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Axel Hutt *Editor*

Sleep and Anesthesia

Neural Correlates in Theory and Experiment

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Foreword: Computing the Mind

After millennia of philosophical debate, neuroscience now tackles the problem of conscious experience. Cognitive neuroscience investigates the neural correlates of perception, action, and cognition in the conscious state. At the same time, anesthesia and sleep are the exclusive models for the investigation of the reversible transitions between conscious and unconscious states. Anesthesia is particularly useful in that it allows a controlled manipulation of the state of consciousness in a graded manner. While certain system parameters in the brain may change rather abruptly, changes in others are rather graded. The interplay of these processes creates an interesting dynamics that is characteristic to each anesthetic agent. The wide variety of known anesthetic agents with respect to their chemical structure and pharmacological profile allows the fine dissection of their specific molecular, synaptic neuronal effects that mediate the agents' local and global functional and behavioral effects. While we know a lot about the interaction of anesthetic agents with molecular and receptor targets, their actions at systems level trails in understanding. Since the early 1980s, metabolic and functional brain imaging has contributed significantly to the understanding of regional changes in the brain in both sleep and anesthesia. However the regional targets of drug effects underlying the observed images have been more difficult to identify. The brain is so highly interconnected that extrapolation of the underlying mechanism from empirical observations is nearly prohibitive. Theoretical models of causal interactions and computational approaches have been invoked to help overcome this difficulty.

Bridging molecular events that occur under anesthesia or sleep, systems level events, and observable behavior is obviously important for a full understanding of the underlying mechanisms. There has been few attempts to explicitly model large-scale interactions in the brain and to examine state-dependent changes in complexity and dynamics with respect to specific functional systems. In this regard, empirical investigations by functional brain imaging and quantitative electrophysiology are leading the progress ahead of systems modeling. Continued progress from modeling homogeneous systems to structured systems with identified neurofunctional modules and networks is necessary.

A gentle warning toward modeling efforts is in order. In order to describe reality more and more faithfully, computational models of the brain are getting more

and more complex. It becomes relatively easy to simulate a particular behavior, especially when modeling is guided by preconceived notions of what the result has to be. Without very tight experimental validation of all elements in the model, the modeling effort easily become circular. For example, we may think that we know from experimental studies how anesthetics alter the EEG, and we are able to simulate such EEG changes in a generic model of the cortical neuronal network, and then conclude that the model explains how anesthetics work. From this point of view, our experimental techniques lag behind our modeling armamentary; which highlights a serious need for advancing our measurement techniques. There is an appeal in keeping the models as simple as possible while reproducing a principal behavior of question, commensurate with the experimental data available to verify the predictions against.

As another cautionary example, many of the computational studies of EEG dynamics to date model anesthetic action or sleep as a reduction in high-frequency components in the beta–gamma range. But the notion that anesthetic agents attenuate these oscillations near the critical concentration that produces unconsciousness is not at all certain. In fact, experimental studies suggest that robust increases in gamma power occur near the transition point of conscious and unconscious states. Moreover, the results are different in humans, primates and small mammals. Yet all creatures can be anesthetized by the same drugs. This means that our current models are not flexible enough to account for the effect of various anesthetic agents, conditions and species. Yet to understand the specific neural correlates of unconsciousness, defined as minimal necessary conditions, we have to find the common ingredient, the final common pathway or functional change. This requirement continues to present a formidable challenge for future research. A synthesis of knowledge across all relevant levels of complexity and variability has not been achieved. However, the works presented in the current book collectively make a serious attempt toward this goal.

There is another, more fundamental issue that points to future perspectives. Most of the modeling work has been focused on particular features of brain dynamics. For example, in case of the EEG, the variables of interest that describe the dynamics include changes in spectrum, bispectrum, synchrony, coherence, state transition and fluctuation, etc. However, we are interested in the neural correlates of consciousness and its removal in unconsciousness. Can we say that a computer that generates particular waking EEG pattern is conscious? At this point of development, obviously not. Perhaps the dynamics has to be implemented in the wetware of the brain. But then something really important is missing from the model. Even if we interpret our results as a description, not simulation, of dynamics in the wetware of the brain, how do we know that this dynamics is sufficient for conscious experience? A zombie or a very smart computer may have the same dynamics, may be behaviorally awake, but not conscious. It may just process implicit (subconscious) information, in spite of the reproduced familiar functional patterns. But we do not yet know what would make this pattern or dynamics conscious as opposed to unconscious. We are facing

the famous explanatory gap between the objective and subjective realms.[1] Can we bridge this gap?

One possibility to make progress is to try to incorporate the missing "extra ingredient" that goes beyond brain dynamics. Short of assuming something extra-physical or transcendental, a possible postulate is information, particularly, integrated information. One then may ask the question: if a certain brain dynamics is present, does it entail processing of information? A modest first step is an attempt to measure the information capacity in a given brain state. This can be done in many different ways and at many levels from regional, columnar, neuronal, synaptic, receptor, molecular, and quantum levels. Clearly, the higher the resolution the higher the information capacity, but the unit of information in the brain is currently unclear. A second step is to realize that what really counts is integrated information.[2] A high number of parallel information channels transmits a large amount information but does not process it. It has large information capacity but lacks integration. Information processing involves the transformation, manipulation, storage and retrieval of information, together with plasticity of the functional architecture performing these operations. Moreover, integrated information is produced by a system with causal, generative architecture. The resulting dynamics of integrated information is thus thought to give rise to the stream of consciousness.

