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Sleep and Anesthesia – Common mechanisms of action

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Introduction

“You are going to go to sleep now” is an oft-repeated colloquialism in every anesthesiologist’s daily practice. The phrase might be useful in allaying the fears of nervous patients, but does general anesthesia actually mimic sleep? Do they travel on the same neural pathways? To what degree does the comparison accurately reflect the underlying mechanisms involved?

Sleep, especially non-rapid eye movement (NREM) sleep, and anesthesia may use common neuronal and genetic substrates. Anesthetics act through sleep neural circuits but not necessarily in the same way.

Arousal pathways

In order to promote and sustain cortical arousal, neuronal pathways have developed two parallel ascending neuronal pathways. The first branch activates the thalamic relay neurons that are crucial for transmission of information to the cortex. Cholinergic signaling originating from the laterodorsal tegmental (LDT) and pedunculopontine tegmental (PPT) nuclei and the basal forebrain promote the cortically activated states of wakefulness and rapid eye movement (REM) sleep. The second branch bypasses the thalamus, activating neurons in the lateral hypothalamic area and basal forebrain (BF), and throughout the cortex. This pathway originates from monoaminergic neurons in the upper brainstem and caudal hypothalamus. The locus coeruleus (LC) provides norepinephrine-mediated inhibition of the ventrolateral preoptic (VLPO) nucleus in the hypothalamus^{1,2}. Therefore, γ -aminobutyric acid (GABA_A)-mediated and galanin-mediated inhibition of the ascending arousal circuits by the VLPO nucleus is inhibited and the awake state is promoted.

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Sleep pathways

Sleep is under control of two processes, a circadian clock that regulates the appropriate timing of sleep and wakefulness across the 24-h day and a homeostatic process (“sleep homeostasis”) that regulates sleep need and intensity according to the time spent awake or asleep³. Sleep is a non-homogenous state that can be divided into NREM sleep and REM (“paradoxical”) sleep. The brain areas identified as important in sleep fall into two general groups, those with an arousing influence and active during wakefulness: LC, dorsal raphe (DR), tuberomammillary (TMN) and BF; and those active primarily during sleep: VLPO. The MPA contains both wake- and sleep-active neurons.

Discrete neurochemical changes accompany the different types of sleep with cholinergic (in brain stem and forebrain), noradrenergic (LC) and serotonergic (DR) all becoming less active in NREM sleep while cholinergic activity increases in REM sleep⁴. Activity in the VLPO is increased in NREM sleep and the GABAergic/galanin input from VLPO inhibits the histaminergic TMN nucleus. Orexinergic pathways from the perifornical nucleus are inactive during NREM sleep (figure 1).

The relatively quiescent LC facilitates a series of changes that includes activation of the galanin/GABA containing neurons of the VLPO nucleus that terminate on and inhibit aminergic neurons within the tuberomammillary nucleus⁵.

Anesthetic-induced unconsciousness results from specific interactions of anesthetics with the neural circuits regulating sleep and wakefulness.

Where do anesthetics collide in sleep pathways?

The currently available imaging techniques can only indirectly measure neuronal activity, for example through changes in blood flow, glucose metabolism or oxygen concentration. We can then understand the difficulty in fully understanding the mechanisms by which anesthesia induces sleep/unconsciousness. A common finding between NREM sleep and anesthesia in imaging studies is the deactivation of the thalamus leading to cortical inhibition. Anesthetic drugs induce unconsciousness by altering neurotransmission at multiple sites in the cerebral cortex, brain stem, and thalamus. The different actions of the different available anesthetics have made the understanding of the exact mechanism even more difficult. Effects of modern anesthetics on subsequent sleep behavior are known for some, but not all anesthetics. No one electroencephalogram (EEG) pattern characterizes the anesthetized state. Different anesthetics and doses have distinct profiles with respect to the EEG activity.

