Anesthesiology 2009; 111:1175–6

Opiates, Sleep, and Pain

The Adenosinergic Link

BARRING a revolutionary breakthrough in pain management,[1,2] opiates will remain the mainstay of analgesia for the foreseeable future. For years, researchers chasing the Holy Grail of opiate pharmacology have sought to dissociate their desirable analgesic properties from their undesirable ones. In addition to their well-known respiratory depressant effects and potential for addiction, opiates also disrupt sleep architecture, blocking access to rapid eye movement sleep and to the deeper restorative stages of non–rapid eye movement sleep. Although all appreciate that the experience of pain impairs sleep, only recently has it been recognized that impaired sleep by itself can directly exacerbate pain by causing hyperalgesia (fig. 1). In the current issue of ANESTHESIOLOGY, Nelson *et al.*[3] investigate the mechanisms through which opiates perturb sleep and discover that opiates decrease adenosine levels in two critical areas that modulate arousal state: the pontine reticular formation (PRF) and the substantia innominata within the basal forebrain (BF). In so doing, their work suggests a promising strategy to break the insidious cycle of opiate use leading to poor sleep, worsened pain, and back to more opiate use.

Homeostasis between sleep and wakefulness is maintained through interactions among dozens of disparate nuclei spread along the entire neuroaxis. The neural circuits regulating arousal state form a flip-flop switch, in which at any given time only sleep- or wake-active neurons are firing. Arousal-promoting nuclei—located predominantly in the pons, midbrain, and basal forebrain—and sleep-promoting nuclei—located predominantly in the preoptic hypothalamus—mutually antagonize each other *via* reciprocal inhibitory connections. Therefore, in the absence of pathology, an organism is stably in a state of either wakefulness or sleep, with rapid and complete transitions occurring between states.[4] Although the exact nature of the switch underlying transitions between states of wakefulness and sleep remains controversial, adenosine is one neuromodulator that accumulates in essential regions during wakefulness and fulfills all criteria to qualify as an endogenous somnogen.[5]

Within the basal forebrain and the pontine reticular formation, fluctuating adenosine levels modulate propensity to sleep. The BF provides much of the cortical cholinergic excitatory input necessary for sensory awareness and cognition. Subsets of BF neurons fire preferentially during wakefulness. During sleep, these BF wake-active neurons are inhibited *via* endogenous adenosine acting directly on G protein–coupled adenosine A_1 receptors. Focally increasing the levels of adenosine in the BF is sufficient to promote sleep. Similarly, microinfusion of adenosine receptor agonists into the PRF promotes sleep by acting presynaptically to increase PRF cholinergic tone. However, the somnogenic effects of adenosine are not limited to actions in the BF or the PRF. Although many wake-active loci are inhibited by adenosine, sleep-promoting ventrolateral preoptic neurons are excited and fire more rapidly in response to adenosine *via* actions at A_{2a} receptors.

These very same sleep- and wake-active populations may also be responsible for the sleep-disrupting effects of opioids. Because opioids such as morphine have the interesting property of causing both sedation and wakefulness,[6] it should not be surprising that the effects of opioids on sleep are site, receptor, and dose dependent. The ventrolateral preoptic nucleus receives endogenous μ- and κ-opioidergic projections, with local administration of μ-receptor agonists impairing sleep and κ-opioid agonists promoting sleep.[7] The arousal-promoting BF and PRF have also been shown to be sensitive to opioids. Sleep disturbances after systemic delivery of opioids can be reproduced with microinjection of opioids into either the PRF[8] or the BF.[9] Therefore, a growing body of evidence indicates that opioids affect sleep by acting on both sleep- and wake-promoting systems. In the current issue, Nelson *et al.*[3] add to this by demonstrating that opioid-induced sleep disturbances likely hinge on local levels of adenosine in the PRF and the BF. Administration of either morphine or fentanyl into the PRF or BF results in a significant decrease in endogenous adenosine measured at the site of drug infusion. In the PRF, this decrease is dependent on μ-opioid receptor agonism, as coadministration of the opioid receptor antagonist naloxone abolished the decrease in adenosine. Furthermore, when morphine is coadministered with the adenosine deaminase inhibitor erythro-9-(2-hydroxy-3-nonyl)adenine (EHNA), the decrease in endogenous adenosine is prevented, raising the possibility that an

◆ This Editorial View accompanies the following article: Nelson AM, Battersby AS, Baghdoyan HA, Lydic R: Opioid-induced decreases in rat brain adenosine levels are reversed by inhibiting adenosine deaminase. ANESTHESIOLOGY 2009; 111:1327–33.