If consciousness is tied to integrated information, this implies that consciousness can be graded in its content and complexity. As the theory stands, the state of consciousness is determined by the total amount of integrated information alone. It has been postulated that in general anesthesia or dreamless sleep, when there is no subjective experience, information integration is reduced in a graded manner to a level incompatible with conscious perception and purposeful behavior.[3] On the other hand, personal experience suggests that we normally lose consciousness abruptly, which may seem to conflict with the theorized graded nature of consciousness. However, such personal impression may in part be a result of amnesia under both anesthetic and sleep conditions. Also, numerous mathematical modeling studies, e.g. by Steyn-Ross and colleagues,[4] suggested that rapid state transitions of neural dynamics can occur upon graded changes in model parameters relevant to anesthesia and sleep. Thus, even if consciousness might exist at many levels, the process of transition across these levels may be accelerated by physiological regulation, as in sleep-wake transitions, and pharmacological interventions, as in general anesthesia. This calls for an investigation of spontaneous transitions of the state of consciousness near the critical state while exogenous stimuli are controlled and neural parameters are recorded.

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[1] Chalmers DJ (1996) The Conscious Mind: In Search of a Fundamental Theory. Oxford University Press.

[2] Tononi G (2004) An information integration theory of consciousness. BMC Neurosci 5:42.

[3] Alkire MT, Hudetz AG and Tononi G (2008) Consciousness and anesthesia. Science 322(5903):876–880.

[4] Cf. Chap. 8 in this book.

Whether specific brain structures or cortical regions are more critical than others to support the degree of information integration necessary for consciousness is an area of active research. It is most likely that certain enabling systems, such as the ascending activating system, are necessary for information integration in the thalamocortical system. In addition, certain cortical regions may serve as hubs of information exchange and may thus be more critical targets of anesthesia than others. Moreover, different brain regions may play the primary role in removing vs. restoring the conscious state.

Finally, an important distinction to be made is the difference between wakefulness and consciousness because even coordinated movement and behavior does not imply the presence of conscious control, e.g., sleepwalking. It is correct when from gross movement or spontaneous speech the anesthesiologist concludes the patient is "waking up" but this may not be conscious awakening. Thus, the neural correlates of wakefulness and consciousness have to be considered separately. Our current models do not fully account for this difference. The same is true to falling asleep. A further distinction to be made is between losing consciousness (induction) and regaining consciousness (emergence), as these processes may, at least in part, be mediated by different mechanisms. To describe transitions in and out of consciousness during anesthesia or dreamless sleep, one should consider the neural correlates of induction, unconsciousness, and emergence separately.

Milwaukee, USA Anthony G. Hudetz

Preface

Natural sleep and the accompanying loss of consciousness is part of everybody's life. Similarly, general anaesthesia is part of the daily routine in hospital surgery whose aim is, inter alia, to induce hypnosis in patients. The two phenomena share some common features, however differ in other aspects. For instance, it has been shown that the final state in deep sleep and anaesthetic-induced unconsciousness are remarkably similar. However a sleeper may be woken up by shaking or noise whereas an anaesthetized person cannot be brought back to consciousness by external stimuli.

Notwithstanding the importance of sleep for all mammals and many other species and the successful administration of general anaesthesia in surgery, the physiological mechanisms of sleep and anaesthesia are far from being understood. The current book aims to elucidate the similarities and differences of sleep and anaesthesia and gives an overview over corresponding experimental and theoretical techniques. The idea for the book came up after two workshops on the same topic that I had organized during the Computational Neuroscience Conferences 2007 in Toronto and 2009 in Berlin. Many of the contributors to this book have participated in these workshops and stimulated discussions triggered the idea to summarize the different experimental and theoretical approaches. Moreover, interestingly not few contributors to this book working on either sleep or anaesthesia have switched between the two topics in the last years illustrating the strong link between the two research topics.

Typical experiments apply invasive electrophysiology, encephalography and high-resolution imaging technique to extract neural correlates during sleep or anaesthesia. Theoretical models aim to explain the experimentally observed activity and attempt to extract the corresponding underlying neural mechanisms frequently by mathematical models. Since both approaches fertilize each other, the book brings together both experimental and theoretical studies reflecting the current status of research and demonstrating their strong link. The first chapter introduces to the physiological basis of sleep and anaesthesia mostly based on experiments and discusses similarities and differences in physiology. The subsequent chapter then introduces into a unifying theoretical model which explains elements of both sleep and anaes-

thesia. More detailed investigations on either sleep or anaesthesia follow in the subsequent two separate sections.

The book gives an overview of the major approaches and concepts in experiments and theory and hence is ideal for graduate students in anesthesiology and sleep science. It also serves theoretical neuroscientists who are new to anesthesia and sleep and would like to gain an overview of the recent theoretical achievements and hypothesis.

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Nancy, France Axel Hutt

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Chapter 1
Sleep and Anesthesia: A Consideration of States, Traits, and Mechanisms

D. Pal and G.A. Mashour

1.1 Introduction

Sleep and anesthesia are distinct states of consciousness that share numerous traits. Like anesthesia, sleep is characterized by the loss of consciousness, behavioral immobility and little recall of environmental events (Pace-Schott and Hobson 2002; Tung and Mendelson 2004). However, unlike anesthesia, sleep is a spontaneous and endogenous process, shows homeostatic and circadian regulation, can be reversed with external stimuli and does not eliminate the sensitivity to pain (Pace-Schott and Hobson 2002; Tung and Mendelson 2004). As opposed to the historical viewpoint of sleep as a passive process consisting of the mere cessation of waking, it is now well established that sleep is actively generated from the interaction of distinct brain nuclei (Steriade and McCarley 2005). There is now experimental evidence supporting the earlier hypothesis (Lydic and Biebuyck 1994) that the effects of anesthesia may also be mediated through the subcortical brain nuclei that control sleep–wake states (Franks 2008; Lydic and Baghdoyan 2005). In this chapter, we will elaborate on the phenomenology and mechanism of sleep and anesthesia, discussing the similarities as well as differences.

