



昼夜节律、疼痛与情感障碍之间的互作关系及其机制

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摘要 昼夜节律现象在生物体中普遍存在, 由其内部的时钟系统即生物钟所驱动, 并受到外部光照等条件的调控。机体对疼痛的感知、情绪状态及其相应的病理状态如慢性痛、情感障碍疾病均具有昼夜节律特征。反过来, 昼夜节律也影响着个体的疼痛感知和情绪状态。生物钟基因突变不仅可导致昼夜节律紊乱和睡眠障碍, 还可能是导致情感障碍疾病如冬季抑郁和躯体感觉异常如慢性痛的原因。临床上, 睡眠障碍、慢性痛和情感障碍存在显著的共病现象, 背后的机制与这些疾病涉及部分共同的脑区(特别是中缝核)、细胞、神经递质(如多巴胺和5-羟色胺)及其受体机制有关。其中, 中脑中缝核向皮层和皮层下多个脑区有着广泛的投射, 形成脑内弥散性投射系统, 可能作为调节共病的“中心脑区”。本文主要揭示了昼夜节律、疼痛和情感障碍彼此之间以及三者之间存在的互作关系, 概述了相关脑区和分子机制。综合现有研究, 我们推测中缝核及其调控的5-羟色胺能和多巴胺能系统, 可能是介导三者之间相互作用的重要结构和分子基础, 为理解这些疾病的共病机制提供了新的理论框架。此外, 本文还对未来的研究方向进行了展望, 旨在推动针对昼夜节律、疼痛以及情感障碍共病机制的深入研究, 为相关疾病的临床治疗提供新思路。

关键词 视交叉上核, 时钟基因, 慢性痛, 中缝核, 5-羟色胺

地球上的生物体, 从微生物到动植物, 其生命活动均呈现出按照一定时间顺序发生周期性变化的规律即节律性。其中, 周期大约为24 h的昼夜节律(circadian rhythm, circadian一词来自拉丁语circa和dies, 分别为approximately和day的意思)现象最为普遍, 如睡眠-觉醒、体温、代谢、激素分泌、免疫功能等。驱动昼夜节律的生物学机制被称为生物钟(circadian clock)^[1]。生物钟的存在使得生物体可以很好地协调其生理活动和行为, 适应地球自转带来的光照和温度等昼夜变化^[2]。而生物钟的异常不仅会导致节律紊乱和睡眠结构改变, 还会影响到一些疾病的发生和发展。大量临床研究表

明, 慢性痛和情感障碍均存在昼夜节律特征, 并且二者有着共同的共病——睡眠障碍。反过来, 昼夜节律也影响着慢性痛和情感障碍疾病的进展。虽然临床起病以某一类疾病为主, 但它们同属于“脑病”, 有着共同的结构基础——大脑。而在大脑的不同功能核团之间存在密切的纤维联系, 以维持不同脑功能的协同进行。因此, 研究昼夜节律、疼痛和情感障碍的共病关系有助于揭示大脑复杂的神经调节网络, 理解它们之间的互作关系, 从而加强我们对大脑功能整合机制的认识。同时, 在疾病进展过程中, 相关功能核团之间会相互诱导可塑性变化的发生, 由此导致疾病的慢性化和共病形

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成。因此,探讨这些脑疾病的共病机制,也有助于揭示疾病慢性化的重要节点或环节,继而针对性地阻断该环节,促进疾病恢复。在治疗方面,目前针对单一疾病的治疗往往只能缓解部分症状,而从共病的角度进行机制研究,可能揭示出导致疾病慢性化和共病发生的关键神经递质、受体、信号分子和调节蛋白等,为相关疾病的治疗提供新靶标。本文将围绕昼夜节律、疼痛和情感障碍三者之间的相互作用展开,并对其脑区和分子机制展开阐述,并探讨可能的干预策略。

1 昼夜节律

生物体的昼夜节律现象与地球自转产生的24 h光暗循环周期有着密切的关系,但昼夜节律的产生不依赖于外环境。几乎所有生物体都有其内在的时钟,通过光周期(主要是日光)和其他环境因素(如温度、饮食)等进行同步^[3]。早在1729年,法国物理学家Jean-Jacques d'Ortous de Mairan在含羞草上证明生物体存在内部时钟。1971年, Ronald J. Konopka与Seymour Benzer发现 *per*(period)基因突变,可导致果蝇昼夜节律发生变化^[4]。1992年, Jeffrey C. Hall与Michael Rosbash团队发现, *per*基因的转录可被其自身蛋白表达产物PER调控,并首次提出了转录-翻译负反馈环路的概念,用以在分子层面解释生物钟的运行机制^[5]。这些发现及其后在哺乳动物生物钟的一系列研究极大地推动了人们对生物钟机制的认识。简单概括起来,生物钟是由一系列转录激活因子和抑制因子组成的、具有自主调节性能的转录-翻译反馈调节环^[3]。

