Clinical Review

The Neurobiology of Orofacial Pain and Sleep and Their Interactions

Journal of Dental Research
2016, Vol. 95(10) 1109–1116

DOI: 10.1177/0022034516648264
jdr.sagepub.com

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Abstract

This article provides an overview of the neurobiology of orofacial pain as well as the neural processes underlying sleep, with a particular focus on the mechanisms that underlie pain and sleep interactions including sleep disorders. Acute pain is part of a hypervigilance system that alerts the individual to injury or potential injury of tissues. It can also disturb sleep. Disrupted sleep is often associated with chronic pain states, including those that occur in the orofacial region. The article presents many insights that have been gained in the last few decades into the peripheral and central mechanisms involved in orofacial pain and its modulation, as well as the circuits and processes in the central nervous system that underlie sleep. Although it has become clear that sleep is essential to preserve and maintain health, it has also been found that pain, particularly chronic pain, is commonly associated with disturbed sleep. In the presence of chronic pain, a circular relationship may prevail, with mutual deleterious influences causing an increase in pain and a disruption of sleep. This article also reviews findings that indicate that reducing orofacial pain and improving sleep need to be targeted together in the management of acute to chronic orofacial pain states in order to improve an orofacial pain patient's quality of life, to prevent mood alterations or exacerbation of sleep disorder (e.g., insomnia, sleep-disordered breathing) that can negatively affect their pain, and to promote healing and optimize their health.

Keywords: temporomandibular disorders, insomnia, sleep-disordered breathing, neural mechanisms, hypervigilance, chronic pain

Introduction

Acute pain is part of a hypervigilance system that alerts the individual to injury or potential injury of tissues. It can also disturb sleep. Disrupted sleep is also often associated with chronic pain states, including those that occur in the orofacial region such as temporomandibular disorders (TMDs) and various trigeminal neuropathic pain conditions. The relationship between pain and sleep is complex. In contrast with acute pain in which the relationship is linear and rapidly reversible, the relationship in chronic pain states has been described as a vicious cycle with mutual deleterious influences between disturbed sleep and pain (Fig. 1). The complexity of this interaction presents clinical challenges in managing patients manifesting a combination of pain and sleep problems. There have nonetheless been recent advances in knowledge of the processes underlying pain and sleep and their interactions, and this article reviews our current understanding of pain, including orofacial pain, and sleep and their interactions.

Overview of Orofacial Pain and Underlying Processes

General Features of Orofacial Pain

The face, mouth, and jaws are very common sites of acute or chronic pain, and chronic orofacial pain states are often difficult to diagnose and control for several reasons: 1) chronic pain is a complex, multidimensional experience encompassing sensory-discriminative, cognitive, affective (emotional), and motivational dimensions; 2) there are several types of chronic orofacial pain; 3) their etiology and pathogenesis are unclear; and 4) many cases are complicated by having comorbidities such as psychosocial problems (e.g., depression, stress), other related chronic pain states (e.g., irritable bowel, chronic fatigue), and, as outlined below, disturbed sleep. Chronic pain in particular can impose severe emotional, physical, and social stresses on patients that may reduce their quality of life and that vary between individuals, depending on their capacity to cope and on the ability of clinicians to manage their condition. These features and their variability between individuals underscore the complexity of pain and its biopsychosocial nature and the

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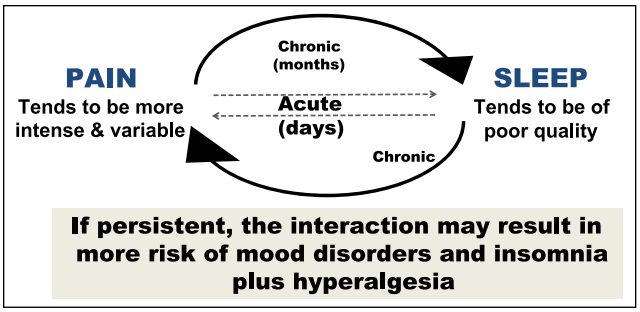

Figure 1. The linear and circular models of pain and sleep interactions (variable from person to person). Horizontal dashed lines indicate acute pain as a "linear model," with pain preceding poor sleep complaints and sleep returning to normal when the acute pain is resolved. Circular full lines depict chronic pain as a "circular model" that may predominate such that a night of poor sleep is followed by a day with more intense and variable pain, which is then followed by a night of nonrestorative sleep and morning-related complaints of unrefreshing sleep.

clinical challenge in effectively managing pain, especially when it is chronic.