1.2 Sleep—A Physiological Altered State of Consciousness

Sleep can be defined as a naturally occurring physiological altered state of consciousness. A consensus definition of consciousness eludes the scientific community, although most of the definitions would include brain arousal and subjective

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experience as two critical components. In common parlance, 'conscious' connotes awake or aroused and is often used interchangeably with the term 'aware.' Scientifically, 'aware' implies the realization of external and internal cues that together define the world around us and is not the same as being awake or aroused. The dissociation of arousal and awareness is evidenced by patients in vegetative states, who exhibit periodic electroencephalographic arousal in the presumed absence of awareness. A distinction between 'arousal' and 'awareness' is important because our understanding of sleep–wake processes is derived primarily from animal experimentation that relies solely on the 'arousal' component that can be objectively assessed, but does not take into consideration the subjective 'awareness' component of consciousness.

Humans have been fascinated with the phenomena of sleep–wake states since the advent of civilization. Some of the oldest references alluding to sleep–wake phenomena can be found in ancient Hindu philosophical texts (Mandukya Upanishads, 16–11 BC). However, because of the lack of objective experimental tools, it was not until the twentieth century that any focused experimental approach could be applied to study sleep–wake states (Gottesmann 2001). The introduction of electrophysiological techniques, in particular electroencephalography, to study sleep–wake states brought the much needed measure of objectivity to an otherwise highly speculative field. The advent of electroencephalography spurred intense efforts to describe brain activity during sleep–wake states, which culminated in the serendipitous discovery of the state of rapid eye movement (REM) sleep (Aserinsky and Kleitman 1953; see Gottesmann 2001 for an excellent review). It was known that the wake state is marked by low-voltage high-frequency electroencephalogram (EEG) that changes to high-voltage low-frequency at the onset of behavioral sleep (Gottesmann 2001). Aserinsky and Kleitman (1953) first reported the occurrence of low-voltage EEG during behavioral sleep, which otherwise could be observed during the wake state. The low-voltage EEG episodes were accompanied by bursts of rapid eye movements, leading Aserinsky and Kleitman (1953) to coin the term REM sleep. Shortly afterwards, a similar state in cats was demonstrated by Dement (1958). Around the same time Jouvet and colleagues (1959) reported that low-voltage EEG episodes during sleep are accompanied by complete atonia of the neck muscles, thus unraveling a hallmark and unique feature of the state of REM sleep. It was also found that during this state, cats exhibited an increased arousal threshold, which was paradoxical because the electroencephalographic recordings showed an active EEG pattern as was observed during the wake state (Jouvet 2004). This led Jouvet (2004) to name the state of REM sleep as 'paradoxical' sleep or 'rhombencephalic sleep' because of the rhombencephalic or hindbrain/brainstem origin. The discovery of REM sleep was a paradigm shift in the conceptual understanding of sleep because it became obvious that sleep is not a homogeneous state. Because of the distinct REM sleep phase, the rest of the high-voltage low-frequency sleep period came to be known as non-REM (NREM) sleep.

Besides the changes in EEG, there are distinct physiological changes associated with different sleep states. During NREM sleep, brain metabolism, cerebral blood flow, heart rate and blood pressure decrease while the onset of REM sleep

causes a marked increase in all of these physiological processes (Rechtschaffen and Siegel 2000). Brain temperature, which decreases during NREM sleep, increases with the onset of REM sleep (Rechtschaffen and Siegel 2000). The neural activity and hence the neurochemical milieu of the brain shows specific changes associated with different sleep–wake states. The monoaminergic neurons [locus coeruleus (LC)—noradrenergic, dorsal raphe (DR)—serotonergic, and tuberomammillary nucleus (TMN)—histaminergic] discharge at the highest rate during wakefulness, slow down at the onset of NREM sleep and reach the lowest point of activity during REM sleep (Aston-Jones and Bloom 1981; Lin 2000; Lydic et al. 1987; Pace-Schott and Hobson 2002; Steriade and McCarley 2005). The cholinergic neurons in laterodorsal/pedunculopontine tegmentum (LDT/PPT) and basal forebrain (BF) show increased discharge with electroencephalographic arousal as during wakefulness and REM sleep (Jones 2008; Thakkar et al. 1998). A state-dependent modulation of GABAergic tone has been reported from multiple sleep–wake-related areas across the brain (Hassani et al. 2010; Pal and Mallick 2010; Steriade and McCarley 2005; Szymusiak et al. 2007). The changes in regional neuronal activity have been broadly confirmed through neuroimaging studies, which showed (i) a selective deactivation of brainstem, thalamus and BF/hypothalamic region during NREM sleep, and (ii) activation of pontine tegmentum, thalamus and BF during REM sleep (Dang-Vu et al. 2007).

Although the universality of sleep is a matter of intense debate (Mignot 2008; Siegel 2008; Zimmerman et al. 2008), all mammals (terrestrial and marine) as well as birds studied so far show NREM and REM sleep (Siegel 2008). Further, it is to be noted that although characterization of sleep–wake states based on electrophysiological parameters has been successful in humans as well as in laboratory animals, there seems to be a compelling argument to include behavioral criteria to define sleep in species in which electrophysiological recording is not feasible either because of the lack of brain structures comparable to mammals or because of the ecological niche (Siegel 2008; Zimmerman et al. 2008). Our current understanding of sleep–wake phenomena is based on the data from laboratory animals (mostly from cats, rats and mice) and clinical studies. However, unlike human sleep, there is no consensus on the characterization of sleep states in animals, leading to a varied description of sleep states by different laboratories. In addition, interspecies differences in sleep architecture and underlying processes have been shown from the behavioral to cellular level, thus making it imperative to exercise caution when extrapolating the results to humans (Capece et al. 1999; Siegel 2008).

