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Isoflurane Anesthesia Does Not Satisfy the Homeostatic Need for Rapid Eye Movement Sleep

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Abstract

BACKGROUND—Sleep and general anesthesia are distinct states of consciousness that share many traits. Prior studies suggest that propofol anesthesia facilitates recovery from rapid eye movement (REM) and non-REM (NREM) sleep deprivation, but the effects of inhaled anesthetics have not yet been studied. We tested the hypothesis that isoflurane anesthesia would also facilitate recovery from REM sleep deprivation.

METHODS—Six rats were implanted with superficial cortical, deep hippocampal, and nuchal muscle electrodes. Animals were deprived of REM sleep for 24 hours and then (1) allowed to sleep ad libitum for 8 hours or (2) were immediately anesthetized with isoflurane for a 4-hour period followed by ad libitum sleep for 4 hours. The percentage of REM and NREM sleep after the protocols was compared with similar conditions without sleep deprivation. Hippocampal δ activity during isoflurane anesthesia was also compared with δ activity during REM sleep and active waking.

RESULTS—Recovery after deprivation was associated with a 5.7-fold increase ($P = 0.0005$) in REM sleep in the first 2 hours and a 2.6-fold increase ($P = 0.004$) in the following 2 hours. Animals that underwent isoflurane anesthesia after deprivation demonstrated a 3.6-fold increase ($P = 0.001$) in REM sleep in the first 2 hours of recovery and a 2.2-fold increase ($P = 0.003$) in the second 2 hours. There were no significant differences in REM sleep rebound between the first 4 hours after deprivation and the first 4 hours after both deprivation and isoflurane anesthesia. Hippocampal δ activity during isoflurane anesthesia was not affected by REM sleep deprivation, and the probability distribution of δ events during anesthesia was more similar to that of waking than to REM sleep.

CONCLUSION—Unlike propofol, isoflurane does not satisfy the homeostatic need for REM sleep. Furthermore, the regulation and organization of hippocampal δ events during anesthesia are unlike sleep. We conclude that different anesthetics have distinct interfaces with sleep.

General anesthesia and sleep are states of consciousness that share numerous traits, including hypnosis, amnesia, and immobility.[1] Accordingly, the investigation of anesthetic mechanisms and sleep mechanisms has converged.[2] This convergence, however, has

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AUTHOR CONTRIBUTIONS GAM designed and conducted the experiments, interpreted the results, and was the primary author of the manuscript. WJL conducted the experiments; LBM, AJW, and AMT assisted in the experiments and analysis of sleep electrophysiologic results. WS and UL performed the analysis of hippocampal δ distribution. GRP helped interpret results and provided experimental guidance. All authors contributed to the production of the manuscript.

focused largely on non–rapid eye movement (NREM) sleep rather than rapid eye movement (REM) sleep. In animal models, REM sleep can be characterized electrophysiologically by (1) low amplitude, desynchronized cortical waveforms, (2) synchronized hippocampal θ activity, and (3) muscle atonia.[3] The IV drug urethane is the only general anesthetic that has been suggested to mimic sleep cycles with periods of NREM- and REM-like activity assessed by electroencephalography (EEG), as well as by cholinergic and monoaminergic neuropharmacology.[4] Because urethane is carcinogenic, it is used only in animal models and thus has no direct relationship to clinical anesthesiology.[5] However, clinically relevant IV anesthetics such as propofol do seem to satisfy the brain's homeostatically regulated need for REM sleep, because there is no observed REM rebound after prolonged propofol infusion.[6] Furthermore, there are no differences in recovery from sleep deprivation between propofol anesthesia and ad libitum sleep.[7] Collectively, these data suggest a neurophysiologic or neurochemical trait that is common to or functionally equivalent during both IV anesthesia and REM sleep.

No underlying mechanisms of REM sleep satiation during anesthesia have been elucidated, in part because there are a number of impediments to studying REM sleep–like traits expressed during general anesthesia. First, there is no obvious neocortical EEG correlate to REM sleep in the anesthetized state. Second, mobility is suppressed during general anesthesia by spinal mechanisms[8] that would mask the periodic supraspinal atonia mechanisms associated with REM sleep.[9,10] Finally, other physiologic perturbations observed during REM sleep, such as heart rate, arterial blood pressure, or respiratory variability,[11] may also be confounded by general anesthetic effects.