Orofacial Pain Mechanisms

The following gives a brief account of the mechanisms within orofacial tissues and the central nervous system (CNS) that are involved in orofacial pain and its modulation. More detailed outlines are provided in other articles in this special issue of the *Journal of Dental Research*, as well as in several other reviews (Iwata et al. 2011; Sessle 2011; Cairns et al. 2014; Dubner et al. 2014).

Primary afferent mechanisms. The trigeminal nerve contains most of the sensory (i.e., primary afferent) nerve fibers innervating orofacial tissues. The larger-diameter afferents (e.g., A-beta afferents) terminate in the tissues as mechanoreceptors that are activated by tactile or proprioceptive stimuli. Some of the smaller afferents (A-delta and C-fiber afferents) end as receptors sensitive to warming or cooling stimuli, but most terminate as so-called free nerve endings that function as nociceptors that are activated by noxious stimulation of the tissues. The nociceptive afferent endings and their cell bodies (predominantly located in the trigeminal ganglion) may also develop a prolonged increase in excitability after orofacial tissue injury or inflammation, a process termed "peripheral sensitization," which may contribute to the hyperalgesia (increased sensitivity and/or excessive response to a stimulus that is normally painful) and allodynia (pain resulting from a stimulus not normally evoking pain) that occur in certain pain conditions. Examples in clinical dentistry are the increased sensitivity of an inflamed tooth and the sensitivity to muscle or temporomandibular joint (TMJ) palpation that is typical of TMDs.

Brainstem mechanisms. From the trigeminal ganglion, the trigeminal primary afferents pass into the brainstem and the vast majority terminate in the trigeminal brainstem sensory nuclear complex (VBSNC). The larger-diameter afferents conducting tactile or proprioceptive information terminate throughout the VBSNC and activate low-threshold mechanosensitive (LTM) neurons. Those afferents activated by warming or cooling stimuli, as well as most of those afferents activated by noxious orofacial stimuli, terminate in the most caudal component (subnucleus caudalis) of the VBSNC. The subnucleus caudalis is often referred to as the medullary dorsal horn because of its many morphological and physiological similarities with the spinal dorsal horn, which processes nociceptive signals from tissues supplied by spinal afferent nerve fibers. Like their spinal afferent counterparts, the central terminals of the trigeminal nociceptive afferents release excitatory neurochemicals (e.g., glutamate and substance P) that can excite the second-order nociceptive neurons upon which the afferent terminals synapse. Some of these nociceptive neurons receive afferent inputs only from facial skin or oral tissues and have properties indicative of a role in encoding superficial pain, whereas others have convergent patterns of nociceptive afferent inputs from deep tissues (e.g., TMJ, muscle) as well as from cutaneous or oral tissues and may contribute to the CNS processes underlying deep pain, including the referral of pain that is typical of orofacial pain conditions involving deep tissues (e.g., TMD) (Sessle 2000; Dubner et al. 2014).

The axons of many neurons in the VBSNC ramify within the VBSNC itself and influence the activity of other VBSNC neurons. Some VBSNC neurons project to other brainstem areas, including the cranial nerve motor nuclei and reticular formation, and thereby participate in the CNS circuitry underlying muscle reflex responses and in autonomic nervous system–based changes in salivary, cardiovascular, and respiratory functions evoked by stimulation of orofacial tissues. In view of the role that the reticular formation and adjacent regions (e.g., raphe nuclei) play in pain modulation and in wakefulness and sleep, the projections to these areas may also be part of neural substrates by which orofacial stimulation may modulate pain and influence sleep and consciousness (see below). Many VBSNC neurons may also contribute to CNS pathways ascending to the ipsilateral and contralateral somatosensory thalamus.

Thalamocortical mechanisms. The orofacial somatosensory information relayed from the brainstem to the thalamus principally passes to the ventrobasal complex (termed the ventroposterior nucleus in the primate), the posterior nuclear group and the medial thalamic nuclei. Thermosensitive neurons occur in these somatosensory thalamic nuclei, and many of them project to analogous neurons in overlying areas of the somatosensory cerebral cortex. Here, their relayed signals are processed to provide for detection and localization of tactile and non-noxious thermal stimuli. These thalamic nuclei also contain nociceptive neurons, most of which in the ventrobasal thalamus have spatiotemporal coding properties and connections to neurons in the somatosensory cortical areas that indicate their role in coding the spatiotemporal features of noxious stimuli and underpinning the sensory-discriminative dimension of pain. In

contrast, most of the nociceptive neurons in the medial thalamic nuclei and posterior nuclear group have spatiotemporal coding properties and connections to cortical areas such as the prefrontal cortex, anterior cingulate cortex, and insula, which are involved in the cognitive, affective, or motivational dimensions of pain.