Although some agents act on excitatory synapses, others act through potentiation of inhibitory synaptic receptors. The **GABA_A** receptors are neurotransmitter-gated chloride channels that exist on cells that may also contain nicotinic acetylcholine receptors, glycine receptors, and serotonin type 3 receptors. Anesthetics such as propofol, etomidate and barbiturates exert their effect through enhancement of GABA-mediated channel activation and prolong post-synaptic inhibitory currents, suppressing neuronal excitability. In brain regions containing neurons that promote wakefulness, GABAergic inhibition has been

shown to cause an increase in sleep. These brain regions include the DR nucleus, TMN, medial preoptic area and ventrolateral periaqueductal gray^{6,7}. In a series of studies involving GABAergic agents, it was reported that unlike NREM sleep, these hypnotic agents did not alter noradrenergic activity in the LC⁸ (figure 1). Instead, these agents converged on the NREM sleep pathway at the level of the hypothalamus⁹. However, short-term administration of the GABAergic agent propofol permitted normal recovery after a period of sleep deprivation^{10,11}.

At clinical concentrations, drugs like N₂O, xenon and ketamine have little or no effect on GABA_A receptors. Instead, these anesthetics mainly potently inhibit *N*-methyl-D-aspartate (NMDA) receptors, which are excitatory cation channels activated by glutamate. These agents reduce excitatory signals in critical neuronal circuits causing unconsciousness. Glutamate levels in the PPT are greater during wakefulness as opposed to NREM and REM sleep^{12,13}. The dissociative state that is produced by ketamine anesthesia can be in part attributed to the different regions to which ketamine promotes glutamate release (nucleus accumbens¹⁴, prefrontal cortex¹⁵ and anterior cingulate¹⁶). It has been shown that isoflurane and sevoflurane reduce glutamate release^{17–19} and inhibit its uptake²⁰ but few in vivo studies have been published to understand the exact mechanism by which isoflurane modulates glutamatergic transmission.

REM sleep rebound after exposure to **volatile anesthetics** suggests that these volatile anesthetics do not fully substitute for natural sleep²¹. In humans, isoflurane anesthesia alone (without surgery) results in no change in subsequent REM or NREM sleep, but a shift in NREM sleep from slow wave sleep to lighter (I and II) stages²². On the other hand, it has been shown that wake-active orexinergic neurons are inhibited by isoflurane and sevoflurane, and that waking up from anesthesia uses neural circuits distinct from those necessary to become anesthetized but similar to the neural circuitry that promotes arousal²³. Furthermore, isoflurane depresses serotonin levels on hypoglossal motoneurons in dogs²⁴ and on mice hippocampus²⁵.

The molecular targets for dexmedetomidine are central **α_2 adrenergic** receptors. It has been shown that α_2 agonists transduce its hypnotic response after binding to the α_{2A} receptor subtype²⁶ in the LC²⁷. Through signaling processes that involve both pertussis toxin-sensitive G proteins²⁸ and effector mechanisms that include inhibition of adenylyl cyclase²⁸ and ligand-gated calcium channels as well as activation of inwardly-rectifying potassium channels²⁹, the noradrenergic neurons become hyperpolarized and are less likely to achieve an action potential. α_2 agonists, like dexmedetomidine, are associated with similar changes in neuronal activity as is seen in deeper stages of NREM sleep^{2,30} apart from the absence of inhibitory effect on the orexinergic neurons in the perifornical nucleus⁹. A functional magnetic resonance study showed that a thalamic nucleus, that receives afferent input from orexinergic neurons, is activated during an arousal stimulus in α_2 - sedated subjects³¹. Children sedated with dexmedetomidine exhibited an EEG pattern that was identical to that seen in stage 2 NREM sleep³².

Though **acetylcholine (ACh)** plays a primary role in generating the brain-activated states of wakefulness and REM sleep, cholinergic receptors are not a main target of common

anesthetics. Nonetheless, ACh interacts with other transmitter systems that are targets of sleep pharmacology, for example the GABAergic agents. The clinical finding that physostigmine (acetylcholinesterase inhibitor) reverses propofol sedation, causing arousal, suggests that propofol produces unconsciousness, in part, by disrupting cholinergic neurotransmission³³. In vitro studies showed that propofol, isoflurane, sevoflurane and ketamine inhibit muscarinic and nicotinic ACh receptors^{34–38}, providing support that these agents cause sedation, in part, by inhibiting cholinergic neurotransmission in brain regions that regulate arousal.