1.2.1 Brain Mechanisms Underlying Wakefulness and NREM Sleep Generation/Regulation

Role of forebrain in sleep–wake generation/regulation The first clear assertion of sleep as an active phenomenon and the existence of sleep and wake regulatory centers can be attributed to Constantin von Economo (reviewed in Triarhou 2006).

He observed that some of the patients afflicted with encephalitica lethargica, the disease that now bears his name, showed extreme lethargy and somnolence whereas other patients in the chronic phase showed insomnia. On the basis of postmortem neuropathological observations, he concluded that the area encompassing posterior hypothalamus/rostral midbrain is involved in wake regulation whereas the anterior hypothalamic region regulates sleep. His clinical observations were later confirmed by experimental evidence that showed the presence of a sleep-promoting structure in the anterior hypothalamus (preoptic area—POA) and a wake-promoting structure in the posterior hypothalamus (Steriade and McCarley 2005; Szymusiak et al. 2007).

Loss/gain of function studies as well as physiological data from neuronal recordings have provided considerable insights into the functioning of the subdivisions of the hypothalamic region in sleep–wake regulation (Szymusiak et al. 2007). Thus, the median preoptic (MnPO) and ventrolateral preoptic (VLPO) subdivisions of the anterior hypothalamic/POA have GABAergic neurons that show increased discharge rate during NREM sleep and are sleep-active neurons (Szymusiak et al. 2007). TMN in posterior hypothalamus (PH) and perifornical area in the lateral hypothalamus (LH) have histaminergic and orexinergic neurons, respectively, both of which are the 'wake-ON' type of neurons (Szymusiak et al. 2007). LH also contains GABAergic neurons intermingled with orexinergic neurons and neurons positive for melanin concentrating hormones (MCH). A recent report showed that in contrast to the orexinergic neurons, which discharge at highest rate during wakefulness, the GABAergic and MCH containing neurons in LH are inactive during wake state and instead fire during sleep (Hassani et al. 2009, 2010; Jones 2008). Therefore, within LH there are two opposing influences on sleep–wake states—orexinergic neurons promote wake/arousal and GABA and MCH positive neurons promote sleep. Cholinergic neurons in the BF are active during wakefulness and REM sleep (Jones 2008), thus contributing to cortical activation. Co-distributed with cholinergic neurons in the BF are GABAergic neurons, which are active during sleep (Jones 2008). To summarize, the forebrain has arousal promoting neurons in (i) LH (orexinergic), (ii) PH (histaminergic) and (iii) BF (cholinergic) whereas sleep related neurons are (i) GABAergic neurons located in VLPO, MnPO, LH and BF, and (ii) MCH neurons in LH (Hassani et al. 2009, 2010; Jones 2008; Lin 2000; Szymusiak et al. 2007).

Role of brainstem in sleep–wake generation/regulation The forebrain is capable of maintaining states resembling sleep and wakefulness in isolation from the rest of the brain (Villablanca 2004). However, normal sleep–wake states are a result of the interaction between forebrain and brainstem processes. There are reciprocal connections between forebrain and brainstem sleep–wake-related neurons (Franks 2008; Jones 2008; Szymusiak et al. 2007; Villablanca 2004). The pioneering studies done in the laboratory of Horace Magoun unequivocally demonstrated the role of rostral brainstem/midbrain in arousal and EEG activation. Electrical stimulation of the midbrain reticular formation (MRF) produced EEG activation (Moruzzi and Magoun 1949) whereas lesions in the midbrain tegmentum caused behavioral stupor and a continuous synchronized (high-voltage low-frequency) EEG (Lindsley

et al. 1949). Neuronal recordings showed the presence of wake-related neurons in MRF (Manohar et al. 1972) and electrical stimulation of MRF excited the wake-ON neurons in LC (Thankachan et al. 2001). Inactivation of MRF and the anterior pontine region by intracarotid injection of thiopental replaced the low-voltage high-frequency EEG with high-voltage low-frequency EEG (Magni et al. 1959). Similar inactivation of the posterior pontine region and medulla oblongata by intravertebral injections resulted in EEG activation, thus indicating the presence of a hypnogenic influence in the caudal brainstem (Magni et al. 1959). Stimulation of the medullary nucleus of the solitary tract (NTS) in caudal brainstem produced EEG synchronization (Magnes et al. 1961) while microinjection of morphine into NTS caused a dose-dependent increase in NREM sleep (Reinoso-Barbero and de Andres 1995). Stimulation of caudal brainstem in free moving, normally behaving cats produced an excitatory effect on the REM-ON neurons in PPT (Mallick et al. 2004). Similar mild electrical stimulation of prepositus hypoglossi in rats increased sleep (Kaur et al. 2001). Further, a recent study has shown the presence of neurons active during REM sleep in dorsal paragigantocellular nucleus (Goutagny et al. 2008). Collectively, these studies demonstrate the role of midbrain in arousal and caudal brainstem in sleep-promoting activity.

