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Sleep and Anaesthesia.

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ABSTRACT

While sleep and anaesthesia are two different states, they have shared characteristics, and clinical and experimental observations in one state can have implications for behaviour in the other. General anaesthesia is a sleep-like state, establishes a foundation for the further functional study of slow waves in the sleep-anaesthesia connection, and directs us to a more refined perspective of the role of gamma activity in consciousness and anaesthetic mechanisms

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"And the LORD God caused a deep sleep to fall upon Adam, and he slept; and He took one of his ribs, and closed up the flesh in its place."

Are patients really 'asleep' during surgery? While sleep and anaesthesia are two different states, they have shared characteristics, and clinical and experimental observations in one state can have implications for behaviour in the other. Sleep is a natural state of unconsciousness, the propensity for which is governed by homeostatic drive and circadian variability. It is influenced by psychological and environmental factors, is inhomogeneous (being composed of distinct stages), and is readily reversed by environmental disturbances or once the sleep need is met. Sleep is a ubiquitous metaphor in the modern practice of anaesthesiology, where it is common to hear patients being told "You are going to sleep now" or "Time for a little nap" as anaesthesia is being administered. Such phrases are reassuring, as sleep has positive connotations of restoration and is a state of reversible unconsciousness that every patient has experienced.

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The metaphor is no doubt rooted in the many phenotypic similarities of sleep and anesthesia.[1] Indeed, these two distinct states share a number of important traits such as hypnosis, amnesia, and immobility.[2] In the mid-1990s, it was hypothesized that general anaesthetics might preferentially act via neuronal mechanisms that have evolved to control sleep-wake states.[3] Since that time, a number of sleep-wake nuclei in the brainstem and diencephalon have been demonstrated to be involved in anaesthetic mechanisms.[4] It has also become clear that there is a functional relationship between sleep and anaesthesia. For example, sleep deprivation in animals accelerates the induction of general anaesthesia and delays recovery,[5] a phenomenon mediated in part by the adenosinergic system.[6]

In contrast, general anaesthesia is a drug-induced state of unconsciousness that can be induced independent of homeostatic, circadian, psychological, or environmental factors. Once established, it is a relatively homogeneous state. Its reversal requires drug elimination. The unconsciousness of either state appears to require activation of similar neurological pathways, and understanding the neurobiology of sleep is a key to a better understanding of mechanisms of anaesthesia. There are similarities between the states in the changes in muscle tone and ventilatory drive that accompany conscious state change and, indeed, those vulnerable to upper airway obstruction in one state tend to be vulnerable to it in the other. Obstructive sleep apnea is a risk factor for a 'difficult airway' during anaesthesia, including problems with tracheal intubation or with airway maintenance. The reverse is also true, suggesting that observations of airway behaviour in one state can have implications for it in the other. While the ability to arouse or awaken protects the sleeping individual, anesthetized patients are at particular disadvantage because of drug-induced suppression of arousal responses, necessitating close peri-operative monitoring until consciousness and the ability to readily arouse are restored.

Anesthesiologists ensures that the patient is immobilized, has no pain response, and has no waking memory of the procedure what so ever.

Resembling sleep, general anaesthesia is by no means a restful experience, with the potential of disrupting a patient's photo-entrained circadian rhythm.[7]

EEG patterns of deep anaesthesia can appear more like coma or brain stem death[8], while sleep EEGs can cycle from an active (spindles and K-complexes) to a slow-wave pattern that is found in NREM stage.[9] Sleep is not at all a passive state and the brain cycles (roughly 90-min intervals) through characteristic periods of low-amplitude, high frequency bursts during REM, converting into the ever-slowing waves of NREM. At the slowest (SWS, or slow-wave sleep), NREM stage 3 resembles the intermediate phase of general anaesthesia. At this shared state, natural sleep switches to active REM, while anaesthesia can be guided deeper. It can be said, then, that the sleeping brain is more active than the anesthetized brain. Regarding the nature of unconsciousness at surgical level, different agents (i.e. propofol, sevoflurane, ketamine and dexmedetomidine), curiously, elicit unique EEG signatures, presumably attributed to pharmacological interruption of select neuronal circuits.[10] The circuits that are associated with sleep/arousal, which are photo-entrained, reveal rhythmicity and may continue to clock-on independently of the anaesthesia-interrupted circuits. Conversely, there may be several linkage-points between anaesthesia-labile neuronal wiring and those of sleep, and these have yet to be fully understood. Can circuitry disruptions during anaesthesia adversely affect future sleep? Or, is emergence from anaesthesia a form of re-booting that only requires minor reinforcement of photo-entrainment?