Modulation of CNS nociceptive processes. Some of the convergent nociceptive afferent inputs mentioned above may induce neuroplasticity in the VBSNC nociceptive neurons These neuroplastic changes result from the effects of neurochemicals released from the nociceptive afferent terminals in the VBSNC and are reflected in an increase in excitability ("central sensitization") of the neurons. Nociceptive neurons at the higher levels of the CNS (e.g., somatosensory thalamus, somatosensory cortex) may also exhibit central sensitization. Central sensitization involves non-neuronal (i.e., glial) as well as neural processes, and these glial processes offer novel targets for developing new or improved analgesic approaches to control pain (Chiang et al. 2011; Sessle 2011; Dubner et al. 2014). Central sensitization has been shown to occur in acute as well as chronic pain states and, along with peripheral sensitization (see above), can explain the allodynia and hyperalgesia as well as pain spread and referral that characterize many orofacial pain states. The neuroplasticity reflected in central sensitization underscores the point that the nociceptive circuits in the CNS are not "hard-wired" but instead are "plastic" and modifiable by events in peripheral tissues related to injury or inflammation as well as by CNS circuits underlying a variety of functions, as noted below.

Central sensitization is just one example of how the transmission of orofacial somatosensory information can be modified at brainstem and thalamocortical levels, in this case reflected in facilitation of transmission. The variety of inputs and interconnections in the VBSNC, such as its subnucleus caudalis, provide the basis for extensive interactions between the afferent inputs to the VBSNC from peripheral tissues and projections to the VBSNC from various CNS areas including the reticular formation, locus coeruleus, raphe nuclei, and cerebral cortex. Several endogenous chemical mediators, such as glycine, gamma-aminobutyric acid (GABA), dopamine, noradrenaline, serotonin (5-HT), orexin (hypocretin), and opioids (e.g., enkephalins and endorphins), provide a chemical substrate by which these inputs may modulate nociceptive transmission and central sensitization. The modulatory influences of behavioral factors, including state of alertness, attention, and distraction, are just some examples in which higher brain areas involved in these states give rise to descending projections to the VBSNC and thereby may contribute to the influence of these behavioral factors on pain. These influences include inhibitory effects exerted by many of these inputs on nociceptive neurons and represent intrinsic CNS mechanisms contributing to the analgesic effects of several therapeutic measures that control pain, including acupuncture, deep brain stimulation, and opiate-related drugs (e.g., morphine) and 5-HT agonist drugs (e.g., amitriptyline), as well as to the phenomenon of placebo analgesia.

The thalamocortical transfer of sensory information is also subject to modulation or "gating" as a result of facilitatory and inhibitory processes involving local neuronal circuits or inputs to the thalamus and cerebral cortex from other CNS areas such as the reticular formation. Gating is a concept of selective sensory filtering that propelled pain research; however, it is not fully supported by research evidence (Moayedi and Davis 2013; Mendell 2014). Such gating may also occur during changes in behavioral state and consciousness such as during sleep, which brings us to consider sleep and its underlying mechanisms as described below.

Overview of Sleep and Underlying Mechanisms

General Features of Sleep and Sleep Disturbances

Sleep is a natural physiological function that is essential for recovery from fatigue and for tissue repair (e.g., heart and skeletal muscles), memory consolidation, and brain function at both the cellular and CNS network levels. Individuals who are totally or partially deprived of sleep may soon become sick from infection or organic dysfunctions, and those without enough sleep tend to be less functional, and within 3 to 4 d may report mood alterations, cognitive problems, immune system changes, and somatic pain-related complaints (Haack and Mullington 2005; Haack et al. 2007).

For most adults, the onset of sleep normally appears within 20 to 30 min after the individual goes to bed and sleep lasts 6 to 9 h, but there is considerable individual variation as a result of different sleep habits, employment requirements, and so forth.

Insomnia, a frequent comorbidity with chronic pain, may also be suspected when sleep onset is longer than 30 min for 3 to 5 times a week, or if spontaneous awakening occurs during the night without the ability to resume sleeping (Lavigne et al. 2009; Morin and Benca 2011; Riemann et al. 2015). Approximately 10% of the general population suffers from chronic insomnia. The presence of concomitant sleep disorders such as sleep-disordered breathing (SDB) or insomnia can also exacerbate chronic pain as described in subsections below (Doufas et al. 2013; Sanders et al. 2013).