1.1 生物钟的分子机制

生物钟基因的转录调控是细胞自主的昼夜节律振荡器的核心,在哺乳动物中包括至少三组相互连锁的反馈调控环(图1)。其中,核心负反馈调节环包含两种含有bHLH-PAS(basic helix-loop-helix/Per-ARNT-SIM)结构域的转录因子——CLOCK(circadian locomotor output cycles protein kaput)和BMAL1(brain and muscle ARNT-like 1),二者结合形成异二聚体,通过识别E-box位点,驱动其他时钟基因(clock-controlled genes, CCGs)的节律性表达^[6],包括周期基因(*Per1*, *Per2*, *Per3*)和隐花色素(cryptochrome)基因(*Cry1*, *Cry2*)。在胞质中翻译的PER和CRY蛋白结合形成复合体,当其积累到一定程度时,入核并抑制CLOCK:BMAL1的功能。与此同时,PER和CRY会经历一系列翻译后修饰最终被降解,由

此解除对CLOCK:BMAL1的抑制作用,后者得以继续驱动时钟基因的表达,开启下一个24 h节律振荡。

除上述核心负反馈调节环之外, CLOCK:BMAL1复合物可诱导REV-ERB(又称为NR1D2, nuclear receptor subfamily 1, group D, member 2)和ROR(retinoic acid receptor-related orphan receptor)的表达,二者可分别作为转录阻遏物和转录激活物,通过识别RORE(ROR/REV-ERB response element)位点,协同调控*Bmal1*等基因的转录^[7]。此外, CLOCK:BMAL1复合物还可诱导DBP(D-box binding PAR-bZIP transcription factor)和NFIL3(nuclear factor, interleukin 3 regulated; 又称为E4BP4, E4 promoter-binding protein 4)的表达,二者分别作为正性和负性转录调节因子,通过作用于D-box位点,调控*Per*等基因的表达^[8]。以上三组相互连锁的转录-翻译调控环路,共同构成了分子层面的生物钟。

1.2 生物钟的结构基础

在哺乳动物中,生物钟基因最早在视交叉上核(suprachiasmatic nucleus, SCN)起搏器神经元中被发现^[9],但随后的研究发现,核心时钟基因在哺乳动物的大多数细胞中都有表达,提示几乎所有组织和细胞都有自己的生物钟^[10]。SCN为位于第三脑室底壁两侧、视神经交叉点上方的双侧结构。人SCN神经元大约有20000个^[11]。SCN接收视网膜一类称为内在光敏性神经节细胞(intrinsically photoreceptive retinal ganglion cell, ipRGC)的信息输入。由于ipRGC表达光敏视黑蛋白(melanopsin),对光的响应缓慢且阈值较高,因此它们具有作为昼夜节律光感受器的内在特性^[12]。ipRGC通过视网膜下丘脑束(retinohypothalamic tract, RHT)投射到SCN,并释放谷氨酸递质和神经肽。谷氨酸受体被激活后,胞内钙离子水平升高,激活cAMP反应元件结合蛋白(cAMP response element binding protein, CREB),CREB继而结合到时钟基因如*Per1*, *Per2*启动子/增强子区域促进其表达,由此实现时钟基因表达与光信号的同步化^[13]。

SCN主要为GABA能神经元,这些神经元呈现出细胞自主且同步的昼夜节律性放电。它们在夜间大多处于沉默状态,黎明时分开始发放动作电位,在日间以缓慢且稳定的速率持续放电^[14]。但SCN具有一定的异质性,其腹外侧(核心区)表达神经肽VIP(vasoactive intestinal polypeptide)、GRP(gastrin-releasing peptide)和calbindin等,接受RHT投射;背内侧(壳区)表达AVP