What is also unclear is whether inhaled drugs such as isoflurane are capable of repaying REM sleep debt as has been suggested for propofol. It has been demonstrated that isoflurane anesthesia induces transient alterations in sleep architecture in humans[12] and that total sleep deprivation before isoflurane induction is associated with reduced anesthetic requirement in animals.[13] However, there have been no studies of recovery from sleep deprivation during inhaled anesthesia. Tung et al.[7] discussed 3 possibilities for the relationship of anesthesia and sleep requirements. First, general anesthesia could be permissive for normal sleep processes to occur, which would allow repayment of sleep debt during general anesthesia. Second, general anesthesia could, similar to the waking state, allow for the further accumulation of sleep debt. Third, general anesthesia could be a distinct state in which sleep debt is neither accumulated nor repaid. The findings of Tung et al.[7] suggest that the effects of propofol are closest to the first condition, i.e., a state conducive to sleep recovery.

Assessing whether inhaled anesthetics such as isoflurane have a similar sleep recovery profile is clinically important. As one example, critical care patients experience sleep deprivation or fragmentation[14] and frequently present for surgical interventions. In patients with disorders such as obstructive sleep apnea, determining which anesthetics best satisfy the need for sleep may potentially attenuate postoperative apnea and hypoxemia associated with sleep rebound phenomena.[15] This is especially true in patients receiving analgesia from epidural catheters or peripheral nerve blocks, because there may be less postoperative suppression of REM sleep with the decreased use of IV opiates.[16] Beyond the immediate perioperative period, REM sleep rebound has been found to occur in the second or third night after surgery, with potential for adverse sequelae.[17,18]

The objectives for this investigation were (1) to test the hypothesis that isoflurane anesthesia facilitates recovery from sleep deprivation as well as natural sleep and (2) to study neurophysiologic features that may be common to both states. REM sleep was the focus of this investigation because (1) it shares many traits with general anesthesia,[1] (2) it is a state of cortical activation[3] and its relationship to general anesthesia is therefore less clear, (3) unlike

NREM sleep, it can be more selectively restricted,[19] and (4) rebound after deprivation may be associated with physiologic complications and is therefore of clinical importance.[15,17,18]

METHODS

Animals

Six male Fischer 344 rats (Simonsen Laboratories, Gilroy, CA) that weighed 350 to 400 g throughout the period of experimentation were used for this study. Experimental procedures were approved by the University of Michigan Committee for the Care and Use of Animals and were in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The rats were allowed to acclimate in the animal care facility for 1 week upon arrival, given ad libitum access to food and water, and maintained on a 12-hour light:12-hour dark cycle (lights on at 6:00 AM).

Animal Instrumentation

Electrodes were implanted under sodium pentobarbital anesthesia, using bregma as a coordinate landmark. We performed aseptic surgical implantation of 2 superficial cortical electrodes (AP: +0.3 and ML: +1.0 for left frontal; AP: −3.0 and ML: −2.0 for right parietal), 1 deep electrode targeted to the left dorsal hippocampus (anteroposterior: −3.0, mediolateral: +2.0, and dorsoventral: −2.9), and 1 sinus ground for the purpose of EEG recording and analysis of behavioral states. The superficial cortical electrodes and sinus ground consisted of stainless steel screws (0.8-mm diameter × 3.2-mm length) affixed with 20 mm stainless steel Teflon-insulated wire. The deep hippocampal electrode was made of stainless steel wire (0.25-mm bare diameter) insulated with polyimide. In addition, 1 insulated, multistranded stainless steel wire (Cooner Wire, Chatsworth, CA) was inserted into each dorsal neck muscle to record nuchal electromyography (EMG). All wires were capped with stainless steel, gold-plated socket contacts and inserted into a 6-channel, plastic pedestal that was secured to the skull by dental acrylic. Other than the EMG electrodes, all materials were supplied by Plastics One (Roanoke, VA). The rats were allowed to recover for at least 7 days before further experimentation. Appropriate postoperative analgesia was provided for the animal.