Sleep cycles and sleep arousal. Sleep is conventionally divided into nonrapid eye movement (NREM) and rapid eye movement (REM) sleep (Fig. 2). During a typical night, there are 3 to 5 NREM to REM cycles that are collectively termed the ultradian rhythm cycle (in contrast with the 24-h circadian cycle). NREM sleep is further divided into light sleep (stages N1 and N2) and deep sleep (stage N3, formerly called stages 3 and 4), which is dominated by slow wave brain activity. REM sleep is often called "paradoxical sleep" because all skeletal muscles are in a hypotonic state, as if the body is paralyzed, yet the CNS and the autonomic nervous system are highly active (Amzica and Lavigne 2009). Sleep oscillates from active periods to quiet periods. There are frequent brain, heart, and

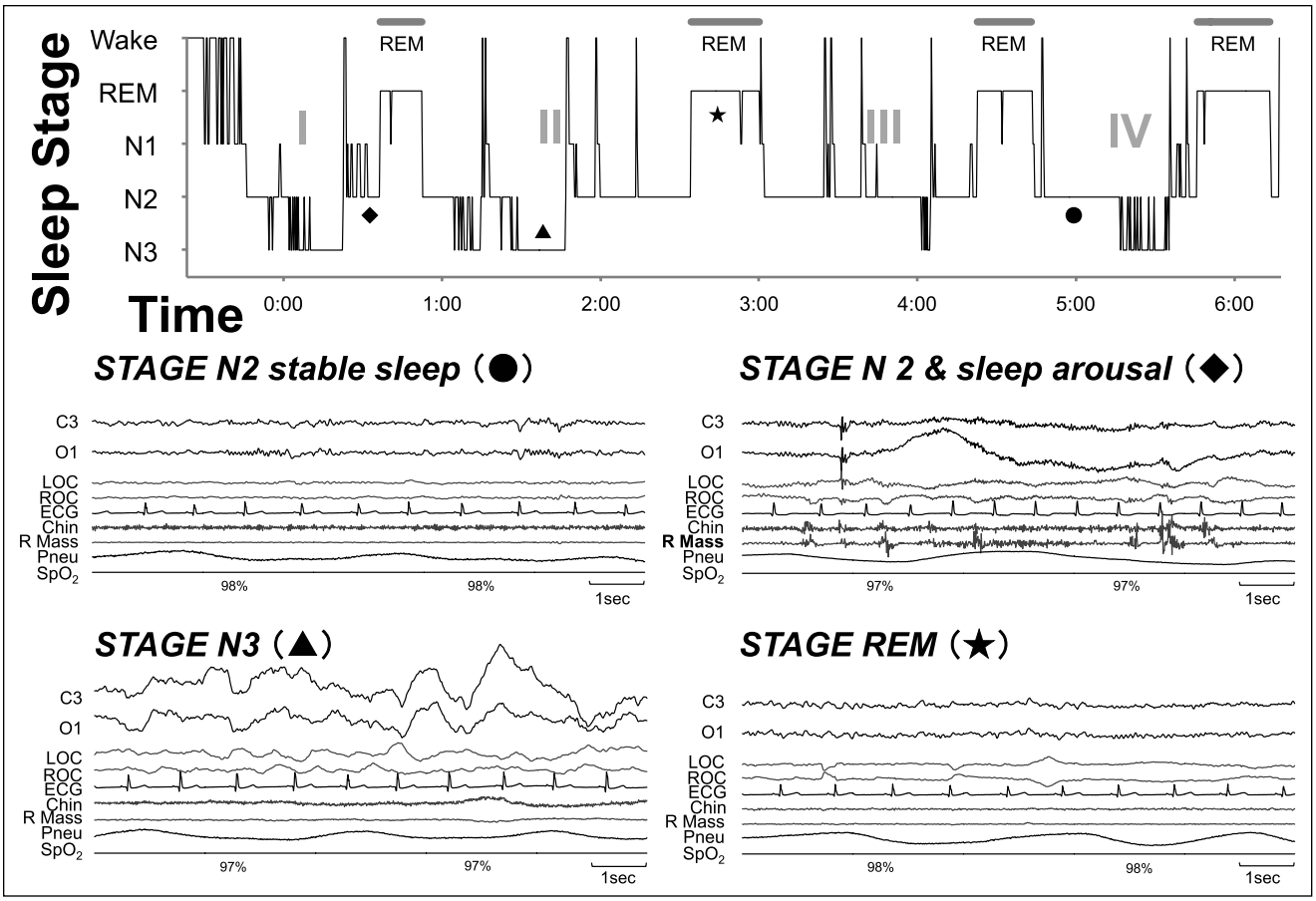

Figure 2. Sleep stages (N1 to N3 and REM) distribution across sleep cycles (I to IV). Hypnogram from an healthy adult with 10-s sleep extracts. The upper right trace represents a sleep arousal event during sleep stage N2 (filled diamond) with an increase in brain activity, heart rate, and jaw muscle activities (chin and right masseter). C3, left central electroencephalogram; Chin, chin muscle electromyogram; ECG, electrocardiogram; EEG, electroencephalogram; EMG, electromyogram; LOC, left ocular movement; NREM, nonrapid eye movement; O1, left occipital electroencephalogram; Pneu, pneumogram; REM, rapid eye movement; R Mass, right masseter; ROC, right ocular movement; SpO_2, oxygen saturation of arterial blood (expressed in % below the trace).

muscle reactivations (each lasting 3 to 15 s) within the active periods, which are termed sleep arousals or microarousals. These arousals tend to reappear 7 to 15 times per hour of sleep in normal subjects and represent "windows," in the sense that the sleeping individual can readjust his or her body position and can become fully conscious if any harmful event is perceived. The alternating active and quiet sleep periods reflect the cyclic alternating pattern (CAP) (Parrino et al. 2007).