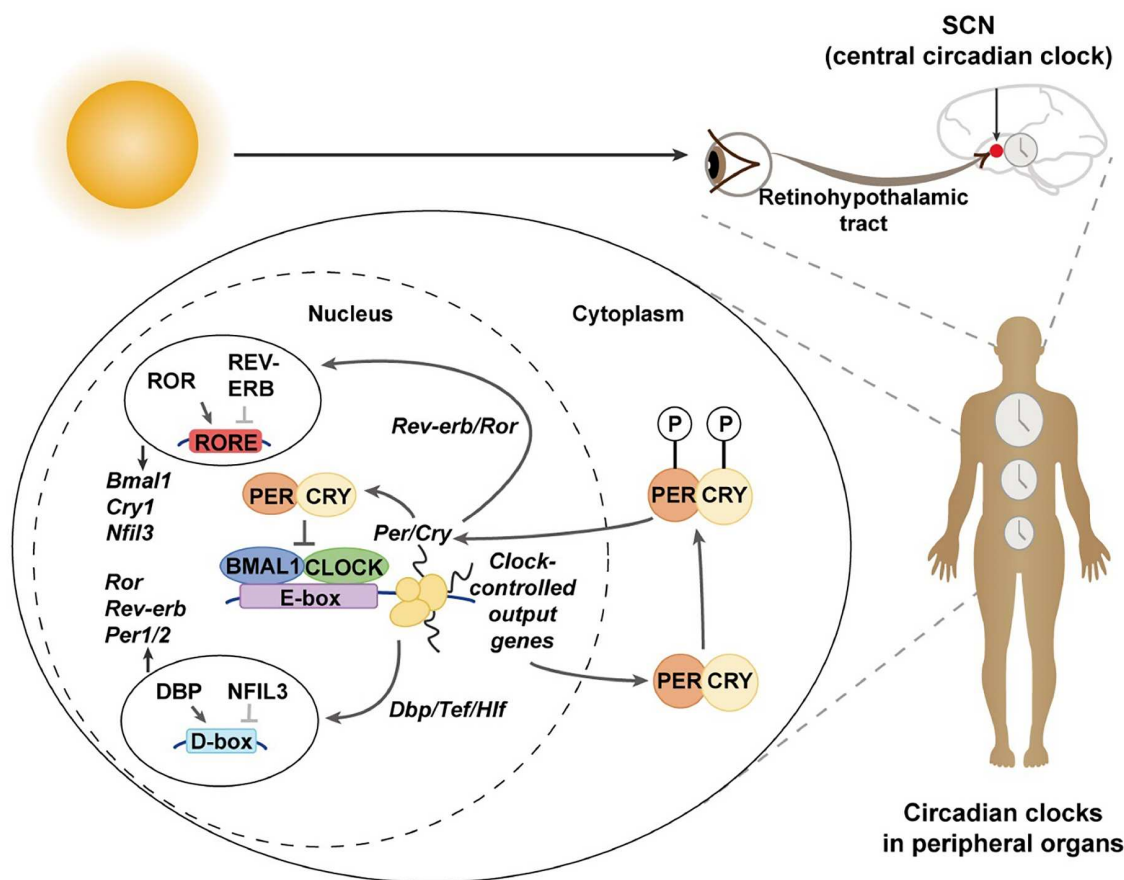


图1 生物钟的分子机制。哺乳动物中, 视交叉上核SCN是昼夜节律起搏器, 它在光照信息下同步, 并调控了外周组织中生物钟基因的节律性表达。细胞自主的昼夜节律振荡器由三组相互连锁的反馈调控环组成, 包括CLOCK:BMAL1对E-box位点的调控、REV-ERB(负)和ROR(正)对RORE位点的调控、DBP(正)和NFIL3(负)对D-box位点的调控

Figure 1 The molecular mechanisms of the circadian clock. The suprachiasmatic nucleus (SCN) serves as the circadian pacemaker in mammals. It synchronizes with light information and regulates the rhythmic expression of clock genes in peripheral tissues. The cell-autonomous circadian oscillator consists of three interlocked feedback regulatory loops, including the regulation of E-box sites by CLOCK:BMAL1, the bidirectional regulation of RORE sites by REV-ERB (negative action) and ROR (positive action) as well as the bidirectional regulation of the D-box sites by DBP (positive action) and NFIL3 (negative action). SCN: Suprachiasmatic nucleus; ROR: retinoic acid receptor-related orphan receptor; RORE: ROR/REV-ERB response element; DBP: D-box binding PAR-bZIP transcription factor; NFIL3: nuclear factor, interleukin 3 regulated; CLOCK: circadian locomotor output cycles protein kaput; BMAL1: brain and muscle ARNT-like 1; *Tef*: thyrotroph embryonic factor; *Hlf*: hepatic leukemia factor

(arginine vasopressin)和calretinin等, 具有细胞自主的节律性基因表达。SCN核心区节律性释放VIP, 同时作用于核心区和壳区的细胞使其去极化、*Per*基因表达, 同时还通过细胞之间的耦合机制, 使不同细胞在电活动、基因转录、翻译、细胞代谢等方面同步化, 从而形成一致的振荡^[8]。

在输出通路上, SCN可发出纤维投射至下丘脑其他区域如亚室旁带(subparaventricular zone, SPZ)、室旁核(paraventricular nucleus, PVN)(包括促肾上腺皮质激素释放激素神经元)、背内侧核(dorsomedial hypothalamus, DMH)、内侧视前区、弓状核(arcuate nu-

cleus, ARC)等, 以及下丘脑以外的其他脑区^[15]。接受SCN投射的这些下丘脑区域调控着自主神经系统输出、激素分泌、体温、进食和代谢等生命活动过程或行为, 由此SCN通过神经或体液等直接途径, 以及体温、进食、代谢调节等间接途径影响外周生物钟。