Experimental Conditions

Before experimentation began, each rat was habituated to the headstage tether on 3 separate days for 3 h/d. Likewise, on 3 separate days, each rat was given three 1-hour habituation sessions on the multiple platforms described below. Each rat was recorded under 4 separate conditions (Fig. 1):

1. 8 hours of natural sleep-wake states.
2. 8 hours of natural sleep-wake states, preceded by 24 hours REM sleep deprivation.
3. 4 hours of isoflurane anesthesia followed by 4 hours of natural sleep-wake states.
4. 4 hours of isoflurane anesthesia followed by 4 hours of natural sleep-wake states, preceded by 24 hours REM sleep deprivation.

All 6 animals underwent all 4 conditions in the order described, with a 1-week recovery period for any experiments involving sleep deprivation or isoflurane anesthesia. Animals were deprived of REM sleep for a 24-hour period using the multiple platforms-over-water method.[19] Animals were placed on 6.5-cm-diameter platforms submerged in water, with access to mounted food dispensers and water bottles. The principle of selective REM sleep deprivation is as follows. When an animal enters a NREM sleep period, it is capable of sustaining its position because of preserved muscle tone. By contrast, when it enters a REM

sleep period, the associated atonia causes the animal to fall into the water and be awakened. Animals were observed constantly by the experimenters in an adjacent room via video monitor for the entire 24-hour period of deprivation and were returned to the platform if unable to do so themselves. There was no electrophysiologic recording during this time period. After REM sleep deprivation, animals were allowed either (1) ad libitum recovery for 8 hours, or (2) 4 hours of isoflurane anesthesia, followed by 4 hours of ad libitum recovery.

Electrophysiologic Recording During Sleep and Isoflurane Anesthesia

Eight-hour recordings began 2 hours into the light phase of the cycle (at approximately 8:00 AM), when sleep predominates in these nocturnal animals. On experimental days using anesthesia, unconsciousness was induced using 2.5% isoflurane mixed with oxygen in an induction chamber. When unconsciousness was observed, marked by a loss of righting reflex, the rat was removed from the induction chamber and placed on the bench where a steady flow of isoflurane was delivered via a nose cone. The isoflurane concentration was reduced to not <1% in oxygen and titrated to a level that would maintain unresponsiveness to toe pinch without causing continuous EEG burst suppression. Pilot data with other instrumented animals suggested that approximately 1.2% isoflurane was an appropriate starting concentration to achieve these goals. An inline Datex gas analyzer (Soma Technology, Cheshire, CT) was used to register the actual concentration of isoflurane delivered. Core body temperature was maintained via a heating blanket and monitored using a rectal thermometer. Respiratory rate was constantly monitored by visual inspection, and anesthetic concentration was modified accordingly. If movement of the animal resulted in displacement of the nose cone, the animal was repositioned to avoid entrainment of room air.

Recordings during isoflurane took place for 4 hours and a toe pinch was performed at 15-minute intervals to verify adequate anesthetic depth. Similar control experiments in other instrumented animals were conducted without toe pinches to exclude stimulus-associated hippocampal θ activity during anesthesia. Animals were allowed to recover from anesthesia for approximately 30 minutes, and then EEG recordings were continued for another 4 hours. Animals were returned to their home cage once the recording session ended.

EEG and EMG were sampled at 667 Hz using Lynx-8 amplifiers (Neuralynx, Bozeman, MT), and signals were filtered between 1.0 and 125 Hz. During the recording sessions, the frontal and parietal cortical electrodes were referenced to each other, the 2 EMG electrodes were referenced to each other, and the deep hippocampal electrode was referenced to the sinus ground. Signals were downsampled to 333 Hz and were analyzed using MATLAB-based sleep-scoring software.[20]

Sleep Scoring and Assessment of Hippocampal θ Activity During Isoflurane Exposure

EEG and EMG recordings from natural sleep states were evaluated during baseline recordings. Low amplitude and desynchronized cortical activity, synchronized hippocampal θ activity (4–9 Hz), quiescent EMG, and behavioral observation of immobility were established as criteria for REM sleep states. During REM sleep epochs, δ/θ ratios were found to be consistently ≤ 1. Three trained experimenters were blinded to the condition of each rat and manually scored each record for REM sleep, NREM sleep, and waking.