Nonrestorative sleep. Nonrestorative sleep refers to the unrefreshed feeling upon awakening. It is present in approximately 10% of the general population and is a frequent complaint of those with insomnia-related symptoms or with fatigue and mood alterations (Haack and Mullington 2005; Lavigne et al. 2011).

Sleep Mechanisms

Ascending pathways or systems in the CNS keep the forebrain awake. The arousal system comprises 2 main branches, both of which activate the cerebral cortex directly or indirectly via the thalamus (Saper et al. 2001; Rye and Freeman 2007; Saper 2013). Each branch originates from different discrete groups of neurons and utilizes a variety of chemical mediators to shift the wake state toward the sleep state, as shown in Figure 3.

The direct pathway is mainly activated serotonin, noradrenalin, and dopamine. The indirect pathway, via the thalamus, is one of the components of the arousal system (lower left gray box in Fig. 3). The indirect pathway originates mainly from cholinergic neurons in the pedunculopontine and laterodorsal tegmental nuclei, and it primarily innervates the thalamus, especially its reticular nucleus and sensory relay nuclei. Transmission through the thalamic sensory nuclei to the overlying cerebral cortex is regulated by the cortical activity (i.e., synchronization) in the sleep-wake cycle and generate sleep spindles, a thalamocortical activity preventing excessive cortical activation during sleep (i.e., concur to preserve sleep stability against arousal). During sleep, the activity in the thalamic reticular nucleus is mainly mediated by GABAergic neurons that project into the sensory thalamic nuclei and inhibit or reduce the sensory-transmission neurons and thereby suppress