Circadian Rhythm

The two-process model of sleep homeostasis as described by Borbely et al integrates sleep debt (“process-s”) and circadian rhythm (“process-c”). This model implicates circadian rhythm and sleep as intertwined, co-dependent processes³⁹. Experimentally distinguishing process-c from process-s presents a challenge in deconstructing causative factors in sleep disorders. Nevertheless, there is a growing body of evidence to suggest that circadian rhythm can be altered independent of sleep deprivation and that anesthetics can specifically change circadian rhythm.

Circadian rhythmicity is thought to be controlled by the suprachiasmatic nucleus and established by processing external cues (zeitgebers) like light, into systemic mediators such as temperature, adrenergic signaling, and circulating hormones (e.g., cortisol and melatonin). This process serves to maintain a diurnal pattern presumably to coordinate intracellular or intersystem function by resynchronizing intrinsic cellular molecular clocks. Briefly, the molecular core of the circadian clock involves the heterodimerization of CLOCK and BMAL1 which act as the canonical arm of the clock, and the heterodimerization of PER1/2 and CRY1/2 which are critical components of the negative feedback arm¹⁹, stabilizing proteins ROR α , REV-ERB, DEC, DBP and E4BP4 act as additional repressors or activators of the canonical arm⁴⁰, and these proteins oscillate through the day and translocate from the cytoplasm to the nucleus in a highly coordinated fashion to provide a reliable rhythm of approximately 24 hours. Disruption of circadian processes is being studied as a relevant contributing factor to multiple human conditions altering, among others, immunity.

Circadian Rhythm and Anesthesia

Initial indications that circadian rhythm is important in anesthetic delivery are the time-of-day variance in susceptibility to general anesthetics^{41,42}. Indeed, the greatest therapeutic effect of general anesthetics in animal models occurs during the animals rest phase for propofol⁴³ and ketamine⁴⁴. Volatile anesthetic effect may also vary according to a diurnal pattern where previously, halothane administration in rats varied with a lower minimum alveolar concentration requirement during the rest phase compared to the active phase⁴⁵. Recently, using bees as a model system, 6-hour isoflurane administration during the rest phase failed to alter the circadian activity patterns of the hive, whereas isoflurane administered in the active phase significantly altered the circadian activity of the hive⁴⁶. Taken together, the time-of-day administration of anesthesia is likely important in both the dose-dependent effect and maintenance of circadian rhythm.

As parameters for outlining circadian rhythm, cortisol and melatonin levels can be used to make assumptions about the effect of general anesthesia on daily cycling in human subjects. Most human studies following these variables involve general anesthesia with the confounding aspect of surgery, and do not incorporate the natural underlying cycling of these hormones adequately. Given these and other significant caveats, with respect to cortisol, a propofol-based anesthetic appears to decrease the amount of plasma cortisol during surgery compared to sevoflurane⁴⁷. Postoperatively, using a thiopental/sevoflurane or thiopental/isoﬂurane based anesthetic, cortisol levels are elevated in men who underwent long duration surgery for larynx or pharynx cancer⁴⁸. Conversely, women undergoing laparoscopic procedures for pelvis surgery, anesthesia with thiopental/sevoflurane reduced amounts of cortisol 2–4 hours after surgery compared with thiopental/isoﬂurane anesthesia⁴⁹. Given that these studies were designed to investigate the anesthetic effects on stress responses and not on circadian rhythm directly, there remains only a suggestion that altered cortisol levels may interfere with circadian rhythm after anesthesia and surgery.