1.3 昼夜节律紊乱与睡眠障碍

昼夜节律由大脑和外周组织中的分子振荡器网络所产生, 它们与环境相互作用, 促进机体节律性地发生睡眠和生存相关行为。昼夜节律系统在维持正常的睡眠-觉醒周期中发挥重要作用^[16], 而昼夜节律系统的紊

乱可导致睡眠障碍,如生物钟基因多态性与睡眠障碍疾病(如睡眠相位改变)等有关^[17]。除了睡眠时间,生物钟也影响睡眠结构。SCN控制的节律系统调节快速眼动(rapid eye movement, REM)睡眠出现的时间、频率以及其转换过程^[18]。然而,这种节律性容易被生活环境、工作、社交、光照模式以及病理或生理因素等变化所干扰,导致睡眠障碍,影响个体身心健康^[19]。

临床上可观察到多种昼夜节律紊乱导致的睡眠障碍。比如,昼夜节律睡眠-觉醒障碍(circadian rhythm sleep-wake disorders, CRSWDs)是一类独特的睡眠障碍,由昼夜节律计时系统及其机制的改变或内源性昼夜节律与外部环境之间的不匹配引起。该种疾病的临床表现为失眠或白天过度嗜睡,常常导致患者精神、身体、社会、职业、教育或其他功能障碍^[20]。延迟睡眠-觉醒阶段障碍(delayed sleep-wake phase disorder, DSWPD),也被称为延迟睡眠阶段综合征,是CRSWDs的一种。大约40%的DSWPD患者有家族史,并以常染色体显性方式遗传,与*PER3*^[21]、*CRY1*^[22]和其他时钟基因的突变密切相关。此外,家族性早睡早起综合征(family advanced sleep-phase syndrome, FASPS)是一种与内源性周期相关的人类遗传性昼夜节律变异疾病,具有常染色体显性遗传特征,可能由调节生物钟功能的等位基因的突变引起^[23],如*hPER2*^[24]等。

褪黑素是由SCN调节松果体释放的一种激素,它不仅可以向生物钟系统传递黑暗的信息,还可以调节夜间的生理功能,例如睡眠/觉醒和新陈代谢^[25]。在正常生理状态下,褪黑素的分泌呈现出明显的昼夜节律特性。黑暗环境会刺激松果体分泌褪黑素,其分泌水平在夜间逐渐升高,并在凌晨达到峰值,随后随着黎明的到来逐渐降低。褪黑素通过褪黑素受体1(melatonin receptor 1, MT1)和2(melatonin receptor 2, MT2)影响睡眠和昼夜节律,MT1与昼夜节律相移和REM睡眠调节相关,MT2与非快速眼动睡眠调节有关^[26]。一些失眠症患者体内的褪黑素分泌出现紊乱^[27],表现为分泌延迟、峰值降低或分泌总量减少等。

2 疼痛

国际疼痛学会(International Association for the Study of Pain, IASP)将疼痛定义为一种与实际或潜在组织损伤相关的不愉快的感觉和情绪体验,或与此相类似的经历^[28]。临床上根据时程不同,疼痛可分为急性痛和慢性痛,前者通常具有“警示”和保护作用,持续时

间短,随组织损伤而愈合,而后者可以看作是机体对疼痛刺激形成的一种异常“记忆”,迁延不愈,反复发作,对个体身心造成严重损害。

2.1 疼痛的昼夜节律特征

早在20世纪80年代科学家就观察到,啮齿类动物对伤害性刺激的反应以及吗啡的镇痛作用均呈现出昼夜节律变化的特征^[29]。在人类多种疾病相关的疼痛中,也观察到了明显的昼夜节律特性,如心绞痛、心肌梗死、偏头痛、类风湿性关节炎和牙痛常常在早晨发生,而夜间疼痛似乎在胆绞痛、癌症和顽固性疼痛患者中更为常见^[30]。此外,关节炎疼痛、肾绞痛、牙痛和分娩疼痛也具有明显的昼夜节律特征^[30]。同时,临床上还发现睡眠障碍是疼痛的一个可靠的预测因素,反过来,疼痛也是睡眠障碍的一个预测因素,睡眠障碍经常与疼痛同时发生且相互促进^[31]。因此,探讨昼夜节律相关的神经环路及分子在慢性痛和睡眠障碍共病中的可能作用,对阐明疼痛的节律性及慢性痛-睡眠障碍共病的发生机制,科学地指导镇痛、催眠药物的使用以及开发新的药物靶点具有重要意义。

