Hyperalgesia Induced by REM Sleep Loss: A Phenomenon in Search of a Mechanism

Comment on: Roehrs T; Hyde M; Blaisdell B et al. Sleep loss and REM sleep loss are hyperalgesic. SLEEP 2006; 29(2):145-151.

Helen A. Baghdoyan, PhD

Departments of Anesthesiology and Pharmacology, University of Michigan, Ann Arbor, MI

THE RECIPROCAL RELATIONSHIP BETWEEN SLEEP AND PAIN IS INCREASINGLY RECOGNIZED AS HAVING DIRECT RELEVANCE FOR INDIVIDUALS WITH CLINICAL and preclinical interests in sleep medicine, pain medicine, and anesthesiology (reviewed in reference 1). Pain causes significant sleep disruption and sleep loss exacerbates pain (reviewed in references 2-7). Sleep itself can influence responses to painful stimuli. Preclinical studies have shown that spontaneous neuronal discharge in pain pathways changes across the sleep-wakefulness cycle.8-10 In animals, behavioral responses to nociceptive input are decreased during sleep,11 as they are in humans (reviewed in references 2,7). Humans maintain the ability to process nociceptive input during all stages of sleep,12 and there is a reduced responsiveness to thermal pain sensation during sleep when the stimulus is brief.13

Human studies of sleep and pain are particularly challenging and must confront potential confounds such as coexisting disease and polypharmacy. Even the drugs used to treat pain can disrupt sleep.14-16 As an example of coexisting disorders, more than 40% of individuals with symptoms of insomnia report at least one chronic painful physical condition.6 The majority of psychiatric disorders is characterized by sleep disruption, and chronic pain patients show comorbidity with psychiatric conditions such as anxiety20,21 and depression.22

The International Association for the Study of Pain (IASP) defines pain as “An unpleasant sensory or emotional experience associated with actual or potential tissue damage . . .” (http://www. iasp-pain.org/defsoffen.html). Chronic pain is defined as pain without apparent biological value that has existed more than 3 months, and the IASP estimates the prevalence to be about 11% in the adult population of developed nations.23 Lavigne and colleagues13 have made the point that it is more appropriate for studies quantifying responses to noxious stimuli during sleep to use the word nociception rather than pain, because the definition of pain assumes conscious awareness.

In this issue of Sleep, Roehrs et al., report the impact of sleep deprivation on nociceptive responses in healthy, pain free subjects. Using healthy subjects overcomes the limitations of coexisting disease and drug use, thus providing the potential for mechanistic insights into the physiological interactions between neural systems regulating sleep and nociception. The Roehrs et al., study tested the hypothesis that sleep loss decreases the time for subjects to move a finger away from a radiant heat stimulus. Finger withdrawal latency was measured after 8, 4, or 0 hours in bed. There was a linear decrease in finger withdrawal latency with increases in sleep restriction. Additional experiments measured finger withdrawal latency following selective REM sleep deprivation. REM sleep deprivation also significantly decreased finger withdrawal latency. Roehrs et al., interpret these results as confirming that sleep loss and REM sleep loss in healthy, pain free subjects causes hyperalgesia.

Research aiming to understand the interactions between sleep and pain has the potential to promote development of adjunctive therapies that can reduce pain without causing sleep disruption. Another concept motivating translational research is the integration of data obtained from human and non-human animals. Previous studies in rat have shown that REM sleep deprivation increases the behavioral responses to noxious stimuli.24 The Roehrs et al., study extends this finding to humans with the demonstration that REM sleep deprivation decreased finger withdrawal latency.

Mechanistic implications from the Roehrs et al., findings are possible, thanks to available data about endogenous molecules and brain regions that regulate REM sleep. Acetylcholine, adenosine, and gamma aminobutyric acid (GABA) are all known to modulate sleep and pain. The pontine reticular formation plays a key role in REM sleep generation and can mediate antinociceptive behavior (reviewed in reference 1). As described below, one mechanism underlying the interaction between REM sleep and nociceptive responses may be the modulation of acetylcholine release in the pontine reticular formation.

Acetylcholine release in the pontine reticular formation reaches its greatest levels during REM sleep, and direct administration of cholinomimetics to the pontine reticular formation causes large increases in REM sleep (reviewed in reference 1). Opioids disrupt REM sleep,25-26 in part, by inhibiting acetylcholine release in the pontine reticular formation.27-29 Morphine also inhibits the release of acetylcholine in the substantia innominata region of the basal forebrain,30 another important area involved in the regulation of arousal.

Preclinical studies have shown that pontine reticular formation administration of the GABAA receptor antagonist bicuculline enhances REM sleep.31,32 Dialysis delivery of bicuculline to the pontine reticular formation increases acetylcholine release,33 implying that endogenous GABA in the pontine reticular formation inhibits REM sleep, in part, by inhibiting acetylcholine release. Emerging data also demonstrate that pontine reticular formation
administration of morphine decreases GABA levels in the pontine reticular formation.14

Clinical studies have shown that intrathecal administration of adenosine can be efficacious for managing certain types of pain.35 Administering an adenosine A1 receptor agonist to the pontine reticular formation increases tail withdrawal latency to thermal stimulation36 and decreases acetylcholine release in the pontine reticular formation.37 In contrast, direct administration of an adenosine A2A receptor agonist to the pontine reticular formation increases acetylcholine release and increases REM sleep.38 The increase in REM sleep induced by pontine reticular formation delivery of an adenosine A2A receptor agonist can be blocked by the muscarinic receptor antagonist atropine.39 Taken together, these findings suggest that in the pontine reticular formation, adenosine A1 receptors inhibit acetylcholine release and decrease antinociceptive behavior, and adenosine A2A receptors increase acetylcholine release. The effects of pontine reticular formation administration of adenosine A2A receptor agonists on nociceptive behavior remain to be investigated. The Roehrs et al., findings encourage efforts to determine the effects of morphine on adenosine levels in regions of the pontine reticular formation that regulate REM sleep and modulate responses to nociceptive stimuli.

ACKNOWLEDGEMENTS

NIH grants MH45361, HL57120, HL65272, and the Department of Anesthesiology.

REFERENCES