During isoflurane exposure, hippocampal "θ dominant" states were evaluated. In addition to its association with the active waking state in animals, hippocampal θ activity is found during REM sleep,[21] isoflurane exposure,[22] and urethane anesthesia.[4] Therefore, we evaluated whether hippocampal θ activity during isoflurane anesthesia functioned as a

surrogate marker for REM sleep–like activity. The criteria for a δ-dominant state during isoflurane anesthesia were (1) the morphologic appearance of synchronized δ (4–9 Hz) in the hippocampal EEG signal, (2) a θ/δ ratio ≤1, and (3) a quiescent EMG (to exclude a waking state).

The θ/δ ratio, the overall δ power, and other spectral values were calculated for each epoch. Each 8-hour recording session was analyzed in 10-second epochs. In rats, 10-second epochs are often used because state changes occur more frequently than in humans.[23] EEG signals were filtered to allow signals between 1.5 and 30 Hz to pass and EMG signals were filtered to allow signals ≥30 Hz to pass. For all rats and conditions, the REM sleep and isoflurane δ-dominant states were calculated as a percentage of total time unconscious during the recording period.

Analysis of Hippocampal θ Distribution During Active Waking, REM Sleep, and Isoflurane Anesthesia

It has been shown that the distribution of waking states follows a "power-law" or "scale-free" organization, whereas sleep states follow an exponential or Gaussian distribution.[24] To assess whether the dynamics of anesthesia were more similar to sleep (exponential) or to waking (power law), we compared the temporal organization of hippocampal θ activity during all 3 states.

Histology

After data collection was completed, rats were deeply anesthetized for histological verification of hippocampal electrode placement. Deep anesthesia was induced with intraperitoneal sodium pentobarbital and intracardiac perfusion was conducted by infusion of 0.9% phosphate-buffered saline followed by 10% formalin. The brains were extracted and placed in 30% sucrose and kept at 4°C until adequately cryoprotected. The brains were sectioned at 30 μm on a cryostat (Leica Microsystems, Bannockburn, IL), thaw-mounted onto glass slides, and stained with cresyl violet. The most ventral extent of tissue disruption was determined to be the tip of the deep hippocampal electrode.

Statistical Analysis

Paired, 2-tailed *t* tests (significance level of <0.05) were conducted on all reported measures to compare REM sleep–deprived conditions with nondeprived conditions. In each case, all 6 rats were compared against themselves for a given condition. Variables analyzed were (1) behavioral states including REM sleep, NREM sleep, waking, and δ-dominant isoflurane, (2) percent isoflurane delivered, and (3) EMG power. Unless otherwise specified, analyses were conducted between the nondeprived and 24-hour REM-deprived conditions.

To compare hippocampal θ frequency and power during active waking, REM sleep, and δ-dominant isoflurane anesthesia, a 1-way analysis of variance was used. The duration data of hippocampal θ periods in the 3 states were compared using the following process: (1) the duration data were normalized by SD: $T_{ki} = t_k/ó_i$, where $ó_i$ is the SD of the unnormalized duration t_k of state I, (2) the maximum likelihood method was used to fit the cumulative density function of normalized data, p(T > t), (3) 2 different fitting models (exponential: $p(t) \sim e^{-\lambda t}$, and power law: $p(t) \sim t^{-\beta}$) were compared on the entire region of the cumulative distribution, and (4) the root mean square errors for the 2 different fitting models were compared: $E_i \sqrt{\frac{1}{n}\Sigma_{j=1}^{n}\left(\tilde{t}_j - t_j\right)^2}$, where $\tilde{t}_j$ is the value predicted by a fitting model and t_j is the target value. The power law and exponential models were chosen because of their association with waking states and sleep, respectively. The MATLAB toolbox for curve fitting was used.

RESULTS

Electrode Placement

Deep electrode placement in the hippocampus was verified with histology (Fig. 2, upper), and characteristic hippocampal θ signals were obtained (Fig. 2, lower). Electrode placement and signal quality were confirmed for all animals.