2.2 疼痛节律性可能的分子机制

疼痛的昼夜节律特性与一系列痛觉相关神经递质、神经肽和炎症因子的昼夜节律振荡有关^[1]。在多种疼痛动物模型中均观察到,谷氨酸、5-羟色胺(5-hydroxytryptamine, 5-HT)、P物质(substance P, SP)、阿片肽、缓激肽、NO、细胞因子(IL-1, IL-6)和前列腺素水平等均存在昼夜节律变化^[32]。

谷氨酸作为神经系统中表达最丰富的兴奋性神经递质,其转运蛋白包括囊泡谷氨酸转运体(vesicular glutamate transporters, VGLUTs)和兴奋性氨基酸转运蛋白(excitatory amino acid transporter, EAAT)可能受生物钟的调节并在睡眠-觉醒周期中发挥重要作用^[33]。在新纹状体和SCN中均可观察到细胞外谷氨酸浓度的昼夜节律变化^[34],并且在SCN中VGLUTs和谷氨酰胺合成酶活性也存在昼夜节律变化^[33]。SCN中谷氨酸可以诱导神经元和星形胶质细胞中生物钟基因的表达^[33]。考虑到谷氨酸在大脑兴奋性突触传递中的核心作用,谷氨酸的节律性变化可能也是疼痛存在昼夜节律的潜在机制之一。

ATP是参与痛觉传递和调节的重要物质,其在外周可激活伤害感受器上的P2X₃受体,促进痛觉信息传

递^[35]。脊髓和脑水平上,神经元或星形胶质细胞来源的ATP也参与慢性痛的调节^[36]。在单侧眶下神经缩窄(constriction of the infraorbital nerve, CION)诱导的小鼠三叉神经痛模型中,海马ATP水平升高,小胶质细胞激活,长时程增强(long-term potentiation, LTP)受损,并且表现出焦虑和抑郁样行为^[37],其中ATP是诱导疼痛及抑郁样行为的共同介质。另一方面,研究发现SCN中ATP浓度存在昼夜震荡^[38],在体外培养的SCN2.2细胞中也可观察到类似的昼夜节律特征^[38],但是SCN中ATP水平节律震荡的意义及其是否参与疼痛调节还有待进一步证实。

神经肽SP通过与神经激肽-1(neurokinin-1, NK1)受体结合并激活下游级联反应,参与痛觉感受及其调控^[39]。在福尔马林诱导的疼痛模型中,CLOCK:BMAL1异源二聚体通过E-Box调控背根神经节(dorsal root ganglion, DRG)中*Tac1*的昼夜节律表达^[40]。此外,与镇痛相关的重要的神经肽——阿片肽也呈现显著的昼夜节律变化。如临床研究中观察到,无论是新生儿还是成人,内源性阿片肽水平存在昼夜节律变化。在人腮腺分泌液中,甲硫氨酸脑啡肽、SP和 β -内啡肽水平在早晨较高^[41,42]。此外,小鼠脑中的阿片肽也呈现昼夜节律变化,与清晨相比,其内啡肽含量在下午显著升高^[43]。

反过来,核心时钟基因*Per1*和*Per3*,不仅调节昼夜节律,在神经病理痛中也发挥一定的调节作用。研究发现,神经损伤可以下调脊髓背角神经元和星形胶质细胞中PER1的表达,并且敲低小鼠脊髓*Per1*,不仅扰乱PER1表达的昼夜振荡,还能诱导后爪机械痛阈值的显著降低^[44]。*Per3*的单核苷酸多态性影响疼痛的下行抑制调节^[45],但其详细机制还有待进一步研究。

此外,褪黑素也与疼痛的昼夜节律性有关。野生小鼠的基础痛阈存在昼夜节律特性,其夜间基础痛阈显著高于光照期间,而切除褪黑素的分泌器官——松果体后,基础痛阈的昼夜节律变化受到抑制,若在光照期间补充褪黑素可以诱导小鼠的热痛阈显著升高。此外,褪黑素与吗啡联合使用还可显著增强吗啡的镇痛效果^[46],其机制与褪黑素与其受体结合,增加 β -内啡肽的释放有关^[47]。

