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Sleep Deprivation Potentiates the Onset and Duration of Loss of Righting Reflex Induced by Propofol and Isoflurane

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Background: **Sleep and anesthesia differ physiologically but produce a similar loss of responsiveness to environmental stimuli. Recent data suggest that neuronal networks active in naturally occurring sleep also play a role in the anesthetized state. Changes in the propensity to sleep may then modify the response to anesthetic agents. The authors tested the hypothesis that sleep-deprived rats would require less anesthetic than rested rats to achieve a similar loss of responsiveness.**

Methods: **Rats were subjected to a 24-h period of either sleep deprivation or *ad libitum* activity. Sleep deprivation was produced by placing rats on a disk that rotated when sleep was detected by electroencephalographic and electromyographic (EEG, EMG) monitoring. A fixed dose of anesthetic agent was then administered, and the time required to induce loss of righting reflex was measured. Anesthetic administration was then stopped, and the time to recovery measured. All rats received both treatments separated by 7 days.**

Results: **Sleep deprivation reduced the time to loss of righting reflex by 40% for propofol ($P < 0.025$) and 55% for isoflurane ($P < 0.025$) and prolonged the time to recovery. In a separate control experiment, exposure to the deprivation environment but with disk rotation modified to allow adequate sleep did not affect the response to anesthetic administration.**

Conclusions: **Sleep deprivation significantly potentiated the ability of inhaled and intravenous anesthetic agents to induce a loss of righting reflex. These results support the hypothesis that neuronal networks active in sleep are also involved in the anesthetized state and suggest that sleep deprivation may partly explain the variability in patient response to anesthesia.**

UNLIKE general anesthesia, naturally occurring sleep is readily reversible with external stimuli, occurs spontaneously, and is associated with discrete patterns of electroencephalographic (EEG) and dream activity. A shared characteristic of sleep and anesthesia, however, is a reduced responsiveness to environmental stimuli. Such similarities have led to hypotheses that the behavioral state characteristic of anesthesia may be produced in part by neuronal networks normally involved in naturally occurring sleep.[1] Labeled positron-emission tomography (PET) scans of the brain during anesthesia, for example, have demonstrated regional changes in brain activity similar to those that occur during sleep.[2] The bispectral index, a processed EEG parameter originally developed to monitor depth of anesthesia, appears to track the onset and "depth" of sleep in humans without sleep disorders as well.[3,4] Finally, anesthetic agents have been shown to increase sleep when administered into brain regions known to regulate sleep.[5] Together, these observations are consistent with a hypothesis that the loss of responsiveness induced by anesthetic agents occurs in part by activating existing regulatory mechanisms normally involved in naturally occurring sleep.

One important difference between sleep and anesthesia is the ability of sleep to fulfill an essential biologic need. Although no physiologic need for anesthesia has yet been defined, sufficiently prolonged loss of sleep results in death in animals.[6] In humans, even short periods of sleeplessness dramatically increase the drive to sleep and produce clearly defined alterations in alertness and ability to concentrate.[7] These alterations strongly suggest an internal regulatory process that modifies the propensity to sleep and provide evidence that the sleep-deprived brain differs physiologically from the rested brain.

A logical consequence of mechanistic similarities between anesthetic and sleep-induced unresponsiveness would be that changes in the propensity to sleep might modify the response to anesthetic agents. The increased drive to sleep resulting from sleep deprivation, for example, should facilitate the ability of anesthetic agents to reduce responsiveness to environmental stimuli. To test this hypothesis, we used a well-established disk-over-water method[8] to induce sleep deprivation in a rat model. We then administered either isoflurane or propofol and compared the time to loss of righting reflex and spontaneous movements and the time to recovery with values obtained with rested rats.

Methods

After approval from the Animal Care Committee at our institution and in accordance with animal care guidelines, male, 250–300 g, Sprague-Dawley rats were anesthetized with intraperitoneal ketamine (70 mg/kg) and xylazine (6 mg/kg). An intravenous catheter (IITC, Woodland Hills, CA) was implanted into the internal

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jugular vein and tunneled to exit through the scalp. Five stainless steel screws were implanted through the skull to serve as dural EEG electrodes, and two electromyographic (EMG) electrodes were implanted in the neck musculature. All electrodes were then connected to an Amphenol socket with Teflon-coated stainless steel wire and cemented in place with dental acrylic. After the surgical procedure, rats were allowed to recover for 7 days in a temperature- and light-controlled colony with free access to food and water. Ambient temperature was 21–24°C, and lights were kept on between 8:00 AM and 8:00 PM and off otherwise.