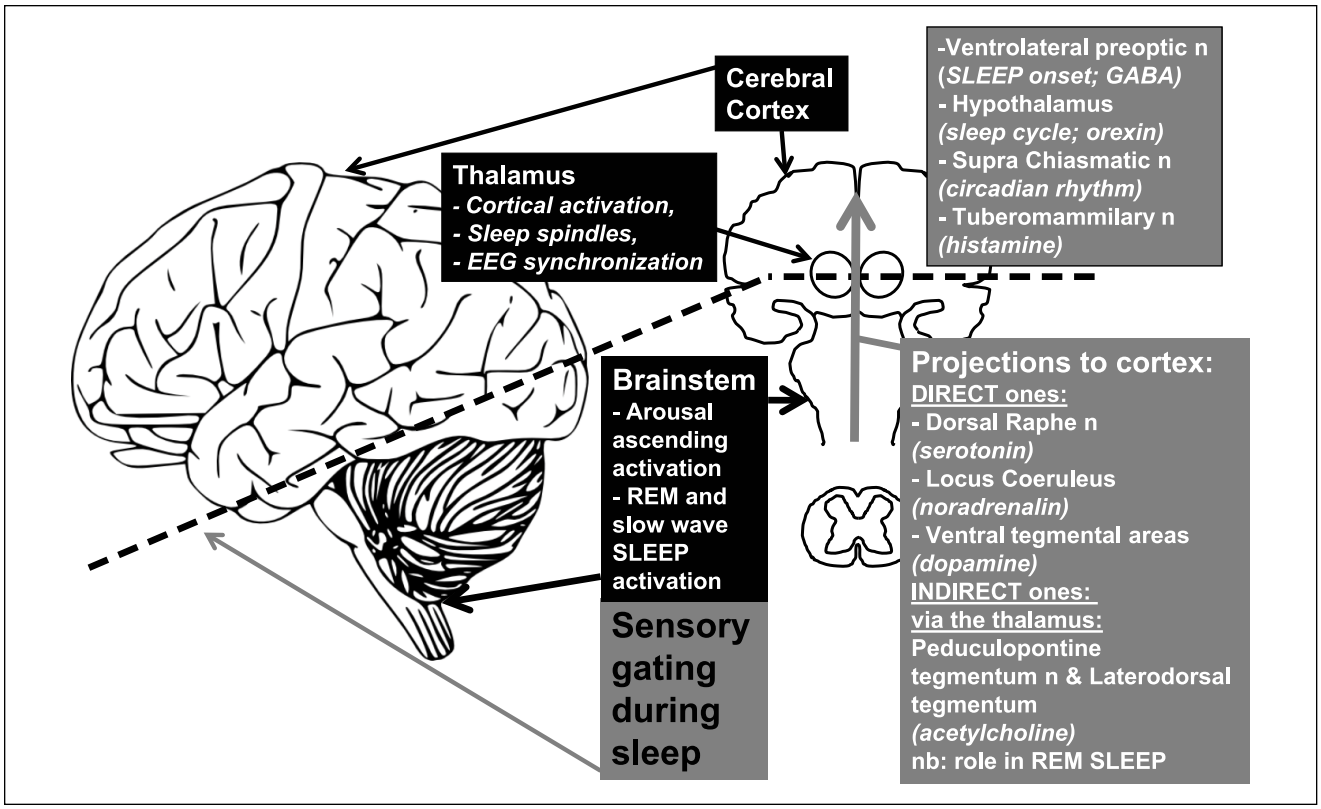

Figure 3. Sleep-generating circuits in the central nervous system. Sleep is generated from brainstem (gray arrow) networks and process by 2 main pathways: to the forebrain 1) direct to the cortex (ventral tegmental areas) and 2) via the thalamus (pedunculopontine tegmentum nucleus and laterodorsal tegmentum) to the cortex. See the upper and lower gray boxes for details. All sensory information, including nociception, is under a gating mechanism filtering (large dashed line) to the external world (e.g., sound, touch) and internal body (e.g., change in brain and/or heart or breathing rate and muscle tone). EEG, electroencephalogram; GABA, gamma-aminobutyric acid; n, nucleus; REM, rapid eye movement.

cortical activation produced by sensory inputs; this is the main zone of sensory gating during sleep (illustrated by the dashed line in Fig. 3). On the other hand, the arousal system can suppress reticular nucleus activity and thus allow thalamocortical sensory transmission to occur for a few seconds (i.e., microarousal) during sleep up to triggering a full wake state.

This complex array of pathways and mediators to the forebrain is supplemented by neurons in the lateral hypothalamus that contain glutamate and orexin (i.e., hypocretin), as well as by cholinergic and GABAergic neurons in the basal forebrain that project to the cerebral cortex (right gray boxes in Fig. 3).

These different components of the arousal system ultimately serve to produce activation of the cerebral cortex so that it can efficiently process sensory inputs projecting to the cortex through the thalamus. However, during stable sleep, the neurons in the ascending arousal system are themselves inhibited by GABAergic inputs mainly coming from neurons in the ventrolateral preoptic nucleus, which innervate most components of the arousal system. Interestingly, these inhibitory GABAergic neurons, located in the ventrolateral preoptic nucleus, can themselves be inhibited by neurons in several components of the arousal system, thus producing conditions for a so-called "flip-flop switch." As one part of this switch gains control in this type of switching circuitry, it suppresses the other part of the switch and thus stabilizes its own firing (Saper 2013). As the arousal system is gradually turned down by the flip-flop switch, the sleeping individual progresses through the different stages of NREM sleep as mentioned above (see also Fig. 2). Another flip-flop switch system, involving neurons in the pons, ventrolateral preoptic nucleus, and the lateral hypothalamus, controls REM sleep and has properties that may account for the relatively fast and complete transitions between NREM and REM sleep (Peever and Sessle 2011).