2.3 疼痛与睡眠障碍共病可能的环路机制

临床观察到疼痛与睡眠障碍高度共病,并存在相互调节作用——疼痛会影响机体的正常睡眠,而睡眠

不足或紊乱会降低痛阈,促进自发性疼痛^[31]。因此,疼痛可能通过影响生物体的昼夜节律,导致睡眠障碍,同时昼夜节律的改变反过来也可能促进疼痛的发生,二者可能共享一些神经环路或分子机制。最近的一项研究发现,睡眠过程中PB(parabrachial nucleus)-aNB(anterior nucleus basalis)-S1(primary somatosensory cortex)环路的激活对慢性痛的产生和维持至关重要,在睡眠阶段抑制这一通路可缓解神经病理痛^[48]。此外,新奇物体引起的急性睡眠剥夺可使大鼠在不产生焦虑情绪的情况下,发生热和机械痛觉过敏。环路机制上,内侧缰核胆碱能神经元到丘脑室旁核和脚间核的投射,介导了上述影响^[49]。

3 情感障碍

常见的情感障碍如焦虑障碍、抑郁障碍等不仅作为独立的疾病存在,通常也是疼痛尤其是慢性痛和睡眠障碍患者常见的共病^[50]。

3.1 情感障碍的昼夜节律特征

情感障碍患者的症状存在昼夜节律变化。在20世纪50年代,研究者就观察到重度抑郁症(major depressive disorder, MDD)患者普遍存在昼夜情绪的变化,通常表现为清晨症状加重,夜晚改善^[51],并且患者的睡眠、激素分泌和体温的节律性变化也会发生一定的改变^[52,53]。此外,双相情感障碍(bipolar disorder, BD)患者在疾病的急性发作期和发作间期,都可观察到昼夜节律紊乱的现象,并伴随睡眠紊乱^[54]。目前研究已经报道包括CLOCK、NPAS2、ARNTL1、NR1D1、PER3、RORB和CSNK1E在内的多个生物钟基因与双相情感障碍相关^[54]。BD患者转录组学测序结果显示,成纤维细胞核心时钟基因*BMAL1*、*NR1D2A*和*DBP*的节律性振荡出现显著变化,并且*DEC2*和*DBP*的mRNA表达量出现显著降低^[55]。在小鼠中,*Clock*基因外显子19的缺失可引起躁狂样过度活跃(manic-like hyperactivity)、抑郁样行为减少、焦虑水平降低和睡眠/觉醒周期异常^[56],并且上述躁狂样行为可以通过锂治疗或恢复腹侧被盖区(ventral tegmental area, VTA)CLOCK蛋白的表达被逆转^[57]。此外,虽然PER3不是生物钟反馈调节环路的核心部分,但它参与了一些生理功能和疾病的昼夜节律调节,如睡眠相位改变和情感障碍疾病等^[21]。因此,生物钟节律基因的突变是一些情感障碍疾病发生的潜在分子机制。

3.2 疼痛、情感障碍和昼夜节律相互作用的结构基础

临床上,慢性痛、情感障碍以及睡眠障碍往往会同时发生。2022年一项针对20~40岁慢性偏头痛患者的研究发现,慢性偏头痛会导致患者休息-活动的节律稳定性降低,睡眠碎片化,并且其休息-活动的节律与患者的焦虑水平存在显著的相关性^[58]。在纤维性肌痛综合征患者中的研究也发现,部分患者存在与抑郁共病,并且其机体外周体温节律与抑郁和疼痛的严重程度存在相关性^[59]。在疼痛、情感障碍和昼夜节律共病患者中,针对其中一种疾病的治疗会同时缓解其他两种疾病。多项临床试验证实,针对失眠的认知疗法也会缓解患者的抑郁情绪^[60,61]。不仅如此,针对骨骼肌肉疼痛和抑郁共病的联合用药及行为干预,对于抑郁和慢性痛均有显著的改善作用^[62,63],由此提示从共病角度开展临床治疗的潜在优势。从预防的角度来看,理解三者的共病关系,有助于早期识别疾病高危人群。如通过监测睡眠障碍人群的痛阈和情绪变化,可以提前发现潜在的情感障碍或慢性痛风险,从而采取早期干预措施,如生活方式调整或针对性的认知疗法,预防疾病的进一步发展。这对于促进个体的健康状态、提高疾病治疗效果、降低医疗成本具有重要意义。

中脑中缝核可以传出大量5-HT能投射到SCN,并且这条传出通路可以促进生物体昼夜节律的稳定^[64]。不仅如此,在离体和在体实验也都观察到,5-HT受体激动剂会引起SCN神经元电活动的相位变化以及昼夜节律的改变^[65,66]。因此,有研究者提出,从中缝核发出到SCN的5-HT能投射可能是昼夜节律和情感障碍之间相互作用的结构基础^[67]。同时,中缝核也是疼痛下行调控通路和上行传导通路中的关键结构^[68]。在多种动物模型及临床前实验中均观察到,背侧中缝核(dorsal raphe nucleus, DRN)参与神经病理痛的调节^[69,70]。最新的研究还发现,生物钟基因*PERIOD3*突变通过抑制DRN色氨酸羟化酶2的表达,减少5-HT合成,导致冬季抑郁的发生^[71]。据此我们推测生物钟或许也可以通过调节5-HT能系统影响疼痛感知。