Accepted for publication August 20, 2009. Supported by the University of Pennsylvania Institute of Translational Medicine and Therapeutics grant, Philadelphia, Pennsylvania; grant Nos. GM077357 and HL007953 from the National Institutes of Health, Bethesda, Maryland; and the Department of Anesthesiology and Critical Care, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

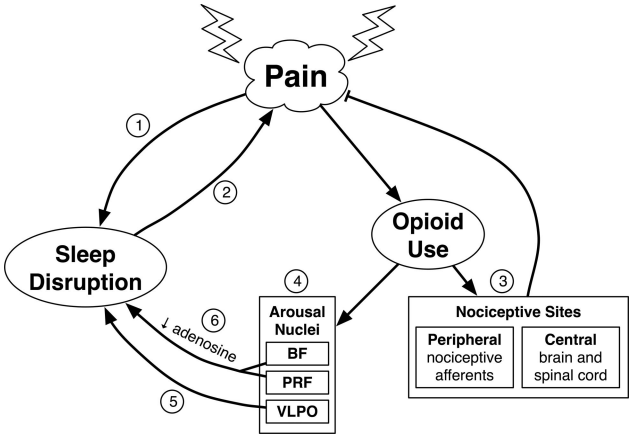

Fig. 1. Schematic cartoon depicting the interactions among pain, opiates, and sleep along with the proposed role of adenosine. (*1*) The experience of pain is known to impair sleep. (*2*) Recently, it has become clear that sleep disruption can directly exacerbate pain. (*3*) The use of opiates to alleviate pain leads to desired analgesia as well as (*4*) undesired side effects on nuclei capable of modulating arousal, such as the substantia innominata of the basal forebrain (BF), the pontine reticular formation (PRF), the ventrolateral preoptic nucleus (VLPO), and other sites. (*5*) It is unknown whether opiates modulate endogenous adenosine levels in sleep-active loci such as the VLPO or in other wake-active loci. (*6*) As reported in the current issue of the Journal, in the BF and the PRF, such effects are likely mediated by a focal decrease in endogenous adenosine. Although not shown, it is worth noting that systemic infusions of adenosine elicit analgesia as evidenced by reduced opioid requirements in animal models as well as in double-blinded clinical studies. However, the fraction of adenosine's analgesic properties that arises from its somnogenic effects awaits evaluation. Conversely, caffeine, which antagonizes the actions of adenosine, is the world's most widely used psychostimulant. One might rightly question whether caffeine use and ensuing sleep disruption leads to opioid dose escalation and hyperalgesia.

adenosine-based adjuvant therapy might reduce the sleep disturbance-related side effects of opioids. The ability of EHNA to prevent opioid-induced decreases in adenosine coupled with the previous findings that adenosine concentration affects sleep architecture suggests that if the opioid-dependent reduction of adenosine is blocked, sleep disturbances may be reduced. Experimental confirmation of this important hypothesis with subsequent assessment of nociceptive thresholds in animals receiving local injections of opiates and adenosine deaminase inhibitors in the PRF and/or BF will hopefully follow.

The current work underscores the importance of understanding arousal state control to improve pain management. Although the quest to counter the troubling and undesirable effects of opiates has seen many promising leads,[10] the implicit strategy outlined in this issue raises a slew of clinically relevant questions (fig. 1) while offering the possibility of reducing both the requirements for opiates and the exacerbation of pain after opiate-induced disruptions of natural sleep. Of course, while the ultimate success or failure of the plan of Nelson *et al.* to inhibit adenosine deaminase in PRF and/or BF will evolve over time, its mission and direction are both noble and soundly grounded in basic science. May their quest be fruitful.

Jason T. Moore, B.S.,* Max B. Kelz, M.D., Ph.D.† *Departments of Neuroscience, Anesthesiology and Critical Care, Center for Sleep and Respiratory Neurobiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. †Department of Anesthesiology and Critical Care, Mahoney Institute for Neurological Science, Center for Sleep and Respiratory Neurobiology, Institute for Translational Medicine and Therapeutics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. kelzma@uphs.upenn.edu

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