Recent studies have shown that the orexin neurons in the posterior lateral hypothalamus project to neurons at many levels of the sleep-wake modulatory system and are involved in stabilizing the sleep and REM switches (Saper et al. 2001; Mignot et al. 2002; Saper 2013). Histamine, from the tuberomammillary nucleus, also contributes to sleep onset and maintenance.

Pain and Sleep Interactions

Pain Perception during Sleep

During normal sleep in healthy adults, nociceptive transmission is partially attenuated to preserve sleep continuity, with a higher threshold or lower response rate to noxious stimuli in light sleep (stages N1 and N2) that is more important in deep

sleep (stage N3) but variable in REM sleep. Indeed, sensory transmission in general is attenuated during sleep such that low-intensity stimuli may have little or no effect on sleep quality when healthy subjects are sleeping in conditions favoring good sleep quality (e.g., a quiet, comfortable environment) (Lavigne et al. 2004; Bentley 2007).

Placebo Analgesia Conditioning Remains Active during Sleep

It is also noteworthy that placebo analgesia induced by experimental conditioning to pain relief and expectation is a mechanism that remains active during sleep and seems to be modulated by REM sleep (Laverdure-Dupont et al. 2009; Chouchou et al. 2015). The placebo analgesia effect during the wake state is mediated through the thalamus and many cortical areas; however, no direct parallel has yet been made for sleep and placebo analgesia (Tracey 2010; Benedetti et al. 2011).

Sleep Duration and Instability in Patients with Chronic Pain

Normal sleep patterns and functions can be altered by most chronic pain states. Patients with chronic pain tend to be short sleepers (i.e., less than 6 h) or long sleepers (i.e., more than 9 h) (Edwards et al. 2008). The long sleeping duration may be partly explained by depressive mood, so clinicians need to be alert to such cases (Kundermann et al. 2008).

Sleep instability (CAP, as described above) seems to also be associated with some types of chronic pain, namely fibromyalgia, but the cause-and-effect relationship is unknown (Parrino et al. 2007).

Nonrestorative sleep, as self-reported by the patient, is one of the most powerful predictors of musculoskeletal pain and it is associated with being female, being middle aged, having a sedentary lifestyle, and reporting fatigue; depression and insomnia are at the second and third levels of risk, respectively (Roizenblatt et al. 2015).

Insomnia and Chronic Pain

As described above, the onset of sleep normally appears within 20 to 30 min after an individual goes to bed. However, the prevalence of insomnia is reported to be as high as 30% to 40% in patients with chronic pain (Lavigne et al. 2011; Kim et al. 2015). Chronic back pain can increase the risk of insomnia (1.4 times), and severe insomnia was observed in 20% of patients with back pain (Agmon and Armon 2014; Kim et al. 2015). Pain may also increase the risk of insomnia in vulnerable subjects; mood (e.g., depression) seems to again explain a percentage of the variability. This risk is also higher if a familial history of insomnia is present (LeBlanc et al. 2009).

Insomnia is also associated with a reduction in pain tolerance and lower sleep efficacy (time asleep/time in bed) in patients with chronic pain (Sivertsen et al. 2015).

Such findings strongly suggest that closer assessment of poor sleep and insomnia is a key factor in planning management of patients with a chronic pain state (MacDonald et al. 2010).

Linear and Circular Forms of Pain and Sleep Interactions

Pain, especially when chronic, can trigger poor sleep quality and disrupt the restorative benefit of sleep; conversely, poor sleep can exacerbate pain perception and related emotional-cognitive reactivity (Fig. 1). The influence of acute pain on sleep is usually short lasting; it appears to follow a "linear model," with pain preceding poor sleep complaints and sleep returning to normal once the acute pain is resolved. However, in many patients with chronic pain, a "circular model" may predominate such that a night of poor sleep is followed by a day with more intense and variable pain, which is then followed by a night of nonrestorative sleep and morning-related complaints of unrefreshing sleep. It is unknown, however, which is dominant: pain or sleep (Lavigne et al. 2011; Tang et al. 2012).

