$P=0.017$)患病率均高于无倒班制障碍者[69]。此外,偏头痛还有一种特殊发作形式——周末偏头痛,即睡眠过多致醒来后出现偏头痛,提示过度睡眠和睡眠剥夺均为晨起偏头痛发作的常见原因[70]。此外,有研究显示,偏头痛患者存在睡眠结构变化,偏头痛发作前非快速眼动睡眠期Ⅲ~Ⅳ期睡眠比例增加,觉醒后偏头痛发作时快速眼动睡眠期睡眠比例增加[71]。

3.偏头痛与睡眠呼吸暂停 偏头痛与睡眠呼吸暂停的关系尚存争议。Kristiansen等[72]通过临床访谈和多导睡眠图(PSG)监测发现,无先兆偏头痛(MO)患者、有先兆偏头痛(MA)患者和健康对照者睡眠呼吸暂停发生率相似。亦有研究显示,偏头痛患者并发睡眠呼吸暂停的风险高于慢性偏头痛患者,而睡眠呼吸暂停通常与晨起偏头痛有关[73-74],表明偏头痛与睡眠呼吸暂停之间存在互为风险的关系[75]。同时,阻塞性睡眠呼吸暂停(OSA)可能是偏头痛易感患者的触发因素,并可能促进偏头痛的进展[76],提示阻塞性睡眠呼吸暂停是发作性偏头痛向慢性偏头痛转变的危险因素。

4.偏头痛与发作性睡病 研究显示,发作性睡病患者偏头痛患病率较健康对照者显著增加[77]。Suzuki等[78]也报告类似结果,他们认为偏头痛在发作性睡病和特发性嗜睡患者中较健康对照者更常见。一项针对儿童患者的研究显示,偏头痛与发作性睡病呈正相关($OR=5.300$, 95%CI: 1.610 ~ 17.400; $P=0.006$)[79]。在另一项关于发作性睡病的多中心病例对照研究中,偏头痛患病率较健康对照者显著增加[80]。食欲素能系统在发作性睡病和偏头痛中发挥重要作用,可以增强下丘脑和脑干神经网络,刺激觉醒和非快速眼动睡眠期睡眠,也可以调节三叉神经血管系统[34,81-83],从而缓解偏头痛。

5.偏头痛与睡眠相关运动障碍 不宁腿综合征(RLS)是临床最常见的睡眠相关运动障碍,是一种以强烈的腿动冲动为特征的疾病,主要发生于晚上或夜间,与周期性肢体运动障碍(PLMD)密切相关,可伴随休息或不活动时不舒适感,这种不舒适感可部分或全部通过腿动缓解。普通人群不宁腿综合征的患病率为7%,而偏头痛患者不宁腿综合征发生率达17%[84],二者均以女性多见[85]。有研究显示,偏头痛患者较紧张型头痛患者更易出现不宁腿综合征[86],此外,偏头痛合并不宁腿综合征患者较未合并不宁腿综合征患者出现畏光、畏声、眩晕、耳

鸣和颈部疼痛的概率更高[87]。频繁发作或严重的不宁腿综合征患者发生偏头痛的风险较高[88]。由此可见,偏头痛与不宁腿综合征常作为共病共存,二者之间可能具有共同的病理生理学机制。神经影像学研究显示,偏头痛和不宁腿综合征共病患者额中回灰质体积变化可能是二者共同的病理生理学机制[89]。

6.偏头痛与异态睡眠 异态睡眠系指入睡时、睡眠期或觉醒时出现的不愉快事件(如梦游、磨牙)或不愉快体验(如噩梦),可发生于非快速眼动睡眠期、快速眼动睡眠期或睡眠觉醒转换期。研究显示,与无先兆偏头痛患者相比,有先兆偏头痛患者出现梦游的概率更高;且接受偏头痛预防性治疗的患者可以减少梦游发生率,甚至治愈[90]。梦游和偏头痛可发生于不同年龄阶段,尤以儿童多见,可能与5-羟色胺代谢障碍有关[91]。磨牙症在偏头痛患者中较常见,与颞下颌关节功能障碍有关。磨牙症和颞下颌关节功能障碍可能是通过激活三叉神经触发偏头痛,或者偏头痛患者更易出现颞下颌关节功能紊乱继发中枢敏化的疼痛[92-94]。

综上所述,偏头痛与睡眠障碍是一种复杂的双向关系,在很大程度上由共同的解剖生理学基础所决定,共病可以进一步改变这种关系并使其复杂化,睡眠障碍如睡眠缺乏、过度睡眠或睡眠觉醒紊乱可能是偏头痛从急性发作向慢性化转变的重要因素[95-98],预防偏头痛可以显著提高睡眠质量[99-101]。这就要求临床实践中重视偏头痛与睡眠障碍共病的诊断与治疗,依靠详细的病史采集和问卷筛查以了解偏头痛与睡眠障碍的临床特征及相互关系,从而制定多元化、个体化、最优化治疗方案,减轻患者痛苦,提高生活质量。

利益冲突 无

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·小词典·

中英文对照名词词汇（四）

生活质量 quality of life（QoL）
生长激素 growth hormone（GH）
生长激素释放激素 growth hormone-releasing hormone（GHRH）
视交叉上核 suprachiasmatic nucleus（SCN）
视觉模拟评分 Visual Analog Scales（VAS）
嗜铬粒蛋白A chromogranin A（CGA）
睡眠呼吸暂停综合征 sleep apnea hypopnea syndrome（SAHS）
睡眠时相延迟综合征 delayed sleep-phase syndrome（DSPS）
睡眠相关节律性运动障碍 sleep-related rhythmic movement disorder（SRMD）
梭形细胞嗜酸细胞瘤 spindle cell oncocytoma（SCO）
胎盘碱性磷酸酶 placental alkaline phosphatase（PLAP）
同型半胱氨酸 homocysteine（Hcy）
头痛影响测验-6 Headache Impact Test version 6（HIT-6）
头晕残障量表 Dizziness Handicap Inventory（DHI）
突触素 synaptophysin（Syn）
^{18}F-脱氧葡萄糖 ^{18}F-fluoro-2-deoxy-D-glucose（^{18}F-FDG）
维生素D结合蛋白 vitamin D-binding protein（VDBP）
无创迷走神经刺激 noninvasive vagus nerve stimulation（nVNS）
无先兆偏头痛 migraine without aura（MO）
P物质 substance P（SP）
B细胞淋巴瘤/白血病-2 B cell lymphoma/leukemia-2（Bcl-2）
线粒体DNA mitochondrial DNA（mtDNA）
线粒体脑肌病伴高乳酸血症和卒中样发作 mitochondrial encephalomyopathy with lactic academia and stroke-like episodes（MELAS）
斜卧呼吸-直立性低氧血症综合征 platypnea-orthodeoxia syndrome（POS）
信号传导与转录激活因子6 signal transducer and activator of transcription 6（STAT6）
需要治疗的病例数 number needed to treat（NNTT）
血管外皮细胞瘤 hemangiopericytoma（HPC）
血氧水平依赖 blood oxygenation level-dependent（BOLD）
血氧水平依赖性功能磁共振成像 blood oxygenation level-dependent functional magnetic resonance imaging（BOLD-fMRI）
N5，10-亚甲基四氢叶酸还原酶 N5, 10-methylene tetrahydrofolate reductase（MTHFR）