1.2.2 Brain Mechanisms Underlying REM Sleep Generation/Regulation

Noradrenergic and cholinergic regulation of REM sleep Brainstem transections along the neuraxis showed that the ponto-medullary region plays a critical role in the generation of REM sleep (Jouvet 1962; Siegel et al. 1984; Vanni-Mercier et al. 1989). Extracellular recordings from different brainstem sites provided the crucial insights into the neural circuitry involved in REM sleep regulation. Initial studies showed the presence of neurons in pontine reticular formation (PRF) that (i) increase discharge before the onset of REM sleep and continue for the duration of the state, known as REM-ON neurons, and (ii) decrease discharge before the onset of REM sleep and remain suppressed for the duration of the state, known as REM-OFF neurons (Chu and Bloom 1974; Hobson et al. 1975; McGinty and Harper 1976; Vertes 1977). Refinement of the histological techniques over the decades allowed the identification of these REM sleep related neurons. Thus, the monoaminergic REM-OFF neurons in the pontine region—noradrenergic neurons in LC and serotonergic neurons in DR—show a state-dependent discharge with maximum activity during wakefulness, which progressively decreases through NREM sleep to almost cessation during REM sleep (Aston-Jones and Bloom 1981; Lydic et al. 1987). The cholinergic neurons in LDT/PPT in the pontine region can be categorized into two sub-populations: (i) REM-ON neurons that start firing just before the onset of REM sleep, and (ii) wake-ON/REM-ON neurons that fire during both wake and REM sleep states (Thakkar et al. 1998). Stimulation of LC, the site of REM-OFF neurons, decreases REM sleep (Singh and Mallick 1996)

whereas stimulation of LDT/PPT increases REM sleep (Datta and Siwek 1997; Thakkar et al. 1996). LC and LDT/PPT receive orexinergic projections from wake-active perifornical hypothalamic neurons (Peyron et al. 1998). Disinhibition of perifornical hypothalamic neurons excites LC noradrenergic neurons (Lu et al. 2007) and bath application of orexin depolarizes PPT cholinergic neurons (Kim et al. 2009). Infusion of orexin, an excitatory neuropeptide, into LC and LDT increased waking and decreased REM sleep (Bourgin et al. 2000; Xi et al. 2001).

LC and LDT/PPT share reciprocal anatomical connections and the neurochemical interplay between the monoaminergic and cholinergic neurons plays a fundamental role in the generation and maintenance of REM sleep (Hobson et al. 1975; Steriade and McCarley 2005). Pharmacological blockade of cholinergic transmission in LC decreases REM sleep (Mallick et al. 2001) whereas blocking noradrenergic transmission in PPT increases REM sleep (Pal and Mallick 2006). Cholinergic efferents from LDT/PPT innervate PRF, which is also known as the REM sleep induction zone (Reinoso-Suárez et al. 2001). Stimulation of PPT increases acetylcholine (ACh) release in PRF (Lydic and Baghdoyan 1993) and ACh levels increase in PRF during spontaneous REM sleep (Lydic and Baghdoyan 2005). Microinjection of cholinergic agonists into PRF increases REM sleep (Baghdoyan et al. 1984), which can be blocked by systemic co-administration of a cholinergic antagonist (Baghdoyan et al. 1989). Therefore, ACh plays an executive role whereas noradrenaline plays a permissive role in REM sleep generation.

Role of GABA in REM sleep generation An increasing number of studies indicate that GABA plays a central role in the generation of REM sleep, possibly through the modulation of pontine REM-OFF and REM-ON neurons (Pal and Mallick 2011). GABAergic neurons in LC and LDT/PPT are active during recovery REM sleep following REM sleep deprivation (Maloney et al. 1999). GABA concentration increases in LC during REM sleep (Nitz and Siegel 1997). Enhancement of GABAergic transmission in LC through GABA microinjection (Mallick et al. 2001) or stimulation of prepositus hypoglossi, which increases GABA concentration in LC, increases REM sleep (Kaur et al. 2001). Microinjection of GABA antagonist into LC decreases REM sleep (Mallick et al. 2001) whereas iontophoretic application of GABA into LC inhibits the putative noradrenergic REM-OFF neurons (Gervasoni et al. 1998). LC receives GABAergic projections from the extended VLPO area and these neurons have been shown to be active during REM sleep (Lu et al. 2002). Microinjection of GABA-A antagonist into PPT decreases REM sleep (Pal and Mallick 2004; Torterolo et al. 2002) whereas GABA-A agonist injection into PPT increases REM sleep (Pal and Mallick 2009; Torterolo et al. 2002). Pharmacological stimulation of GABAergic substantia nigra pars reticulata, which should increase GABA levels in PPT, increased the time spent in REM sleep (Pal and Mallick 2009). Therefore, GABA in LC and PPT promotes REM sleep (Mallick et al. 2001; Nitz and Siegel 1997; Pal and Mallick 2004, 2009; Torterolo et al. 2002). In addition, there is strong evidence that GABA from ventrolateral periaqueductal gray and dorsal paragigantocellular nucleus plays a critical role in REM sleep regulation, possibly through the modulation of the pontine monoaminergic and cholinergic neurons

(Goutagny et al. 2008; Sastre et al. 1996; Vanini et al. 2007). Interestingly, a recent study showed that the GABA levels in mPRF are lowest during REM sleep as compared to wake state (Vanini et al. 2011). This is in contrast to LC and LDT/PPT where the GABA level/tone is high during REM sleep (Nitz and Siegel 1997; Maloney et al. 1999). Therefore, the GABAergic modulation of sleep–wake states is site dependent.