After the recovery period, rats were subjected to either sleep deprivation or *ad libitum* activity for 24 h. To minimize circadian variability, the sleep deprivation and *ad libitum* activity periods were timed to begin and end at 12:00 noon. Rats were sleep deprived using the disk-over-water method.[8] Specifically, rats were placed on a 45-cm diameter disk suspended over a pan of water with continuous computerized EEG and EMG monitoring. On detecting a sleep state, the computer rotated the wheel at a rate of 3 revolutions/min, causing the rat to wake up and walk to avoid falling into the water. Once the rat awakened, the rotation stopped. Rats receiving *ad libitum* activity were exposed to the same environment, except that a platform was placed over the wheel to eliminate the water hazard and effects of wheel rotation. EEG and EMG data were divided into 30-s epochs and scored by a previously validated computer algorithm[9] as waking, rapid eye movement (REM), or non-REM sleep. Random segments of the EEG were scored by hand to verify accuracy of the computerized system.

After the 24-h intervention (sleep deprivation or *ad libitum* activity), an intravenous infusion of propofol was begun at a rate of 800 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The infusion rate was chosen to produce our behavioral end-point in sufficient time to detect an accelerated response with sleep deprivation. Rats were gently prodded or positioned on their back or side every 15–30 s to determine their vigilance state. When no righting attempts or movements in response to repeated positioning on their back or side were observed, the infusion was discontinued. Rats were then gently prodded every 15 s to determine onset of recovery, defined as the return of righting reflex. An investigator blinded to the deprivation history of the rat determined the time from initiation of the propofol infusion to loss of righting reflex and from discontinuation of the infusion to recovery. Rats were then returned to their temperature- and light-controlled colony. After a 7-day recovery period, the above intervention was repeated, with each rat receiving the opposite treatment (24-h sleep deprivation or *ad libitum* activity). All rats received both treatments in random order.

In a second, separate experiment, the response to inhaled anesthetic agents was tested. Ten additional rats underwent surgery and recovery as described above, minus the placement of intravenous catheters. Rats were then subjected either to sleep deprivation or *ad libitum* activity as described above. Immediately after the intervention period, rats were placed in a 13 cm × 13 cm × 23 cm clear Lucite box fitted with a gas inlet and outlet. A compressed oxygen tank and a standard isoflurane vaporizer (Cyprane Ltd, Keighley, England, UK) were used to direct a constant 3 l/min flow of oxygen containing 1.1% isoflurane (Abbott Labs, Chicago, IL) through the box. The isoflurane concentration was also chosen to allow ready detection of an accelerated response with sleep deprivation. The isoflurane concentration was monitored constantly using a Puritan-Bennett Datex model 254 airway gas monitor (Puritan Bennett, Carlsbad, CA) calibrated before each use with a reference gas containing 1.5% isoflurane (Biochem Int, Waukesha, WI). Time to loss of righting reflex with repeated repositioning and time to recovery were measured as described above. The righting reflex was tested by rotating the box gently and by observing the rat to verify that no attempt to achieve the upright position was made. As with rats given propofol, all received both treatments separated by 7 days.

To verify that exposure to the disk-over-water apparatus itself did not play a role in altering the response to anesthetic agents, two additional control experiments (one for each anesthetic tested) were performed. In each, rats were subjected to either *ad libitum* activity or to a stimulus equivalent to that used to produce sleep deprivation. The equivalent stimulus was produced by first calculating the total amount of wheel rotation required over 24 h to produce sleep deprivation in the propofol and isoflurane groups. The wheel was then reprogrammed to turn on at the beginning of each hour, deliver a fixed amount of wheel rotation, and turn off for the remainder of the hour so that the 24-h total amount of wheel rotation would equal the average amount required to produce sleep deprivation in the original rats.

As controls for each anesthetic agent (propofol and isoflurane), 10 rats were subjected after surgery and recovery periods to either *ad libitum* activity or the preprogrammed "timed" wheel rotation described above. Rats were first acclimated for 24 h to the testing environment to normalize sleep patterns. After the intervention period, the anesthetic was administered, and the time to loss of righting reflex and recovery measured as described previously. All rats received both treatments (timed wheel rotation or *ad libitum* activity) in random order. Twenty rats were tested, 10 with propofol and 10 with isoflurane.