Investigation into the effect of anesthesia on melatonin cycling, points more directly to a circadian rhythm effect. A comparison of general anesthesia (thiopental/isoﬂurane) to spinal anesthesia for orthopedic procedures showed a significant reduction in melatonin levels in the first post-surgical night compared to baseline levels, interestingly there was no significant difference in the reduction of melatonin between the experimental groups indicating that the effect was independent of the anesthesia, and pointed to the possibility of a significant surgical influence or post-operative opiate use on melatonin secretion⁵⁰. In patients undergoing general anesthesia (thiopental/isoﬂurane/fentanyl) for laparoscopy a modest reduction in 13-hour average melatonin secretion was noted in the evening after surgery compared to the pre-surgical night with a large increase in melatonin secretion on the second night after surgery⁵¹. Corroborating these data, in patients undergoing major abdominal surgery with general anesthesia and concomitant use of a thoracic epidural there was a similar modest reduction in basal melatonin secretion on the first postoperative day followed by a significant increase on the second postoperative day⁵². Following urine metabolites of melatonin (aMT6s), general anesthesia (thiopental/propofol), decreased the maximal concentration and delayed the peak of aMT6s⁵³. Short mask inhalation anesthetics (21 minute average duration) for dilation and curettage showed no difference in melatonin secretion compared to non-surgical controls⁵⁴. Experimental models allow for more specific examination of melatonin secretion and general anesthesia apart from surgical effect. Rats anesthetized with propofol for 25–30 minutes around the peak of serum melatonin secretion showed a significant reduction in melatonin secretion for the 3 hours following anesthesia, a subsequent increase 20 hours after the anesthetic, and a phase advance of cyclical melatonin secretion of 40 minutes consistent with the approximate duration of anesthesia⁴¹. Whether in humans or rats, it seems consistent that melatonin levels are reduced in the immediate post-operative/anesthetic period with a rebound phenomenon observed thereafter, it remains unclear in the human subjects what component of the observed effect can be attributable to either surgery or anesthesia.

The effect of anesthetics on intrinsic molecular circadian clocks is beginning to be explored in experimental models. In rats, 6 hours of sevoflurane anesthesia changed the expression pattern of approximately 1.5% of 10,000 genes surveyed. Interestingly the expression of

Per2 was the only circadian protein in the brain that was significantly reduced after the anesthetic⁵⁵. The effect of reduced expression of Per2 and an auxiliary clock gene Dbp persists for 24 hours⁵⁶. Both infusions of propofol and dexmedetomidine likewise reduced the expression of Per2 in rat brain 6 hours after anesthetic delivery but the effect persisted for 24 hours only in the dexmedetomidine⁵⁷. Further investigation demonstrated that a 4-hour sevoflurane anesthetic blunted Per2 mRNA production in the SCN in response to a light stimulus and created a delayed activity rhythm in the anesthetized mice⁵⁸. Repression of Per2 expression by sevoflurane anesthesia was most significant when administered between the hours of 8am–12pm as compared to other time points, but activity patterns of anesthetized animals were delayed for all time points of anesthetic administration⁵⁹. Bees anesthetized with a 6-hour course of isoflurane during the day had a reduction in the amplitude of Cry expression and phase delay of both Cry and Per2 expression in whole bee brains compared to bees anesthetized during the evening, leading to alterations in circadian governed homing patterns and foraging times⁴⁶. With respect to the molecular clock, general anesthesia appears to significantly affect critical clock proteins in a time-of-day dependent fashion and corresponds to changes in activity patterns consistent with circadian disruption.

Circadian Control of Immune Function

A separate line of investigation has focused on the influence of circadian rhythm on immune function. Evidence exists noting that the time of day is important in human subjects in terms of susceptibility to infection⁶⁰, asthma attacks⁶¹ or flares of rheumatic arthritis⁶², all of which suggest circadian principles underlying these immune mediated processes.

Circulating pools of many immune cells cycle throughout the day indicate the influence of circadian timing. Natural Killer (NK) cells peak in both activity and numbers in the human circulation in the early morning and likely marginate away from circulation during other points of the day⁶³. In mouse models, after lipopolysaccharide (LPS) administration, macrophages circulate cyclically to the spleen⁶⁴. Importantly, the circadian molecular clock exists and functions in NK cells,^{65,66} macrophages, dendritic cells, and B cells^{64,67}. Indeed, approximately 8% of the macrophage genome is classified as falling under the control of circadian transcription factors⁶⁴, and critical immune transcription factors such as signal transducer and activator of transcription family (STATs) and nuclear factor kappa B (NF- κ B) are regulated by clock proteins⁶⁸. Studying the functional consequence of disturbing circadian molecular clock proteins in immune subsets is generating interesting data. Injection of LPS at specific time points caused significantly elevated cytokine production in both macrophage restricted *Bmal1* knock-out (KO), and systemic *Rev-Erba* KO mice compared to the chronometric 12-hour opposite time point (antiphasic control)⁶⁹. *Cry1/2* double KO mice have elevated NF- κ B activity causing increased baseline inflammatory cytokine expression *in vitro* and generated greater inflammation when challenged with LPS *in vitro* and *in vivo*⁷⁰. Examining lymphocyte function has similarly elucidated at least some aspect of circadian gating. *Per2* KO mouse lymphocytes had a robust increase in proliferative capacity after being immunized *in vivo* when compared to their antiphasic control⁷¹. Isolated T cells cultured from mouse lymph nodes proliferated after stimulation in a circadian manner, an effect that was abolished in *Clock* mutant mice⁷². Both observationally and experimentally it has been shown that certain immune cells traffick