1.3 Anesthesia—A Pharmacological Induced Altered State of Consciousness

Sleep is a ubiquitous metaphor for the state of general anesthesia because it serves as our experiential basis of unconsciousness and has the reassuring association with restoration. Sleep, like anesthesia, is characterized by the loss of consciousness. The decrease in global cerebral metabolism during NREM sleep is similar to that observed under anesthesia (Boveroux et al. 2008). Furthermore, regionally specific metabolic decreases in the polymodal cortices (the fronto-parietal network) during NREM sleep is comparable to that occurring under intravenous (IV) and inhalational anesthesia (Boveroux et al. 2008). Most general anesthetics produce high-voltage low-frequency EEG, which is also a characteristic feature of NREM sleep. Halothane and propofol cause spindles in EEG, which show a remarkable similarity to the spindles occurring during NREM sleep (Ferenets et al. 2006; Keifer et al. 1996). In spite of the apparent similarities in the behavioral and electroencephalographic traits, sleep and anesthesia have notable differences. Sleep is a naturally occurring altered state of consciousness whereas anesthesia is exogenously induced. As opposed to anesthesia, sleep does not eliminate the sensitivity to pain, is homeostatically regulated and is tightly coupled with hormonal release. Unlike sleep, the neurophysiology of general anesthesia is not characterized by cycles of cortical deactivation and activation, but rather a stable pattern once steady-state drug levels have been achieved. Furthermore, electrophysiological correlates of deeper anesthesia such as burst suppression are not observed during natural sleep.

There is a growing body of literature supporting the thought that loss of consciousness associated with anesthesia results in part from the activity at the subcortical nuclei involved in sleep–wake regulation (Franks 2008; Lydic and Baghdoyan 2005; Lydic and Biebuyck 1994). Anesthetics can induce loss of consciousness by inactivating the arousal-related centers or by activating the sleep or EEG synchrony areas. The arousal network is comprised of (i) monoaminergic neurons in LC, DR, TMN, (ii) cholinergic neurons in LDT/PPT and BF, and (iii) orexinergic neurons in LH-perifornical area (Franks 2008; Jones 2008; Lydic and Baghdoyan 2005; Steriade and McCarley 2005). The sleep or EEG synchrony-inducing neurons are located in anterior hypothalamic-POA, BF and NTS (Magnes et al. 1961; Mallick et al. 1983; Szymusiak et al. 2007). Redundancy is a common feature of the central nervous system, which is also true for sleep–wake/arousal pathways. The redundancy of the sleep–wake structures was highlighted by a recent report

that the daily wake levels were unaltered after the ablation of three arousal-related neuronal populations—cholinergic BF, noradrenergic LC and histaminergic TMN (Blanco-Centurion et al. 2007). Therefore, it is unlikely that any one group of neurons will be sufficient to generate arousal or sleep states. By corollary, it can be argued that a functional network rather than a single locus may underlie the state of anesthesia. Although more is known about the neuronal structures involved in sleep–wake regulation (Franks 2008; Jones 2008; Lydic and Baghdoyan 2005; Steriade and McCarley 2005), our understanding of the mechanism underlying the anesthetic-induced loss of consciousness is rapidly growing.

1.3.1 GABAergic Processes and Anesthetic Mechanisms

GABA-A agonist injection into the septohippocampal system potentiates the effect of general anesthetics by reducing the dose required for the induction of loss of righting reflex (Ma et al. 2002). Infusion of muscimol, a GABA-A agonist, into TMN produced a dose-dependent sedation as measured by the loss of righting reflex (Nelson et al. 2002). By contrast, GABA antagonism in TMN decreases the efficacy of systemically administered propofol and pentobarbital as reflected by a decrease in the duration of loss of righting reflex (Nelson et al. 2002). Devor and Zalkind (2001) reported that infusion of pentobarbital into mesopontine tegmentum induced a short latency, short lasting anesthesia-like state, which is similar to the state of anesthesia induced by systemic pentobarbital injection. The pentobarbital microinjection into mesopontine tegmentum caused a marked decrease in the neuronal activity (as measured by c-fos assay) throughout the cerebral cortex as well as subcortical structures, an effect replicated by intraperitoneal pentobarbital administration (Abulafia et al. 2009). Interestingly, lidocaine injection into the same site did not induce an anesthesia-like state, which indicates that the pentobarbital-induced loss of consciousness is not mediated through the local inactivation of this area (Devor and Zalkind 2001). It has been demonstrated that carbachol (cholinergic agonist) injections in and around mesopontine tegmentum induces REM sleep in rats (Bourgin et al. 1995), indicating similar neuroanatomic loci underlying sleep and anesthesia. Further, a number of studies have demonstrated the effect of GABA-active sedative/anesthetics on sleep architecture and sleep–wake-related areas. Systemic administration of pentobarbital and propofol (i) increased c-fos expression in VLPO, which is a part of the sleep-promoting network, and (ii) decreased c-fos expression in TMN, which is a part of the arousal promoting network (Nelson et al. 2002). Barbiturates (pentobarbital) and benzodiazepines administered systemically at sub-anesthetic doses increase the intermediate stage of sleep at the expense of REM sleep (Gottesmann et al. 1998). Infusion of pentobarbital (Mendelson 1996), triazolam (Mendelson and Martin 1992) and propofol (Tung et al. 2001a) into medial preoptic area decreased sleep latency and increased NREM sleep. GABA in medial pontine reticular formation (mPRF) increases arousal (Xi et al. 1999) whereas GABA levels in mPRF decrease during isoflurane anesthesia (Vanini et al. 2008).

Increasing GABA transmission in mPRF increased the isoflurane induction time (i.e., reduced efficacy) whereas decreasing GABA transmission in the same site decreased isoflurane induction time (Vanini et al. 2008). Keifer et al. (1996) reported that halothane decreases the release of ACh in mPRF. Infusion of GABA antagonist into mPRF increases ACh release, possibly by blocking the pre-synaptic GABAergic receptors on the cholinergic terminals (Vazquez and Baghdoyan 2004). In a recent study, Vanini et al. (2011) showed a significant increase in PRF GABA levels during wake state as compared to REM sleep. These studies reinforce the idea that a neuronal network rather than a single locus underlies a behavioral trait, which is also an outcome of the interaction among multiple neurotransmitter systems.