REM Sleep Recovery After Isoflurane Anesthesia

Rats that underwent 24-hour REM sleep deprivation demonstrated a robust and statistically significant increase in REM sleep during the first 4 hours of recovery. In the first 2 hours of recovery (8 AM–10 AM), there was a 5.7-fold increase ($P = 0.0005$) and in the second 2 hours (10 AM–12 PM) there was a 2.6-fold increase ($P = 0.004$) (Fig. 3, upper). There was no significant difference in the percentage of REM sleep in the second 4 hours of recovery (12 PM–4 PM) compared with controls.

After REM sleep deprivation and 4 hours of isoflurane anesthesia from 8 AM–12 PM, animals were allowed to recover for ≤30 minutes and then were recorded for another 4 hours in natural sleep/wake states. If isoflurane anesthesia was associated with sleep homeostasis, then REM sleep rebound should not be observed after 4 hours of anesthesia because this was the time period of observed recovery for the ad libitum sleep condition. Instead, there was a 3.6-fold increase ($P = 0.001$) in REM sleep in the first 2 hours of recording after isoflurane and a 2.2-fold increase ($P = 0.003$) in the second 2 hours (Fig. 3, lower). There was no statistically significant difference in the first 4 hours of recovery after REM deprivation compared with the first 4 hours of recovery after both REM deprivation and isoflurane anesthesia (Table 1).

Anesthetic Requirements After REM Sleep Deprivation

In post hoc analysis, we found that a higher concentration of isoflurane was delivered in the nondeprived condition compared with the 24-hour REM-deprived condition (1.27% vs 1.12%, respectively, $P = 0.007$) to achieve the same end point of unresponsiveness without consistent burst suppression. EMG power was not statistically different between the deprived and nondeprived conditions, suggesting that a similar behavioral end point was achieved despite the differences in anesthetic concentration (Table 2).

Hippocampal θ Activity During Active Waking, REM Sleep, and Isoflurane Anesthesia

There was no increase in the number of θ-dominant epochs during isoflurane anesthesia after REM deprivation compared with the control condition without deprivation (Fig. 4A), suggesting that hippocampal θ activity during anesthesia is not regulated as it is during sleep. Hippocampal θ activity during anesthesia also had a significantly slower frequency than either the active waking or REM sleep states (Fig. 4B), which is a previously described effect of isoflurane.[22]

We analyzed the probability distribution of hippocampal θ events in the nondeprived animals during 3 states to assess whether the dynamic organization of anesthesia was similar to sleep. Figure 4C shows the cumulative probability distributions of normalized durations using pooled data for REM sleep, active waking, and θ-dominant anesthesia in semilogarithmic and double logarithmic (inset) scales. The cumulative probability distributions of the active waking state and θ-dominant anesthesia were more similar to each other than to REM sleep. For the waking state and the hippocampal θ during isoflurane anesthesia, the power law model fit the data well, but the exponential model was excluded. For REM sleep, however, the exponential distribution fit the data well, whereas the power law was excluded. The root mean square errors of power law/exponential models were

0.25/0.81 for the waking state, 0.22/0.96 for general anesthesia, and 0.69/0.3 for REM sleep (the lower the error, the better the fit). Longer durations of hippocampal δ epochs (>6-fold SD) occurred during the waking state and isoflurane anesthesia, which created the tail on the probability distribution. In contrast, longer durations of hippocampal δ did not occur in the sleep state.

DISCUSSION

Unlike prior studies of propofol,[6,7] isoflurane anesthesia does not satisfy the homeostatic need for REM sleep. Furthermore, hippocampal δ activity is not homeostatically regulated during isoflurane anesthesia as it is during REM sleep and the organization of δ events does not resemble that of sleep. In light of past studies with IV drugs,[4,6,7] our current data suggest that behavioral or neurophysiologic interfaces of sleep and general anesthesia may be different with inhaled drugs.