according to apparent circadian parameters, possess oscillating intrinsic molecular clocks, have critical transcription factors controlled by clock proteins, and demonstrate altered function when clock proteins are perturbed.

Sleep Disruption and Cognitive Dysfunction in Sedated ICU Patients

Sleep disruption in critically ill patients is a common occurrence in the ICU with the potential to adversely impact patients' outcome and also provide a direct financial detriment with respect to the length of hospital stay and depletion of healthcare resources. Early polysomnographic studies had revealed extreme sleep disruption in ICU patients with decreases in total sleep-time, altered sleep architecture (predominance of stage 1 and 2 sleep, decreased or absent stages 3 and 4 NREM and REM sleep), and sleep fragmentation^{73,74}; also, up to 50% of the total sleep-time occurred during daytime. Among the possible causes that contribute to sleep disruption in the ICU are those related to the patient's acute illness and co-morbidities, environmental factors (including noise and inappropriate light), and iatrogenic factors including frequent care-related interruptions and medications prescribed for analgesia and sedation^{75,76}. Among those that are potentially amenable to modification, excessive noise does not contribute as much as was anticipated⁷⁷ and attention has focused on sedative practices⁷⁸. Sedative-hypnotic agents are widely used to facilitate sleep in the ICU; however, depending on the sedative agent, it may not produce appropriate sleep hygiene and instead will aggravate the problem by producing less of the restorative properties of natural sleep.

Several studies have now demonstrated the association between the use of benzodiazepine (BZD) and increased incidence⁷⁹ and duration⁸⁰ of delirium in medical ICU patients although the relationship of the development and duration of delirium to sleep disruption was not ascertained. Acute withdrawal from long-term sedation with BDZs and opiate narcotics results in profound sleep disruption⁸¹. The pivotal work of the MENDs trial^{79,82,83} indicated the benefits of a specific anesthetic agent, dexmedetomidine in the outcome of ICU population.

Conclusion

Appropriate sleep hygiene is crucial for repair in states of disease and injury and in restoring function especially in the central nervous and immune systems. Lack of sleep hygiene results in cognitive dysfunction, contributes to the delirium that is prevalent in patients within the ICU, adversely affects immunity, and independently increases both morbidity and mortality. Anesthetics used in hospital care have different action targets and ultimately different consequences. Those which act by modulating the GABA_A receptor converge at the level of the hypothalamus while α_2 adrenergic agonists converge on sleep pathways within the brainstem. Thus, thoughtful attention must be made in selecting an anesthetic agent that best mimics natural sleep. Future studies will further elucidate the benefits of dexmedetomidine as a good anesthetic/sedative candidate to mimic natural sleep.

While the fields of investigation into the anesthetic effect on circadian rhythm and the circadian influence on immune function remain disparate to our knowledge, there exists the

plausible concatenation that anesthetics, by altering circadian rhythm (possibly independent of sleep deprivation), affect immune function. Given that anesthetics are often employed adjunctively to facilitate therapeutic interventions, it would be worthwhile to elucidate whether more precise applications of anesthesia could improve immunologic outcomes for patients who require them.

Anesthesia is not the same as sleep. The actions of anesthetics on sleep pathways and the restorative properties of natural sleep for the central nervous system are undeniable and essential, yet they also advance a concomitant advantage to the immune system with fewer infections and greater likelihood of survival from sepsis.

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Key Points

- Anesthetic drugs induce unconsciousness by altering neurotransmission at multiple sites.
- α_2 agonists, like dexmedetomidine, are associated with similar changes in neuronal activity as is seen in deeper stages of NREM sleep.
- The effects of anesthetics on circadian rhythm possibly lead to immune deregulation
- Thoughtful attention must be made in selecting an anesthetic agent that best mimics natural sleep.