大脑多巴胺能(dopamine, DA)系统与生物钟有着密切的互作关系。如在SCN给予DA受体激动剂可以调节大鼠生物钟基因的表达,并受到昼夜节律的影响。日间注射DA1受体激动剂SKF38393,可以显著上调*Per2*和*Clock*的表达,下调*Per1*和*Bmal1*的表达;而夜间给药则可以上调*Per2*的表达,降低*Per1*、*Clock*和*Bmal1*的表

达^[72]。反过来,生物钟基因也对多巴胺系统发挥调节作用。如REV-ERBa可与核受体相关1蛋白(nuclear receptor-related 1 protein, NURR1)竞争抑制*Th*基因转录,进而驱动酪氨酸羟化酶的昼夜节律性表达^[73]。生物钟基因表达异常还可通过影响DA系统,导致情感障碍^[74]。如敲除REV-ERBa编码基因或药理学抑制中脑腹侧被盖区REV-ERBa活性,可诱导高多巴胺能状态,小鼠出现躁狂样行为。此外,中脑边缘DA系统还参与疼痛的调节^[75]。由于中缝核内富含5-HT能神经元和部分多巴胺能神经元^[76],并向中脑腹侧被盖区和伏隔核等DA系统的核心结构发出纤维投射^[70,77],因此中缝核及其调控的5-HT和DA能系统可能是介导昼夜节律紊乱、慢性痛和情感障碍共病的关键结构和分子基础^[54,78]。

综上所述,我们推测中缝核可能是昼夜节律、疼痛与情绪障碍三者共同的调节中枢(图2)。在伤害性刺激或其他应激刺激等的作用下,中缝核活性发生改变,

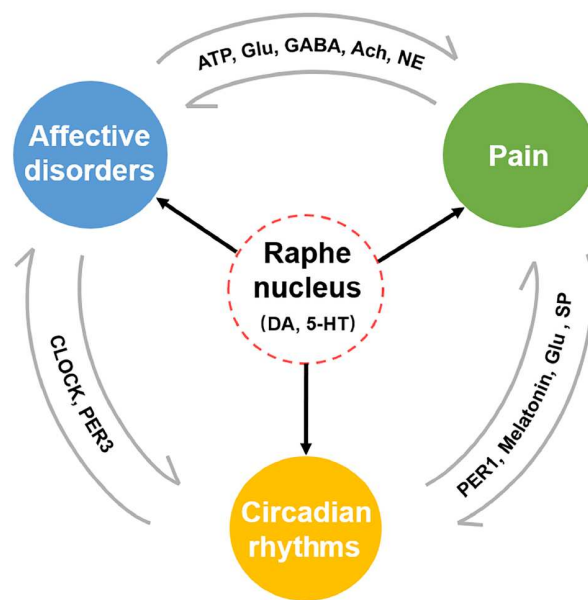


图2 昼夜节律、疼痛和情感障碍之间的相互作用。昼夜节律、疼痛和情感障碍之间存在密切的相互作用,三者之间可以通过多种神经递质、神经肽及生物钟分子互相调节。中缝核可能通过调控5-HT能和DA能系统成为三者互作的调控中心

Figure 2 The interactions among circadian rhythms, pain, and affective disorders. There are close interactions among circadian rhythms, pain, and affective disorders and they mutually regulate each other through a variety of neurotransmitters, neuropeptides, and clock molecules. The raphe nucleus may act as a regulatory hub for the interactions among them by regulating the serotonergic and dopaminergic systems. DA: Dopamine; 5-HT: 5-hydroxytryptamine; ATP: adenosine triphosphate; Glu: glutamate; GABA: γ -aminobutyric acid; Ach: acetylcholine; NE: norepinephrine; CLOCK: circadian locomotor output cycles protein kaput

并通过纤维投射至SCN, 影响昼夜节律, 同时通过对下游5-HT能和多巴胺能系统的复杂调节, 影响机体对疼痛的感知及其情绪状态。

4 总结及展望

本文主要对昼夜节律、疼痛和情感障碍三者之间的相互调节关系及其分子机制进行了阐述。生物体内可能存在复杂的调节途径, 调控着疼痛、情感障碍和睡眠障碍的共病。在神经环路层面, 虽然我们已经知道中缝核等脑区参与三者的交互作用, 但具体的神经环路连接和信息传递机制仍不清楚。对共病状态下相关脑区如何协同工作, 相应环路之间的交互作用以及不同环路之间的信号整合, 尚不能做出准确的回答。在分子机制方面, 尽管已经发现了一些关键分子如5-HT和多巴胺, 但它们在不同疾病状态下的动态变化和相互作用网络仍有待深入研究。例如, 在不同的疼痛模型和情感障碍疾病中, 5-HT受体亚型特异性的功能变化及其分子互作机制尚不清楚。我们还缺乏对相关分子或信号通路在不同脑区和细胞类型中的时空特异性表达和调控机制的深入理解。这种局限性可能来源于以下3种原因: 首先, 在动物模型中很难同时重现人类昼夜节律紊乱、疼痛和情感障碍共病时的所有症状和生理变化。因为人类作为高级动物, 会受到社会环境、认知心

