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The circadian clock at the intercept of sleep and pain

Vinko Palada[1], Ian Gilron[2], Barbara Canlon[1], Camilla I. Svensson[1], Eija Kalso[1,3,]*

[1]Department of Physiology and Pharmacology, Karolinska Institute, Stockholm, Sweden

[2]Department of Anesthesiology and Perioperative Medicine, Queen's University, Kingston, Canada

[3]Pain Clinic, Department of Anesthesiology, Intensive Care, and Pain Medicine, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

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*Author of correspondence:

Name: Eija Kalso, MD, PhD

Address: Pain Clinic, Helsinki University Hospital, Haartmaninkatu 2A (PB 140), 00029 HUS, Helsinki, Finland

Telephone number: +358-9-47175885

Fax number; +358-9-4717641

Email address: eija.kalso@helsinki.fi

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1. Introduction

It is estimated that 50-88% of the patients with chronic pain suffer from inadequate sleep.[94] Not only does pain disturb sleep, but insomnia symptoms often precede the onset of pain in patients with e.g. fibromyalgia[74], musculoskeletal pain[79] and headache.[80] Insomnia also leads to increased pain intensity.[105] Recent studies suggest that both sleep and pain are regulated by the circadian clock and circadian genes have been associated with nociception and an altered sleep-wake cycle.[38,93] Most of the current knowledge regarding circadian regulation of pain comes from animal models; thus, there is an urgent need to better understand the effect of circadian rhythms in the development and maintenance of chronic pain in humans. Therefore, in this topical review we discuss the association between the circadian clock, sleep and pain focusing on circadian regulation of neuropathic and inflammatory pain, headache and migraine. We will also address the effect of circadian regulation on pain pharmacology and analgesia.

1.1. Bidirectional relationship between sleep and pain

The relationship between sleep and pain is bidirectional since insufficient sleep can precede and maintain pain while pain can impair one's ability to initiate and maintain sleep.[62] Experimental studies show that acute sleep deprivation leads to reduced pain thresholds[55,58,77,92,98], increased pain sensitivity[3,53,70,89], and a female-specific reduction in descending pain inhibition.[33,95] A recent fMRI study revealed that acute sleep deprivation in healthy adults caused increased pain reactivity in primary somatosensory cortex and reduced activity in insula and striatum[55] – brain regions involved in descending pain inhibition.[102] In addition to a direct effect on pain, sleep deprivation has been found to promote depression and anxiety, which are frequent pain

comorbidities.[5,6,57,66,75] However, some studies also report that sleep deprivation can have anti-depressant effects.[16]

1.2. Circadian clock at the interplay between sleep and pain

Emerging data suggest that both sleep[4,24,56,84,88,101,107,108] and pain[20,23,31,62,99,104,109,113] can be regulated by the circadian clock on the physiological and molecular level (Figure 1). Master regulators of the mammalian circadian clock are the light responsive neurons in the suprachiasmatic nucleus (SCN) of the hypothalamus which respond to light stimuli from retina[48] and synchronize the clocks in peripheral tissues through the autonomic nervous system and secretion of hormones and neurotransmitters (e.g. melatonin, cortisol, noradrenaline and dopamine) involved in regulation of sleep-wake cycle and nociception.[51] The SCN neurons suppress synthesis of melatonin from the pineal gland during daytime whereas pineal melatonin production is elevated during the night to induce sleep.[19] Disturbed melatonin secretion has been suggested to contribute to insomnia, particularly in the elderly[64] and melatonin administration was shown to improve the sleep quality[34] and to exert analgesic effects.[106] Similarly, secretion of cortisol from the adrenal cortex shows circadian oscillations. The levels of cortisol increase steadily during sleep progression to promote wakefulness and to initiate gluconeogenesis resulting in peak cortisol levels in the early morning.[39] Long-term stress has been associated with elevated cortisol levels in the evening, and at sleep onset, which is linked to insomnia[103] and pain chronification.[78] It is important to note that diurnal fluctuation in the cortisol levels can also occur due to psychological distress[28,69] and physical activity[10] may influence the melatonin levels which might indirectly affect the diurnal rhythmicity in pain intensity independently of the circadian input from the SCN. Diurnal rhythmicity due to psychological distress, physical activity and yet unknown mechanisms independent of circadian regulation, might also explain

the variable levels of coupling between the circadian clock and pain in different pain cohorts as reported in patients with migraine.[31,83] Additionally, it has been shown that SCN neurons indirectly project to noradrenergic neurons in the locus coeruleus (LC)[8,44] as well as to ventral tegmental area (VTA) containing dopaminergic neurons.[67] Levels of noradrenaline in the blood circulation are reduced during sleep in humans compared to wakefulness[71] which is in line with higher discharge rates of noradrenergic LC neurons in rats during wakefulness compared to sleep.[9] Also, a recent study on mice showed that inhibition of VTA dopaminergic neurons suppresses wakefulness to promote sleep while optogenetic stimulation induced long-term wakefulness and suppressed sleep.[32] Besides regulation of the sleep-wake cycle, both noradrenaline and dopamine are key modulators of the descending pain inhibition pathway.[11] On the molecular level, circadian regulation of sleep and pain is achieved through the feedback loops that promote the rhythmicity in gene expression and endogenous periodicity of circa 24h.[54] The main regulation loops of the circadian genes are described in Figure 2.