Data Analysis

Overall, four separate experiments were performed (fig. 1). In each, the response to one of two anesthetic agents (propofol or isoflurane) was observed after one of

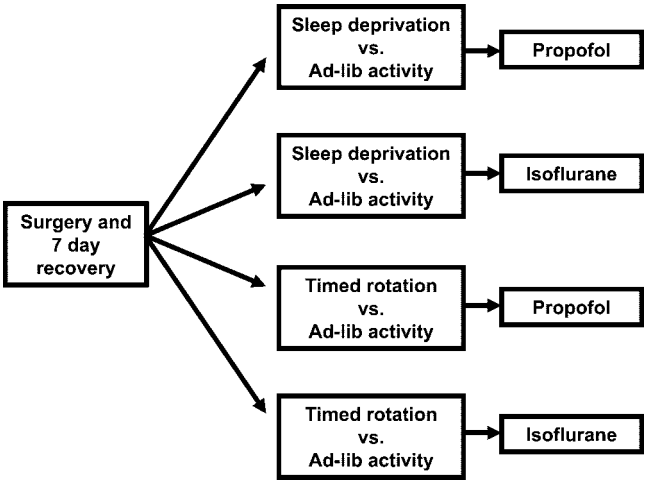

Fig. 1. Experimental design is shown. Four separate experiments were performed. Either sleep deprivation or timed wheel rotation were compared with *ad libitum* activity. For each comparison, time to loss of righting reflex was determined with either propofol or isoflurane.

two behavioral interventions (sleep deprivation *vs. ad libitum* activity or "timed" wheel rotation *vs. ad libitum* activity). Data collected included weights and ages, REM, non-REM, and total sleep times for rats during sleep deprivation and *ad libitum* activity periods, and cumulative duration of wheel rotation for all groups. Time to loss of righting reflex and time to recovery for all groups were collected. All data were compared using a paired Student *t* test with significance at *P* less than 0.05. Experiments involving timed wheel rotation were performed separately because calculating the average duration of wheel rotation necessary to produce sleep deprivation required first completing the deprivation phase of the study.

Results

Average weights and ages for rats in all groups were similar (table 1). Analysis of variance revealed no effect of age or weight on time to loss of righting reflex or on recovery. Rats allowed *ad libitum* activity slept 52.2 ± 3.4% of the 24-h period (3.4 ± 1.3% REM sleep), a figure consistent with previous data.[8] The disk-over-water protocol reduced total sleep to 13.9 ± 4.4% (fig. 2) and

Table 1. Weights and Ages of Rats in Each Arm of the Study

	Propofol Group		Isoflurane Group	
	Sleep Deprivation	Timed Wheel Rotation	Sleep Deprivation	Timed Wheel Rotation
Age (days)	68.9 ± 8.8	84.0 ± 9.5	95.4 ± 15.8	83.8 ± 10.4
Weight (g)	302.2 ± 27.2	319.9 ± 18.3	337.8 ± 36.7	301.8 ± 18

Four separate experiments are represented: sleep deprivation *versus* ad-lib activity for both propofol and isoflurane and timed wheel rotation *versus* ad-lib activity for both propofol and isoflurane. All values are expressed as mean ± standard deviation.

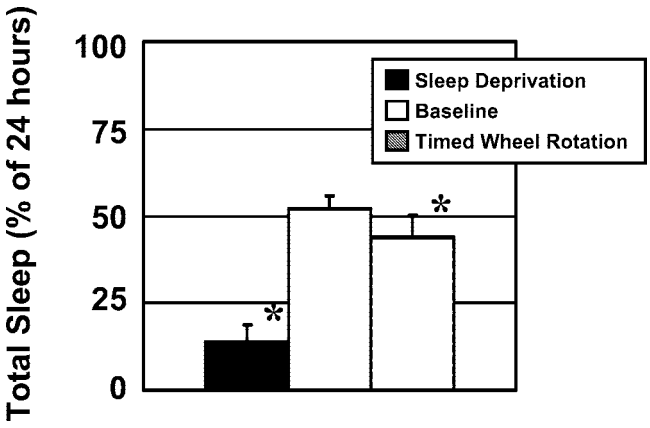

Fig. 2. Total sleep times in rats subjected to sleep deprivation, *ad libitum* activity, or timed wheel rotation conditions (see text). Values are expressed as mean % of 24-h recording time ± SD. Asterisks denote $P < 0.025$ for sleep during sleep deprivation and timed wheel rotation when compared with *ad libitum* activity.