1.3.2 Cholinergic Processes and Anesthetic Mechanisms

A vast body of literature supports cholinergic generation of arousal states (Jones 2008; Lydic and Baghdoyan 2005). Cholinergic neurons in (i) LDT/PPT through efferents to intralaminar and midline thalamic nuclei, and (ii) BF through efferents to cortex, promote behavioral and electroencephalographic arousal (Jones 2008; Lydic and Baghdoyan 2005; Steriade and McCarley 2005). ACh levels in cortex, thalamus and mPRF are highest during waking and REM sleep, the states characterized by cortical activation (Jones 2008; Lydic and Baghdoyan 2005; Lydic et al. 1991; Steriade and McCarley 2005). Therefore, it is evident that ACh suppresses the high-voltage low-frequency EEG and the spindles associated with NREM sleep. Halothane decreases ACh release in mPRF (Keifer et al. 1994, 1996) and in addition causes EEG spindles that are similar to the spindles observed during NREM sleep (Keifer et al. 1994). Microinjection of cholinergic agonist carbachol into mPRF before halothane administration significantly reduced the number of EEG spindles (Keifer et al. 1996). Ketamine has also been shown to decrease ACh release in mPRF (Lydic and Baghdoyan 2002) whereas intraperitoneal propofol decreases the cortical and hippocampal ACh levels in a dose-dependent manner (Kikuchi et al. 1998). 192IgG-Saporin lesion of cholinergic neurons in BF, which should putatively decrease the cortical and hippocampal ACh levels, enhanced the potency of propofol anesthesia (Laalou et al. 2008). Infusion of nicotine into the centromedian thalamus, which receives afferents from LDT/PPT, restored mobility and righting in sevoflurane-anesthetized rats (Alkire et al. 2007).

Cholinergic involvement in anesthetic mechanisms is further demonstrated by a study showing that the dose required to induce loss of consciousness is increased following prior IV administration of a cholinesterase inhibitor, physostigmine (Fassoulaki et al. 1997). IV administration of physostigmine following propofol-induced anesthesia reversed the anesthetic-induced loss of consciousness (Meuret et al. 2000) and significantly reduced the recovery time following IV ketamine administration (Toro-Matos et al. 1980). The arousing effect of physostigmine could be reversed with the prior administration of scopolamine, a cholinergic antagonist

(Meuret et al. 2000). Physostigmine has also been shown to antagonize the hypnotic effects of sevoflurane (Plourde et al. 2003). Therefore, a decrease in the central cholinergic tone is conducive to the state of anesthesia.

1.3.3 Monoaminergic Processes and Anesthetic Mechanisms

Noradrenergic and histaminergic systems are causally and positively related to behavioral and EEG indices of arousal (Aston-Jones and Bloom 1981; Berridge and Foote 1996; Bovet et al. 1958; Lin 2000). The activity of histaminergic neurons has been shown to be linked to vigilance and the degree of alertness (Takahashi et al. 2006). Inhalational anesthetics hyperpolarize neurons in LC and DR (Sirois et al. 2000; Washburn et al. 2002). Infusion of an alpha-2 agonist, dexmedetomidine, into LC produces hypnosis that could be prevented through simultaneous infusion of alpha-2 antagonist atipamezole (Correa-Sales et al. 1992). The sedation produced by the action of dexmedetomidine on LC is through the disinhibition of VLPO neurons, which are thought to play an executive role in the generation of NREM sleep (Nelson et al. 2003). Activation of adrenergic alpha-1 receptors decreases whereas antagonism of alpha-1 receptors increases barbiturate anesthesia time (Mason and Angel 1983; Matsumoto et al. 1997). Pretreatment with a beta-adrenergic blocker also increased barbiturate anesthesia time in a dose-dependent manner (Mason and Angel 1983). Halothane decreased the histamine release in anterior hypothalamus, which is also reported to occur during sleep (Mammoto et al. 1997; Strecker et al. 2002). Intracerebroventricular (ICV) administration of histamine decreased pentobarbital-related hypnosis and hypothermia (Kalivas 1982). A recent study by Luo and Leung (2009) showed that the infusion of histamine into BF during isoflurane anesthesia in rats caused a decrease in burst suppression, which could be blocked by a prior infusion of H1 antagonist into BF. Further, histamine significantly reduced the time to recovery whereas H1 antagonist into BF significantly increased the time to recovery (Luo and Leung 2009). Collectively, these studies indicate that the activation and inactivation of monoaminergic nuclei, respectively, inhibit and enhance the efficacy of anesthetics.

1.3.4 Orexinergic Processes and Anesthetic Mechanisms

Orexinergic neurons in LH-perifornical area send dense projections to the arousal-related nuclei LC, DR, TMN, PPT and LDT (Peyron et al. 1998). ICV or local infusion of orexins into LC increases wakefulness (Bourgin et al. 2000). Interestingly, ICV application of orexin (i) decreased ketamine-induced noradrenaline release in medial prefrontal cortex, a target site of LC neurons (Tose et al. 2009), and (ii) reduced the time under anesthesia induced by ketamine (Tose et al. 2009) and barbiturates (Kushikata et al. 2003). Similar results have been reported with the use

of inhalational anesthesia. ICV orexin in isoflurane-anesthetized rats reduced burst suppression and produced EEG activation (Yasuda et al. 2003). Infusion of orexin-A into BF of isoflurane-anesthetized rats caused electroencephalographic arousal and a significant increase in the cortical ACh release (Dong et al. 2006). In sevoflurane-anesthetized rats, infusion of orexin-A into BF caused not only electroencephalographic arousal but also significantly decreased emergence time from anesthesia (Dong et al. 2009).