2. Circadian clock and sleep

The sleep-wake cycle can be divided into wakefulness, non-rapid eye movement (NREM), and rapid eye movement (REM) sleep. The electroencephalogram (EEG) can distinguish between REM sleep and wakefulness characterized by fast desynchronized oscillations and NREM sleep with synchronized cortical oscillations.[91] Several single nucleotide polymorphisms (SNPs) in the core circadian genes *CLOCK, BMAL1, CRY1, PER2* and *PER3* have been associated with inter-individual differences in sleep time, sleep duration as well as with sleep disorders. [4,56,60,84,101] Double Cry1/2$^{-/-}$ knockout mice display hypersomnolence and recurrent episodes of prolonged sleep, associated with increased duration of NREM sleep in the EEG and followed by changes in the expression of circadian genes in the cerebral cortex.[107] Changes in the cortical expression of

the mouse clock genes *CLOCK*, *BMAL1*, *CRY2* and *NPAS2* due to sleep deprivation were found to correlate with differences in EEG patterns between different mice strains indicating that circadian gene expression might drive the EEG differences among these strains.[108] The EEG measurements on *BMAL1* knockout macaque monkeys indicated reduced REM and NREM sleep duration during the evening[88] which is opposite to increased sleep duration observed in Bmal1 knockout mice[61] indicating the differences in sleep regulation by BMAL1 between diurnal and nocturnal species. A recent study in healthy adults showed that the *PER2* SNP, rs6753456, shapes sleep and EEG patterns in humans evidenced by reduced EEG power density during NREM sleep and lower slow-wave activity in the early part of the sleep.[24]

3. Circadian clock rhythmicity and pain

Pain intensity is characterized by diurnal fluctuations both in clinical conditions and experimental pain.[20,42] Circadian clock rhythmicity plays an important role in regulating the rhythmic expression of the voltage-gated calcium channel subunit $\alpha_2\delta_1$[59] and NMDA glutamate receptor subunits on nociceptive neurons in dorsal root ganglions (DRGs).[113] The circadian genes *CLOCK* and *BMAL1* also regulate the rhythmic expression of the *TAC1* gene in DRG neurons which encode for the neuropeptide substance P.[113] Besides DRGs, circadian rhythm was also associated with rhythmic expression of μ-opioid receptors in periaqueductal gray, part of brainstem important for descending pain inhibition[99] and with expression of the NMDA receptor subunit NR2B in the dorsal horn of spinal cord.[109]

3.1. Circadian regulation of neuropathic pain

Patients with neuropathic pain in conditions such as diabetic neuropathy and postherpetic neuralgia, usually experience the most severe pain in the evening hours.[40, 82] The morning-

evening pain intensity difference has been observed to be more pronounced in females and in diabetic neuropathy compared with postherpetic neuralgia suggesting that various biological factors affect the circadian control of pain.[41] Altered circadian expression of opioid and melatonin receptors was reported in the spared nerve injury (SNI) mouse model of neuropathic pain. Gene expression of melatonin MT1A and MT1B receptors in hypothalamus was significantly higher in SNI mice at 2:00 and lower at 8:00 time point compared with sham controls.[81] Spinal dorsal horn expression of circadian genes *PER1*, *PER2* and *CRY1* was suppressed in the lumbar dorsal horn 7 days after partial sciatic nerve ligation (PSNL) in mice, which was followed by increased mechanical hypersensitivity.[73] These studies suggest that altered expression of clock genes in sensory tissues can contribute to neuropathic pain following peripheral nerve injury. Considering that neuroinflammation also associates with neuropathic pain, it is important to notice that microglia-derived inflammatory cytokines TNF-α, IL-1β, and IL-6 show strong rhythmic expression in CNS.[35,76]

