Opiates, Sleep, and Pain

The Adenosinergic Link

BARRING a revolutionary breakthrough in pain management, 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. 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. 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.

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 A1 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 A2a 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, 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. 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 or the BF. 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. 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
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, 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.

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