Sleep-Anesthesia Interfaces

Anesthesia could potentially (1) satisfy sleep debt, (2) accrue sleep debt, or (3) be neutral with respect to sleep debt. The findings of Tung et al.[7] suggest that the effects of propofol satisfy sleep debt, which is supported by earlier work demonstrating that prolonged propofol infusion is not associated with a subsequent rebound in REM or NREM sleep.[6] Thus, propofol seems to be in the first category. The current data, however, suggest that isoflurane anesthesia is most similar to the third category, i.e., a state distinct from both sleep and waking that is neutral with respect to sleep processes. Indeed, the percentage of both REM and NREM states were unchanged by isoflurane exposure (Table 1). Understanding the precise relationship of different anesthetics to sleep homeostasis has clinical relevance. For example, if isoflurane does not satisfy the need for REM sleep as well as other anesthetics in humans, it may be a less desirable choice in patients with obstructive sleep apnea who are at risk for adverse sequelae because of REM-rebound phenomena.

Although not statistically different, the REM sleep rebound after isoflurane anesthesia was less pronounced than the natural recovery state compared with control conditions. The relatively small number of animals in this study introduces the possibility of a type 2 error, in which case there would be a true difference. Three explanations could account for this. First, partial REM sleep satiation could occur during isoflurane anesthesia. Second, isoflurane could suppress REM sleep in the postanesthetic period, such that full recovery was not yet possible. Third, there could be some REM sleep satiation in the recovery time immediately after anesthesia, but before natural sleep-wake recordings resumed. However, Table 1 indicates that the actual time spent in REM sleep in the first 4 hours of recovery with or without isoflurane exposure was comparable, which argues against recovery during anesthesia or postanesthetic REM sleep suppression. Ongoing studies are addressing these possibilities, but the observed data are nonetheless distinct compared with the previously described effects of propofol on sleep profiles.

Of interest is the reduction in anesthetic requirements in the REM sleep–deprived condition. Although assessing anesthetic sensitivity in response to sleep deprivation was not a primary goal of the study, the data collectively suggest that the effects of sleep characteristics on anesthesia (Table 2) may be dissociable from the effects of anesthesia on sleep characteristics (Fig. 3). In other words, sleep deprivation could increase anesthetic sensitivity even though anesthesia does not satisfy the homeostatic need for sleep.

Hippocampal θ Activity During Isoflurane Anesthesia and REM Sleep

Hippocampal θ events during isoflurane did not increase with REM sleep deprivation, suggesting that the mechanisms regulating θ during anesthesia are different than those during REM sleep. Furthermore, the organization of θ events during isoflurane exposure was distinct from that of sleep, but similar to that of waking. It is important to note, however, that θ events during anesthesia were associated with a significantly slower frequency, and therefore the similarities to the waking state were likely not due to awakening of the animal. The neurophysiology of REM-like traits during anesthesia warrant further study, especially given the recently identified features of REM sleep–like activity during emergence from propofol and desflurane that was associated with dreaming in humans.[25]

Limitations

Our study has numerous limitations. First, although animal models have significantly advanced the field of sleep research, data regarding sleep-wake states in rodents warrant verification in humans. Second, only one inhaled anesthetic was studied; further studies could include comparison with other volatile anesthetics. Third, only REM sleep deprivation was studied. As noted above, our goal was to perform a more specific deprivation paradigm, especially because there are relatively few studies of the relationship between REM sleep and general anesthesia. Ongoing studies are investigating recovery patterns after total sleep deprivation. Fourth, we did not perform electrophysiologic recording during the deprivation protocol. However, our method using 6.5-cm platforms has long been demonstrated to reduce REM sleep in the rodent, while sparing NREM sleep.[26] Finally, a longer exposure to isoflurane or a longer period of recording during recovery could be associated with different results. The 4-hour duration was chosen because it was the period in which recovery from REM sleep deprivation was observed to be completed in our control protocol.

CONCLUSION

We demonstrate that, unlike propofol, isoflurane does not satisfy the homeostatic need for REM sleep. Furthermore, the regulation and organization of hippocampal θ events during anesthesia are unlike sleep. Additional work is required to clarify the neurochemical or neurophysiologic traits of general anesthesia that account for the sleep recovery differences among anesthetics.