reduced REM sleep to 0%. This degree of sleep deprivation was achieved with an average of 335 ± 136 min (approximately 5.5 h) of wheel rotation over the 24-h deprivation period. To duplicate this duration of wheel rotation in the control group, the wheel was reprogrammed to rotate continuously 14 min out of every hour (336 min total). A 24-h exposure to this timed wheel rotation regimen slightly reduced total sleep to 44 ± 3.2% of the 24-h period (2 ± 0.9% REM sleep). Although all rats received two treatments separated by 7 days (either sleep deprivation or *ad libitum* activity followed by administration of anesthesia), the sequence of treatments did not affect the amount of either baseline sleep or wheel rotation required to produce sleep deprivation.

When compared with a 24-h period of *ad libitum* activity, a 24-h period of sleep deprivation reduced the time to loss of righting reflex and spontaneous movement with propofol administration from 938 ± 154 s to 567 ± 117 s ($P < 0.025$). When 1.1% isoflurane was used, sleep deprivation reduced the time to loss of righting reflex from 963 ± 154 to 448 ± 129 s ($P < 0.025$; fig. 3). The time to recovery was also significantly increased for rats receiving propofol ($P < 0.025$) and isoflurane ($P < 0.025$; fig. 4). The magnitude of the sleep deprivation effect was similar for both anesthetic agents. Times for sleep deprivation and *ad libitum* activity groups did not depend on whether rats had received the sleep-deprivation or the *ad libitum* activity treatment first. Sleep-deprived rats did not behave differently immediately after recovery, responding similarly to cage tapping and handling as rested rats.

When compared with *ad libitum* activity, a 24-h period of timed wheel rotation (14 min out of every hour) reduced total sleep slightly (from 52.2% to 44%) and did not change the time to loss of righting reflex (figs. 3 and 4). Rats exposed to timed wheel rotation did not differ in

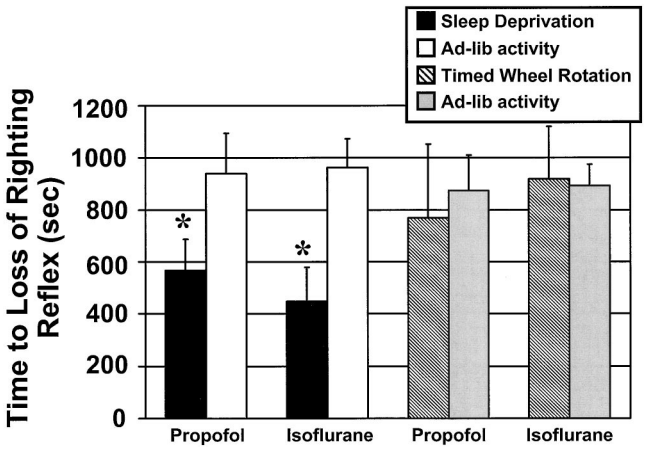

Fig. 3. Comparison of times required to produce a loss of righting reflex with either propofol or isoflurane is shown. Four separate experiments are represented: effects of isoflurane or propofol after either sleep deprivation or *ad libitum* activity, and effects of isoflurane or propofol after either timed wheel rotation or *ad libitum* activity. Values are expressed as mean number of seconds required to reach the behavioral end-point ± SD. Asterisks denote $P < 0.025$ for sleep deprivation when compared with *ad libitum* activity.

appearance or behavior from rats exposed to either *ad libitum* activity or the deprivation paradigm.

Discussion

Although general anesthesia is often portrayed as "going to sleep," descriptive characteristics of naturally occurring sleep differ significantly from those of general anesthesia.[10] Key components of general anesthesia include amnesia, analgesia, hypnosis, and muscle relaxation.[11] In contrast, sleep is characterized by full reversal with sufficient external stimuli, a characteristic ultradian pattern of EEG activity, and fulfillment of a fundamental biologic need.[10]