3.2. Inflammatory pain and circadian clock

Patients with inflammatory pain conditions such as rheumatoid arthritis (RA) have the most severe joint pain and stiffness in the morning.[13] While pain in osteoarthritis (OA) is primarily associated with abnormal mechanical loading of the joints,[37] some OA patients also have an inflammatory pain component. It has been reported that pain in OA patients has higher intensity in the morning and early afternoon compared with the evening hours when the level of physical activity is reduced.[2,12,14] This temporal pattern is apparent also in acute inflammatory pain conditions,[18] and interestingly, this is distinctly different from the pattern in neuropathic pain conditions where pain generally gets worse in the evening. The inflammatory pain pattern in RA patients is associated with circadian rhythmicity in the serum levels of the pro-inflammatory

cytokine IL-6 with the highest concentrations in the early hours of the day (7-10 AM).[7] The overnight increase in the level of pro-inflammatory cytokines is partially due to reduced release of cortisol in RA patients.[25,26] Furthermore, addition of pro-inflammatory cytokines IL-1β or TNF-α to cultured synovial fibroblasts from RA patients delayed the peak of circadian *BMAL1* expression by up to 6 hours[49] while the protein level of PER2 was reduced in RA synoviocytes upon lipopolysaccharide (LPS)‐induced inflammation.[63] Finally, a recent study on partial medial meniscectomy model of OA pain showed that activation of REV-ERBα with the agonist SR9009 leads to reduced *BMAL1* expression, decreased mechanical hyperalgesia, and less severe cartilage degeneration.[29] These studies suggest that pain in RA and OA is under strong circadian regulation.

3.3. Role of circadian clock in migraine and headache

Migraine has a 24h pattern which is characterized by frequent morning onset although migraine patients have reported headache episodes during the whole day.[31,83,96] Interestingly, forebrain specific knockdown of the calcium voltage-gated channel $Ca_V2.1$ in a mouse model of migraine led to impaired circadian rhythmicity as the mice were running both during the active phase at night and at the resting phase during daytime.[68] Patients with cluster headache (CH) usually experience the most severe pain in the middle of the night[90,97] and both cortisol and melatonin levels are dysregulated in patients with CH.[20,104] In a recent study, the *CLOCK* gene SNP rs12649507 was significantly associated with CH and with elevated gene expression of *CLOCK* in primary fibroblasts from CH patients.[36]

4. Circadian regulation of analgesia and pharmacology of analgesics

So far, most studies of circadian effects on pain medication have focused on opioid-induced analgesia. The circadian pattern of analgesic efficacy was observed for morphine injections in mice, with the highest efficacy and fastest recovery from tolerance observed during the dark, compared with the light phase. This is consistent with the 24h rhythm of μ-opioid receptor expression.[110] Mice with deletion mutation in *Per2* gene showed reduced morphine-induced tolerance and withdrawal.[87] Interestingly, a recent study reported that mice presenting opioid-induced hyperalgesia after chronic morphine exposure had overexpression of circadian core genes such as Per2 and Per3 in pain regulating trigeminal ganglia and nucleus accumbens compared with controls.[114] Rhythmicity in analgesic efficacy of opioids was detected in healthy human volunteers with peak efficacy of fentanyl reported at 17:30 whereas the efficacy of dihydrocodeine and tramadol was highest at 20:00 compared with efficacy in the morning.[17,52] Diurnal variation was previously described for opioid requirements after gastric surgery with morning doses of morphine 15% higher compared with the evening dosage and with the peak analgesic efficacy at 09:00.[47] This time-dependent analgesic efficacy was also observed for the $\alpha_2\delta_1$ ligands gabapentin and pregabalin. The i.p. injection of gabapentin alleviated tactile allodynia in the PSNL mouse model of neuropathic pain at 5:00 compared with 17:00 which correlated with the circadian oscillation of the $\alpha_2\delta_1$ protein level in DRGs.[59] Additionally, i.p. administration of the NMDA-receptor antagonist ketamine to rats during the resting phase reduced secretion of melatonin from the pineal gland and locomotor activity up to 3 days after anesthesia[72] and was shown to reduce *Per2* oscillation in NG108-15 neuronal cells up to 12h after ketamine administration.[15]

In addition to the pharmacodynamic effects, the circadian rhythms may have effects on the pharmacokinetics of analgesics. Peak concentrations (C_{max}) of morphine and morphine-6-glucuronide (M6G), an active metabolite of morphine, in plasma from patients with cancer pain were detected at 18:00 compared with 14:00 and 10:00 time points.[46] The synthetic opioid analgesic pethidine showed peak C_{max} and area under the drug concentration-time curve (AUC) values in serum during the dark phase (21:00) compared with the light phase (9:00) whereas the total serum clearance had the opposite trend in Balb/C mice.[112] The C_{max} and AUC values of the opioid analgesic bucinnazine were significantly increased at 9:00 compared with 21:00 in serum from i.p. injected Sprague Dawley rats.[111] Furthermore, mice with pain due to streptozotocin-induced diabetic polyneuropathy showed the highest analgesic efficacy when oral pregabalin was administrated at the early dark phase which was associated with increased absorption due to circadian oscillations in the intestinal expression of organic cation transporter Octn1.[1]