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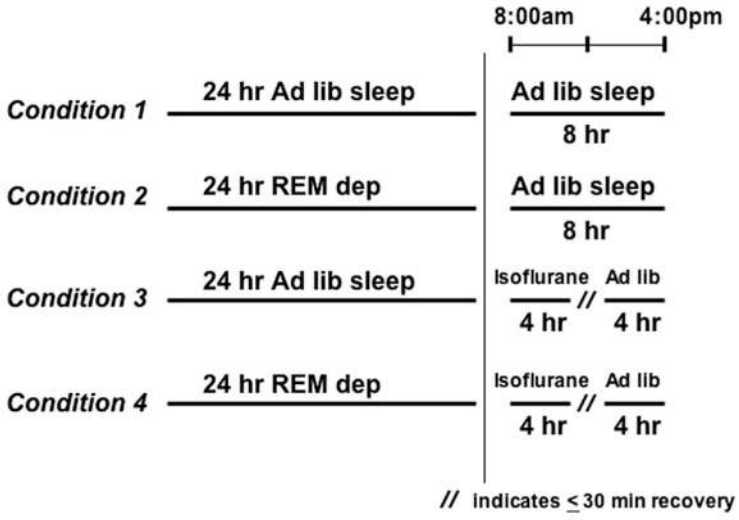

Figure 1.
Schematic of rapid eye movement (REM) deprivation experiments.

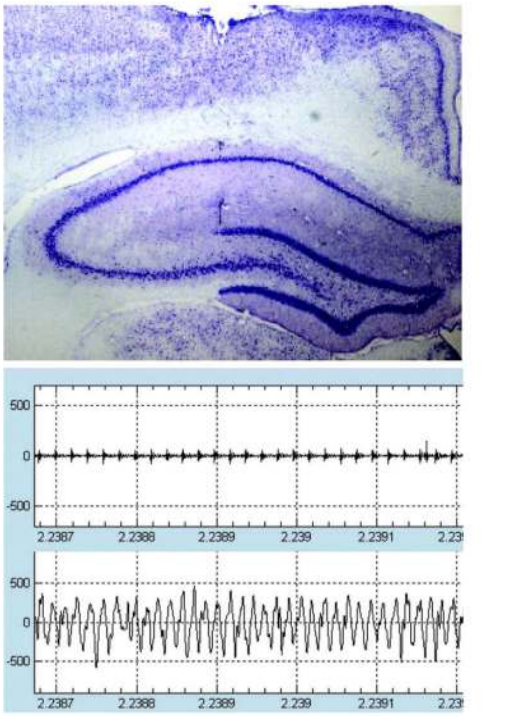

Figure 2.
Confirmation of electrode placement in the hippocampus and Δactivity during rapid eye movement (REM) sleep. A, Electrode in the left dorsal hippocampus. B, Top row of signals, electromyography; lower row, hippocampal electroencephalography.

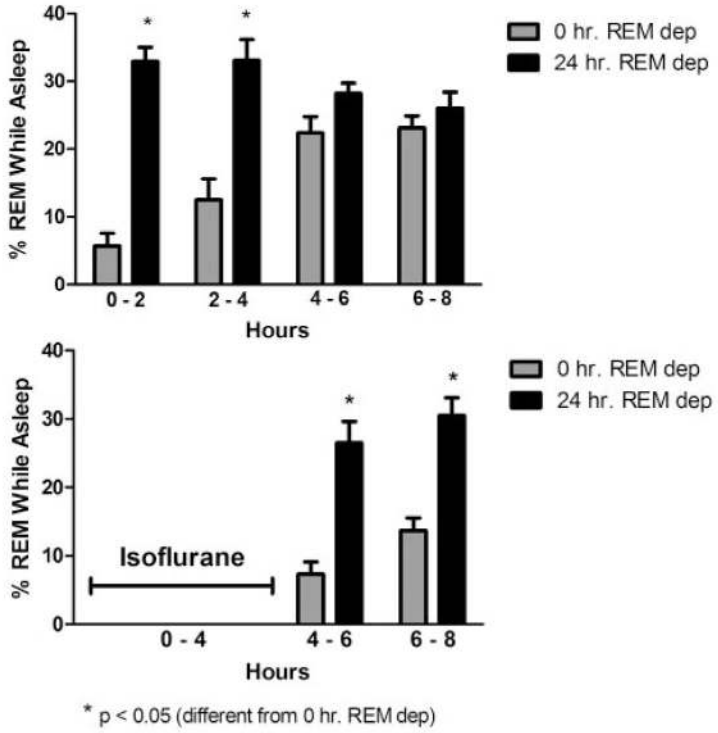

Figure 3.