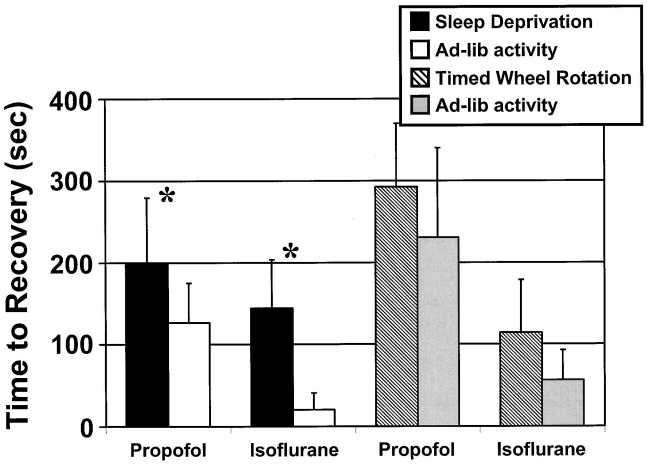

Fig. 4. Comparison of times required for recovery of righting reflex after cessation of anesthetic administration. Four separate experiments are represented: recovery from isoflurane or propofol after either sleep deprivation or *ad libitum* activity, and recovery from isoflurane or propofol after either timed wheel rotation or *ad libitum* activity. Values are expressed as mean number of seconds required to reach the behavioral end-point ± SD. Asterisks denote $P < 0.025$ for sleep deprivation when compared with *ad libitum* activity.

A shared component of general anesthesia and sleep is a reduced responsiveness to external, non-painful stimuli that are normally arousing. Although little is known about how either state generates or maintains this decreased responsiveness, some have hypothesized that drugs capable of producing general anesthesia may do so at least in part by duplicating activities of specific brain regions important in initiating or maintaining sleep.[1] PET and metabolic scanning[2] and microelectrode recordings of thalamic relay neuronal activity[12] demonstrate reductions in thalamic activity during anesthesia. These changes in thalamic activity simulate an important characteristic of naturally occurring sleep.[13] Preliminary data suggest that dexmedetomidine administration may decrease noradrenergic activity in the locus ceruleus, an event that also occurs during sleep.[14] Finally, microadministration of the intravenous anesthetic propofol into the medial preoptic area in rats increases sleep in a dose-dependent fashion.[5] In light of these observations suggesting similarities between sleep and anesthesia, interventions, such as sleep deprivation, that increase the propensity to sleep may reasonably enhance the ability of anesthetic agents to induce a state of decreased environmental responsiveness.

We found that in a rat model, a 24-h period of sleep deprivation administered using the disk-over-water paradigm significantly enhanced the ability of isoflurane and propofol to reduce responsiveness to external stimuli. When a constant dose of either anesthetic agent was administered, sleep-deprived rats lost their righting reflex and ability to respond to non-painful prodding significantly sooner than rested rats. The time to recovery once anesthetic administration had been terminated was also prolonged in deprived rats. When a stimulus equivalent to that used for sleep deprivation was applied in a way that allowed sleep, no potentiating effect was observed for either anesthetic agent. These findings indicate that sleep deprivation alone can increase susceptibility to anesthetic agents and support the hypothesis that general anesthetic agents and naturally occurring sleep may share common neurobiological mechanisms.[1]

How might sleep deprivation potentiate this end-point of anesthetic action? Although effects of sleep deprivation at the molecular level are incompletely understood, regional increases in neurotransmitter concentration have been observed during sleep deprivation and may be partly responsible. Systemic administration of adenosine, for example, potentiates hypnosis induced by intravenous anesthetic agents[15] and reduces intraoperative anesthetic requirements.[16] Extracellular adenosine concentrations in the basal forebrain (BF) of rats and cats increase with sleep deprivation and decrease with recov-

ery sleep.[17] Direct application of adenosine reuptake inhibitors or adenosine itself into the BF reduces the discharge rate of BF neurons and increases sleep,[17] whereas the adenosine A1 antagonist cyclopentyltheophylline produces the opposite effect.[18] Because BF output plays an important role in normal arousal,[13] accumulation of adenosine at this site may reduce arousability to external stimuli and potentiate anesthetic action. Alternatively, sleep deprivation may result in accumulation of a benzodiazepine-like sleep factor. Such a hypothesis has been suggested previously,[19] and benzodiazepines are known to potentiate effects of inhaled anesthetic agents.[20]

We chose as our end-point for anesthetic action in the rat the loss of response to prodding and of attempts to self-right despite repeated positioning on the back or side. As sleeping rats retain righting reflex and response to prodding, these criteria allowed us to exclude sleep as a confounding behavioral end-point. To minimize bias in determining the end-point for anesthetic administration, all observers were blinded to the deprivation history of the rat. We did not use a more traditional measure of anesthetic potency such as minimum alveolar concentration (MAC) for several reasons. First, determination of MAC can require a period of anesthesia several hours long. Although it is unknown to what degree sleep "debt" built up during sleep deprivation can be discharged in the anesthetized state, rats appear to be able to discharge accumulated sleep debt during prolonged (12-h) sedation with propofol.[21] The extended period of anesthesia required to accurately determine MAC may have allowed some recovery from sleep deprivation, introducing variability in the "dose" of deprivation. In addition, MAC is unchanged by spinal cord transaction in rats[22] and thus may represent primarily effects of anesthetic agents on spinal cord reflex pathways. Although successful righting is in part also spinally mediated, righting attempts occur despite transections as high as the postcollicular level.[23] Finally, MAC cannot be determined with intravenous agents such as propofol.