Orofacial Pain and Disturbed Sleep

Disturbed sleep also occurs in patients with orofacial pain. For example, 20% of patients with trigeminal neuralgia or another orofacial neuropathic pain condition or with TMD report being aware of episodes of wakefulness during their sleep or having a poor quality of sleep (Benoliel et al. 2009; Porto et al. 2011; Kim et al. 2015; Schmitter et al. 2015). Indeed, a sleep laboratory polysomnographic study of patients with TMD revealed that approximately 36% of these individuals have insomnia and 28% have sleep apnea (Smith et al. 2009). A recent home-recording sleep study showed that patients with myofascial TMDs had more sleep disturbances than control subjects and a lower sleep quality; moreover, 70% of patients with TMDs reported transient orofacial pain in the morning and sleep bruxism (Schmitter et al. 2015). Nevertheless, as shown by this study and 3 observational prospective control studies, the morning pain was not correlated with a higher frequency of jaw muscle contractions related to sleep bruxism (Raphael et al. 2012; Yachida et al. 2012; Abe et al. 2013; Schmitter et al. 2015). Thus, the so-called cause-and-effect relationship between pain and hyperactive jaw muscles (i.e., elevated frequency of rhythmic masticatory muscle activity as a marker of sleep bruxism) is not supported by these findings.

One of these sleep laboratory polysomnographic studies revealed, however, that patients with TMDs tend to present sustained but low-grade masseter muscle activity during sleep, supporting a form of hyperarousal in patients with TMDs (Raphael et al. 2013). It is unknown whether such reactivity is similar to what occurs in insomnia (Bonnet and Arand 2010; Riemann et al. 2010, 2015). These findings highlight the importance of identifying the contribution of insomnia that occurs in approximately one-third of TMD cases, as noted above, and seems to predict an enhancement of pain intensity over time (Smith et al. 2009; Quartana et al. 2010).

In addition, the role of sleep apnea, SDB, or sleep-related hypoxia in pain and sleep cannot be neglected. Sleep laboratory studies have shown that 28% of TMD cases had evidence of obstructive sleep apnea (OSA) and that female patients with TMD but without OSA still presented a mild form of SDB known as respiratory effort-related arousal (Smith et al. 2009; Dubrovsky et al. 2014). Moreover, results of the Orofacial Pain Prospective Evaluation and Risk Assessment study, a multicenter prospective TMD risk cohort study, revealed that signs and symptoms of OSA were associated with increased incidence (odds ratio, 3) of first-onset TMD in adults (Sanders et al. 2013).

Therefore, identification of comorbidities is essential in order to select the most effective management approaches. This is a first step in personalized medicine.

Processes Underlying Pain and Sleep Interactions

Sleep, as described above, involves a partial physiological deafferentation of sensory inputs into the CNS, with reduced neuronal activity at the thalamocortical level but with transient reactivations of the transmission of neural signals being relayed from the spinal cord or brainstem during arousal (Parrino et al. 2007; Krueger et al. 2008; Peever and Sessle 2011). This modulation may contribute to the decreased responsiveness to external stimuli during NREM sleep in order to preserve sleep continuity.

Very limited information is available on the mechanisms involved in orofacial pain and sleep interactions.

The excitability of the trigeminal sensorimotor system during NREM sleep is decreased compared with the wake state and may involve inhibitory mechanisms within the trigeminal motor nucleus (Yao et al. 2013; Adachi et al. 2014). The sensorimotor behaviors tested in these 2 studies involve interneurons in or adjacent to the motor nucleus or the VBSNC, and a complex gating mechanism takes place in the rostral components of the VBSNC during sleep and wakefulness (Dubner et al. 1978; Sessle 2006). The activity of many neurons in the rostral VBSNC, as well as their responses elicited by orofacial stimuli, including noxious stimuli (dental pulp), are attenuated during REM sleep through glycine and GABA processes (Soja et al. 1987, 1991). However, it is not known whether comparable state-dependent processes occur in more caudal VBSNC nociceptive (e.g., caudalis) neurons, which play a crucial role in trigeminal nociceptive transmission, as noted above. It is unclear which modulatory mechanisms are involved in the challenging pain and sleep interactions in chronic pain conditions.

Author Contributions

G.J. Lavigne, B.J. Sessle, contributed to conception, design, and data interpretation, drafted and critically revised the manuscript. Both authors gave final approval and agree to be accountable for all aspects of the work.

Acknowledgments

The authors' own research has been supported by the Canadian Institutes of Health Research, the Québec Health Research Fund, and the Canada Research Chair programs. The authors thank Dr. Yoshitaka Suzuki for help in the preparation of this review. The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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