It is becoming more apparent that the timing of analgesic administration may be important for improved efficacy. A well-studied example of the chrono-release drug is prednisone which is a glucocorticoid anti-inflammatory drug for RA. It has been reported that administration of prednisone with modified release (at 2am or 4am) to RA patients is more effective in reducing morning stiffness and/or joint pain compared with immediate-release standard glucocorticoids taken in the morning.[21,22,27] Similarly, oral administration of sustained release indomethacin, a nonsteroidal anti-inflammatory drug, to patients with osteoarthritis showed a different efficacy based on the timing of administration with evening dosing being more effective in patients with predominantly nocturnal or morning pain whereas morning or noon dosing was more effective in patients with afternoon or evening pain.[65] When considering chronotherapy for different drugs, it is important to consider not only the half-life of the compound but also whether the target is

rhythmic. Interestingly, the targets of many commonly used drugs are controlled by circadian genes making the timing of administration important[115], especially when the half-life of the drug is short. These drugs include e.g. rituximab for rheumatoid arthritis (targeting circadian genes Fcgr2b, Ms4a1, Fcgr3), lidocaine patch for pain (targeting circadian genes Slc22a5, Cyp2b10, Egfr, Abcb1a), and eszopiclone for insomnia (targeting circadian genes Ptgs1, Tspo, Gabra3).[115]

5. Future prospects

Emerging evidence suggests a vicious cycle between sleep and pain which are both regulated by the circadian clock. Whereas the association of genetic variants in circadian genes with sleep regulation and sleep disorders is well characterized, currently there are no genome-wide association studies (GWAS) performed on pain cohorts to identify associations between circadian SNPs and pain with only recent report of association between variable number tandem repeat variant PER3[5/5] and reduced descending pain modulation during day in healthy subjects.[23]

Studies on mouse models investigating the connection between sleep and pain should consider that most of the inbred mouse lines are melatonin deficient except for C3H/He and CBA strains.[45,86] Data from patients and experimental models demonstrate a circadian effect on the efficacy and dosage of analgesics, which suggests that time-targeted analgesic administration should be considered to optimize efficacy. Future pharmacological studies should investigate the potential of small-molecule inhibitors for core circadian genes to fine-tune the circadian clock and to improve pharmacokinetics of currently available analgesics.[50] Circadian cycle enhancing molecules (CEMs), which can regulate circadian oscillation in gene expression, present novel therapeutic targets for dysregulated circadian clocks in sleep and pain.[43]

Finally, since the majority of current preclinical pain research is conducted on nocturnal animals such as rodents which are active during the night and sleep during the day, it is crucial to consider the circadian effect on pain and analgesia to successfully translate the findings from nocturnal animal models to patients with diurnal variation in the sleep-wake cycle.

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FIGURE LEGENDS

Figure 1. **Circadian clock at the interplay between sleep and pain.** Light responsive neurons in the suprachiasmatic nucleus to light stimuli from retina are master regulators of circadian clock[100] which synchronize the peripheral clocks in peripheral tissues through the autonomic nervous system and secretion of hormones, cytokines and neurotransmitters involved in regulation of both sleep and pain.[35,76,93] Furthermore, the core circadian genes promote stable oscillations in gene expression for some genes involved in regulation of sleep and pain.[54] The relationship between sleep and pain is bidirectional since insufficient sleep can precede and maintain pain while pain can impair our ability to initiate and maintain sleep.[62]

Figure 2. **The molecular clock machinery**. The core mammalian circadian genes are two transcriptional factors, circadian locomotor output cycles kaput (CLOCK) and brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1 (BMAL1), which – in the form of CLOCK/BMAL1 heterodimer – promote the rhythmic transcription of repressor proteins Period (Per1/2/3) and Cryptochrome (Cry1/2).[30,100] The PER and CRY proteins drive the negative feedback loop by forming a complex which translocates into the nucleus during the evening to repress the transcription of CLOCK/BMAL1 and therefore its own transcription.[85] In addition to regulation of Per and Cry transcription, CLOCK/BMAL1 activates the nuclear receptors retinoid-related orphan receptor alpha (RORα; also known as NR1F1) and REV-ERBα (also known as NR1D1) which compete with each other to bind a promotor of Bmal1. The RORα is an activator, whereas REV-ERBα is a repressor, of Bmal1 transcription which contributes to cyclic expression of the Bmal1 gene.[54]