

# Volatile Anesthesia Does Not Satisfy Rapid Eye Movement Sleep Debt

A common statement made to patients before they undergo a general anesthetic is, “We will watch you very carefully while you are asleep.” The relationship between states of sleep and anesthesia raises clinically relevant questions. For example, sleep deprivation enhances pain, worsens obstructive sleep apnea, impairs immune function, and contributes to cognitive decline.<sup>1</sup> If a patient is sleep deprived, and if anesthesia is similar to sleep, will the sleep debt be diminished by anesthesia? In addition to being homeostatically regulated, mammalian sleep occurs with a prominent circadian rhythm. If a general anesthetic is administered during a patient’s normal sleep time, will the patient be less sleepy after the anesthetic, as if he had maintained his normal sleep cycle?

In a report published this month by Pick *et al.*,<sup>2</sup> the authors demonstrate that after a 6-h general anesthetic with sevoflurane, isoflurane, or halothane, mice exhibited a rapid eye movement (REM) sleep deficit, followed by a REM sleep rebound. The study also reports a nonrapid eye movement (NREM) sleep debt and rebound only after halothane. Pick *et al.* used an ingenious experimental design that made it possible to evaluate the effects of time, light-dark cycle, type, and duration of anesthetic agent on states of wakefulness, NREM sleep, and REM. Their results documented significant main effects on the temporal organization of sleep and wakefulness caused by both duration and type of anesthetic. Analogous to the oxygen debt of exercise being compensated by an increase in minute ventilation, the Pick *et al.* results support the interpretation that the ability of volatile anesthetics to satisfy the homeostatic drive for sleep differs as a function of anesthetic agent and the NREM or REM phase of sleep. Pick *et al.* also raise the intriguing suggestion that the duration of anesthesia or sleep/wake states is monitored by



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some, as yet unknown, control systems. Their findings imply that the brain stores this information regarding the temporal organization of behavioral states and, after recovery from anesthesia, reactivates neuronal networks that generate the appropriate amount and type of sleep needed to reestablish homeostatic balance.

States of sleep are different from states of anesthesia. Apply a painful stimulus and the individual who is asleep will awaken. One goal of a general anesthetic, of course, is to eliminate responsiveness to external stimuli. During sleep, humans cycle approximately every 90 min between the REM and NREM phases of sleep. During REM sleep, which is characterized by dreaming and skeletal muscle atonia, there are rapid eye movements, increases in brain metabolic and electrical activity, heart and respiratory rate irregularities, erection of the clitoris or penis, and oscillations in a large number of hormones.<sup>1</sup> In contrast, one of the goals of balanced anesthesia is to maintain prolonged intervals of stable autonomic function.

In this last decade, there has been much progress documenting the similarities and differences between sleep and anesthesia. As recently reviewed,<sup>3</sup> there is consensus that states of anesthesia, like sleep, are actively generated by multiple brain regions, overlapping networks, and a humbling complexity of neurotransmitters and signal transduction cascades. Studies of sleep and anesthesia benefit from a viable interaction between clinical and basic research. Clinical concerns have led to interesting basic studies. Do patients in an Intensive Care Unit who are sedated for long periods get enough sleep? That question influenced a study in which sleep-deprived rats that received either propofol or isoflurane lost the righting reflex more quickly and also took longer to recover from anesthesia.<sup>4</sup> Additional studies found that sleep-deprived rats that received propofol showed reversal of both REM and NREM sleep debt.<sup>5</sup>

Illustration: J. P. Rathmell.

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Interestingly, the Pick *et al.* data from mice are consistent with recent data obtained from other studies. For example, rats deprived of REM sleep for 24 h that received isoflurane for 4 h had the same amount of REM sleep rebound as rats that were allowed to sleep *ad libitum*.<sup>6</sup> When rats were deprived of REM and NREM sleep and administered 6 h of sevoflurane, signs of NREM sleep deprivation were reduced to half the time of rats that did not receive sevoflurane anesthesia. REM sleep debt was not reduced by sevoflurane anesthesia, and sevoflurane induction time was significantly reduced in sleep-deprived rats.<sup>7</sup>

The Pick *et al.* findings raise an interesting historical point regarding isoflurane. Most anesthesiologists today probably did not practice anesthesia during the early 1980s, when isoflurane was introduced. At that time, excluding enflurane, halothane was the most commonly used anesthetic. Recovery after isoflurane is remarkably fast compared with halothane, in large part because the metabolism of halothane releases bromide. The increase in bromide is related to minimum alveolar concentration hours of exposure, as the rise in bromide approaches sedative concentrations. In an editorial published in this journal in 1976, Nicholas Greene summarized other studies showing elevation of plasma bromide levels after halothane.<sup>8</sup> He noted that prolonged sedation can be seen after halothane anesthesia and that the peak levels of plasma bromide are in the range that can cause sedation.<sup>9</sup> The fact that recent studies searching for a relationship between sleep and anesthesia have not included halothane is probably because halothane is no longer used in many countries, including the United States.

Going forward, more work is needed on the clinically relevant topic of sleep and anesthesia. The study limitations acknowledged by Pick *et al.* point to an exciting opportunity for bench-to bedside investigations designed to document anesthetic effects on human sleep. Most patients who receive

anesthesia also have pain on awakening, and sleep is significantly disrupted both by pain and by the use of opioids to treat pain.<sup>10</sup> The excellent study by Pick *et al.* encourages future research aiming to elucidate the contributions of pain to the sleep-altering effects of anesthetic molecules.

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