Orexinergic neurons in C57BL/6J mice show decreased c-fos expression, a marker for neural activity, under isoflurane and sevoflurane anesthesia (Kelz et al. 2008). Systemic administration of orexin-A antagonist delayed the emergence from the inhalational anesthesia (Kelz et al. 2008). Delayed emergence from sevoflurane and isoflurane was also observed in orexin/ataxin-3 narcoleptic mice, which have a deficient orexinergic system (Kelz et al. 2008). Studies from different laboratories have indicated the pre-eminence of orexin-A over orexin-B in the mediation of anesthetic effects (Dong et al. 2006, 2009; Kelz et al. 2008; Kushikata et al. 2003; Tose et al. 2009). Orexin-A directly depolarizes the PPT neurons (Kim et al. 2009), which innervate PRF (Reinoso-Suárez et al. 2001). Microdialysis delivery of orexin-A into PRF increases local ACh release (Bernard et al. 2003), whereas halothane and ketamine decrease the ACh release in PRF (Keifer et al. 1994, 1996; Lydic and Baghdoyan 2002). Therefore, it is evident that inactivation of orexinergic system is associated with the hypnotic component of general anesthesia. Furthermore, the orexinergic system interacts with noradrenergic and cholinergic systems to maintain arousal states and possibly emergence from certain anesthetics.

1.3.5 Adenosinergic Processes and Anesthetic Mechanisms

Adenosine, a purine nucleoside, is a product of serial dephosphorylation of adenosine triphosphate. Adenosine receptors are expressed in high concentration in brain, where adenosine acts as a neuromodulator through extracellular and intracellular signaling pathways (Dunwiddie and Masino 2001). A role for adenosine in neuroprotection, epilepsy, vasodilation, and analgesia has been demonstrated (Dunwiddie and Masino 2001). Adenosine has hypnogenic properties and has been shown to play a role in sleep–wake homeostasis (reviewed in McCarley 2007). Adenosine concentration in BF has been reported to increase during sleep deprivation (McCarley 2007). Systemic and ICV application of adenosine agonist in rat increases delta power and the changes produced in EEG power spectra were comparable to that observed after sleep deprivation (Benington et al. 1995). In addition to a role in the modulation of sleep–wake states, adenosine is also known to impact the effects of anesthetics. Sleep deprivation decreases the time to loss of righting reflex and increases post-anesthetic recovery time (Tung et al. 2002). However, pretreatment of sleep-deprived rats with systemic and/or local administration of adenosine antagonist into BF increased the time to loss of righting reflex and decreased the

post-anesthetic recovery time, demonstrating a role for adenosine in increased sensitivity to anesthetics after sleep deprivation (Tung et al. 2005). Intraperitoneal administration of adenosine shortened the induction time and enhanced the potency of thiopental, propofol and midazolam (Kaputlu et al. 1998). Perioperative administration of adenosine decreased the requirement for isoflurane anesthesia and postoperative analgesics (Segerdahl et al. 1995) whereas theophylline, an adenosine antagonist, partially reversed the effects of isoflurane in dogs as indicated by increased cerebral metabolic rate for oxygen and the appearance of higher frequencies in EEG (Roald et al. 1990). Dialysis delivery of adenosine A1 receptor agonist into mPRF of cats produced a significant delay in the post-halothane recovery and a decrease in the ACh release in mPRF (Tanase et al. 2003). The effect of adenosine agonist on post-halothane recovery period and ACh release in mPRF could be reversed with co-administration of an adenosine antagonist (Tanase et al. 2003). IV administration of adenosine caused significant reduction in minimum alveolar concentration (MAC) for halothane in dogs (Seitz et al. 1990). Although the effects of IV adenosine in dogs could be blocked by concurrent administration of the adenosine antagonist aminophylline (Seitz et al. 1990), aminophylline alone has not been shown to affect halothane MAC in dogs (Nicholls et al. 1986). Similar results were obtained in human volunteers in whom aminophylline administration alone did not affect desflurane MAC (Turan et al. 2010). However, in the same study it was reported that aminophylline increased the time to loss of consciousness and decreased the time to regain consciousness in humans subjects anesthetized with propofol (Turan et al. 2010).

1.4 Functional Relationship of Sleep and Anesthesia

Both sleep and anesthesia are marked by a significant decrease in global cerebral metabolism and immobility. Further, the anesthetic state is a period of physiological and behavioral quiescence, which may provide a sleep-like experience. Tung and colleagues (2001b) found that prolonged IV administration of propofol in rats did not cause sleep rebound during the post-propofol recovery period, indicating that no sleep debt had accrued during the time under anesthesia. Under normal conditions, sleep deprivation is followed by a period of increased sleep or rebound in sleep, thereby compensating for the lost sleep time. Administration of propofol for 6 h in previously sleep-deprived rats demonstrated no difference in sleep during the post-anesthesia period as compared to natural recovery, thereby suggesting that the period under propofol anesthesia may serve a restorative purpose akin to sleep (Tung et al. 2004). In contrast to the propofol study (Tung et al. 2004), we recently showed that 4 h of isoflurane treatment following 24 h of selective REM sleep deprivation did not allow the recovery of REM sleep (Mashour et al. 2010). However, as has been reported earlier for total sleep deprivation (Tung et al. 2002), selective REM sleep restriction reduced the anesthetic requirement to achieve the same behavioral and electrophysiologic endpoint (Mashour et al. 2010). Thus, propofol allows the