In any study examining effects of sleep deprivation, effects of sleep deprivation should ideally be separated from effects of the stimuli used to produce sleep deprivation. In this respect, the disk-over-water paradigm used in this study has been validated as able to produce near-total sleep deprivation while allowing nearly normal amounts of sleep when applied randomly.[24] In our rats, approximately 14 min of wheel rotation out of every hour resulted in a nearly 90% efficacy in preventing sleep. This duration of rotation translated into 1.0 km/d, a distance readily exceeded by rats provided with an activity wheel.[25] When applied in a predictable fashion, the same duration of rotation only slightly reduced sleep and did not significantly alter the response to anesthetic administration. It is thus unlikely that fatigue or environmental stress was responsible for our observations.

We did not measure end-tidal isoflurane levels or blood levels of propofol in this study. It is thus possible that our observations may have been partly the result of effects of sleep deprivation on pharmacokinetic properties of isoflurane and propofol. Dehydration during the deprivation period, for example, may have altered drug disposition similarly with both anesthetic agents. We believed, however, that such effects were unlikely to fully explain our findings. First, the magnitude and direction of the sleep deprivation effect was similar for isoflurane and propofol. To ascribe these effects solely to pharmacokinetic changes induced by sleep deprivation would require that deprivation affect the uptake and distribution of propofol and isoflurane equally. Because sleep deprivation with the disk-over-water paradigm typically induces polyphagia,[24] significant hypovolemia probably did not occur. Second, no known mechanism links sleep deprivation to a pharmacokinetic change large enough to produce the results we observed. In normal rats, a continuous infusion of propofol produces increasing blood levels for at least 30 min, indicating a reasonable correlation between blood levels and infusion duration.[26] Finally, we only deprived rats of sleep for 24 h. With the disk-over-water paradigm, sleep deprivation results ultimately in death, but it requires approximately 2 weeks of continuous application to do so and is preceded by marked physical changes.[24] In our study, sleep-deprived rats were indistinguishable in appearance from rested rats and could be identified only by an increased propensity to sleep and an increased susceptibility to anesthetic agents.

Our results imply that adequacy of preoperative sleep may affect perioperative management. In addition to altering anesthetic potency, sleep deprivation in humans affects respiratory muscle strength,[27] adrenergic state, and cortisol secretion.[28] Because the relationship between these effects and the "dose" of deprivation is unclear, a 24-h duration of sleep deprivation in the rat cannot be correlated to an equivalent duration of sleeplessness in humans. Nevertheless, in one preliminary report, inadequate preoperative sleep ($<$ 80% of baseline) resulted in longer recovery and increased use of pain medicines after outpatient surgery.[29] In otherwise healthy men, four consecutive nights of restricted sleep (5 h/night) significantly enhanced the sedative effects of alcohol.[30] In children undergoing radiologic procedures, sleep deprivation can inhibit effects of chloral hydrate.[31] These studies suggest that even mild sleep deprivation may impact anesthetic care. Finally, enhanced respiratory depressant effects of benzodiazepines and narcotics have been noted in patients with sleep apnea.[32,33] Overall, these data are consistent with an effect of sleep adequacy on the pharmacology of several drugs relevant to anesthesiologists and suggest that sleep loss may be

partly responsible for the variability in patient response to anesthetic agents.

In conclusion, we report a significant enhancing effect of sleep deprivation on the ability of isoflurane and propofol to reduce responsiveness to external stimuli in a rat model. When compared with rested rats, administration of either anesthetic in sleep-deprived rats resulted in more rapid loss of righting reflex and a delayed recovery. Our results suggest that mechanisms involved in the regulation of naturally occurring sleep can affect anesthetic potency and increase the possibility that naturally occurring sleep and the anesthetized state may act *via* common neurophysiologic pathways. Further work is needed to clarify the mechanisms linking sleep deprivation and anesthetic action.

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