Post-operative sleep disturbance is common in the first six nights (Rosenberg-Adamsen et al. offer a comprehensive starting point in this field of medical research).[8] For the first couple of nights in the hospital, most patients exhibited sleep deprivation in the form of total sleep decline with noticeable REM and SWS impairment. Others presented with fragmented sleep, referring to a disruption of sleep rhythmicity. Following the first couple of nights, then, REM and SWS normally rebound with patients spending more time in these specific stages of sleep. Most sleep disturbances then resolve themselves. Still, 25% of post-surgery patients exhibited sleep quality changes lasting more than two weeks after discharge. Furthermore, the duration of post-operative sleep disturbance correlated with the duration of the surgery. It stands to reason that anaesthesia may, at the very least, be considered complicit in bringing about sleep disturbance. But, there are many other factors that could contribute to sleep disturbance, including the invasiveness of the surgery (pain, cytokine release etc.), environmental factors (noise, lighting, noxious odours, unfamiliarity etc.), psychological factors (anxiety, psychosis, stress etc.), and a myriad of care-related issues (vitals, medications, diagnostic procedures etc.) particularly as the implementation of EMR protocols are now taking priority. Not surprising, the number one factor that patients noted in questionnaire-type studies as contributing to sleep disturbance was 'pain'. What if these other factors were left out, like, for example, in a study of non-surgery volunteers that have undergone 3- hour general anesthesia? In this study, isoflurane caused a modest reduction in SWS and an increase in NREM stage 2 for only one postoperative night, and there were no REM changes noted.[11] While the restorative benefits of NREM stage 2 are readily not apparent, the restorative importance of SWS is described throughout the literature; so, one can speculate that anaesthesia with isoflurane may either act as a minor surrogate for SWS, or alternately, transiently impair the SWS stage. In light of all the data, it may be fair to surmise that the role of anaesthesia in sleep disturbance following surgery is rather small (compared to the other factors described above), but that this role may be highly variable depending on the health status and age of the individual. Continued surveillance of this medical issue is desired, particularly in the elderly.

More research is needed, for example, in defining the molecular correlates to the restorative properties of sleep, in order to assess the role of anaesthesia in affecting these restorative mechanisms. Sleep wake cycles have been modelled to include non-transcriptional mechanisms involving redox processes, such as antioxidant peroxiredoxin proteins.[12] The synchronization of redox repair and the sleep stages may indeed provide the explanation of the restorative nature of sleep. Further investigation using animal models, including zebra fish which have strict requirements for periods of light-dark, may yield translatable results. It would be wise to focus on archetypal ancestral proteins, like the highly-conserved and abundant housekeeping enzyme, GAPDH (MIM: 138400). GAPDH is pivotal in regulating light events in plants. In humans, it is known to regulate GABAergic signals, a logical starting point for investigating the cyclical modulation of sleep-circuits. GAPDH's rather long half-life may represent a neuronal sensor of redox degeneration of all cellular proteins, signaling a cycle of repair and regeneration.

So, are patients really 'asleep' during surgery? Yes and no. Portions of brain waves do show some resemblance. Yet, the differences may suggest that the restorative events that occur in sleep may be disturbed with deep anaesthesia. Discovering proactive measures to prevent restorative sleep loss, thereby increasing positive outcomes, should be a research goal for the future.

CONCLUSION

The study of Murphy et al.[13] supports the hypothesis that general anaesthesia is a sleep-like state, establishes a foundation for the further functional study of slow waves in the sleep-anaesthesia connection, and directs us to a more refined perspective of the role of gamma activity in consciousness and anaesthetic mechanisms.

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