Rapid eye movement (REM) sleep rebound in the first 4 hours of natural recovery and in the first 4 hours postisoflurane. If isoflurane anesthesia satisfied the homeostatic need for sleep, we would expect no sleep rebound phenomenon in hours 4 to 8. Instead (bottom panel), the observed REM sleep rebound after isoflurane suggests that recovery from deprivation had not occurred during the anesthetic. Mean ± SE shown; * $P < 0.05$

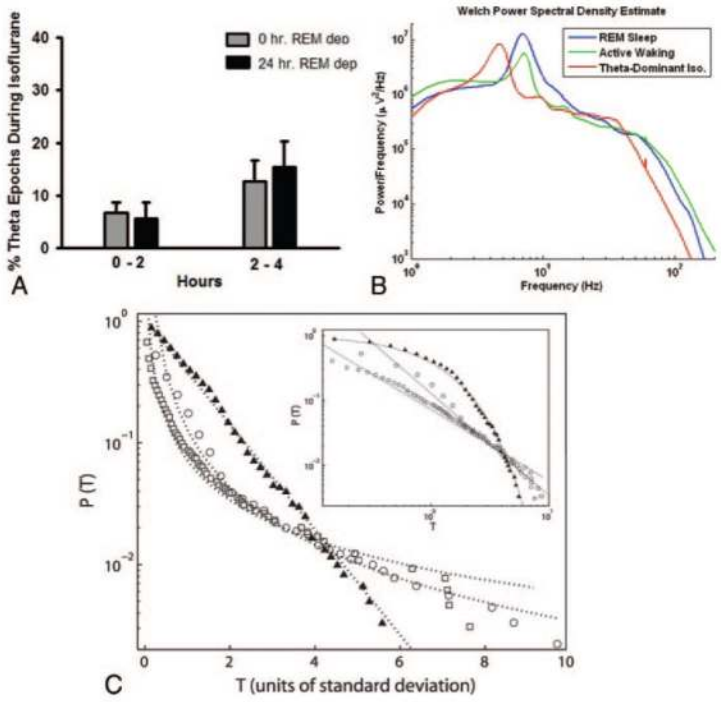

Figure 4.

Behavior of hippocampal θ activity during rapid eye movement (REM) sleep, active waking, and isoflurane anesthesia. A, The percentage of hippocampal θ dominant epochs during isoflurane anesthesia was not changed by REM sleep deprivation. B, Spectral analysis of active waking, REM sleep, and θ dominant isoflurane (iso) anesthesia: a 1-way analysis of variance indicates that θ frequency during the anesthetized state is significantly lower, which is consistent with previous studies of isoflurane.[22] C, The cumulative probability distributions of the normalized hippocampal θ duration data are presented in semilogarithmic and double logarithmic (inset) scales. The power law fitting for the data of the waking state (square) and anesthesia (circle), as well as the exponential fitting for the sleep data (triangle), are denoted with dotted lines.

Table 1

REM Sleep Rebound Is Not Reduced by Isoflurane Anesthesia

Condition	% REM	% NREM	% Waking
4 h post-REM deprivation	21.95 ± 1.83	45.30 ± 3.49	32.75 ± 4.64
4 h post-REM deprivation and isoflurane	19.02 ± 1.96	48.06 ± 3.19	32.92 ± 4.12
P	0.12	0.47	0.97

Values are mean ± SE.

REM = rapid eye movement; NREM = non–rapid eye movement.

After 24-h REM deprivation, the first 4 h of ad libitum sleep-wake states with or without isoflurane exposure are not statistically different, suggesting that isoflurane anesthesia does not repay REM sleep debt.

Table 2

Anesthetic Requirement Is Significantly Reduced After REM Sleep Deprivation

	% Isoflurane delivered	EMG power (μV^2)
0 h REM deprivation	1.27 ± 0.02	157.3 ± 24.3
24 h REM deprivation	1.12 ± 0.03	113.8 ± 27.8
P	0.007	0.17

Values are mean ± SE.

REM = rapid eye movement; EMG = electromyography.