理因素等的影响, 这些都是无法通过现有的动物模型进行复现的。其次, 昼夜节律、疼痛和情感障碍作为复杂的多因素导致的疾病, 涉及人体多个系统的变化, 仅针对神经系统层面的研究, 并不能提供疾病的全局视野, 因此跨系统的整合生物学研究将会成为未来研究的目标及方向。最后, 目前的研究手段对于解析大脑中复杂的神经环路和分子网络仍存在一定的局限性, 期待未来科技的进步, 让我们能够更充分地了解三者之间的共病机制。

针对上述局限性, 未来需要注重动物模型和临床样本的结合使用, 并采用光/化学遗传学、神经调控等方法, 精准调控特定脑区和神经元类型的活动, 并开展跨系统的整合式研究, 比如神经-免疫、神经-消化、神经-代谢的研究, 以解析这些系统在昼夜节律、疼痛和情感障碍共病中的协同作用及其机制。同时, 整合转录组学、蛋白质组学、表观遗传组学和代谢组学等多组学数据, 全面分析共病状态下基因表达、蛋白质修饰和代谢变化的特征。如通过对共病患者的相关体液样本和动物模型的组织样本进行多组学分析, 寻找共同的生物标志物和潜在的治疗靶点, 同时结合前瞻性临床研究, 追踪共病患者的疾病进展和治疗效果, 以评估这些标志物在临床应用的可行性和干预的有效性, 探索新的治疗策略。

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Summary for “昼夜节律、疼痛与情感障碍之间的互作关系及其机制”

The interplay among circadian rhythm, pain and affective disorders and the underlying mechanisms

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Most organisms exhibit the phenomenon of circadian rhythm, which is driven by the self-sustained, endogenous oscillations generated by circadian clocks under the entrainment of external light. Pain perception and emotional states, and some of their corresponding pathological states such as chronic pain and affective disorders, can exhibit circadian rhythm. An increasing amount of evidence demonstrates that nociceptive threshold and mood states fluctuate across the 24-hour cycle. Conversely, circadian rhythm affects pain perception and affection. Sleep disorders resulting from circadian rhythm disruptions can increase the risk of developing affective disorders or chronic pain. Mutations in circadian clock genes, for example, *Per2* and *Clock*, can not only lead to disruptions in circadian rhythms and sleep disorders, but may also contribute to mood disorders such as winter depression and somatic sensory abnormality such as chronic pain. Clinically, there is a significant comorbidity among sleep disorders, chronic pain, and mood disorders, with underlying mechanisms linked to shared brain regions, cellular mechanisms, neurotransmitters, and the corresponding receptors. The raphe nucleus, a midbrain structure that is enriched in serotonergic neurons, projects to diverse brain regions, including cortical and subcortical areas. It serves as a hub modulating dopaminergic system and serotonergic system and we speculate that it may act as a “central brain region” regulating the comorbidity of circadian rhythm disorders, chronic pain, and mood disorders. The current paper elucidates the interrelationships among circadian rhythms, pain, and mood disorders, as well as the interactions among the three, and summarizes the potential critical brain regions and the underlying molecular mechanisms involved in the interactions. Based on the current research, we hypothesize that the raphe nucleus might serve as one of the critical brain regions mediating the interactions through its regulation on the serotonergic and dopaminergic systems, which provides a new theoretical framework for understanding the mechanisms of the comorbidity. In addition, we attempt to analyze the limitations in the current studies of the comorbidity of sleep disorder, mood disorder and chronic pain. Building upon these critical gaps, we provide an outlook on future research directions, aiming to promote the in-depth exploration of the mechanisms for the comorbidity of circadian rhythm disorders, chronic pain, and mood disorders, and offer new ideas for the clinical treatment of the related diseases. We hope to catalyze a paradigm shift from phenomenological observation to mechanism-driven therapeutics, ultimately enabling precision interventions that concurrently target pain, mood disorder and circadian rhythm disruption in treatment for refractory diseases.

suprachiasmatic nucleus, clock genes, chronic pain, the raphe nucleus, 5-HT

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