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Sleep, Anesthesiology, and the Neurobiology of Arousal State Control

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Sleep, like breathing, is a biologic rhythm that is actively generated by the brain. Neuronal networks that have evolved to regulate naturally occurring sleep preferentially modulate traits that define states of sedation and anesthesia. Sleep is temporally organized into distinct stages that are characterized by a unique constellation of physiologic and behavioral traits. Sleep and anesthetic susceptibility are genetically modulated, heritable phenotypes. This review considers 40 yr of research regarding the cellular and molecular mechanisms contributing to arousal state control. Clinical and preclinical data have debunked and supplanted the primitive view that sleep need is a weakness. Sleep deprivation and restriction diminish vigilance, alter neuroendocrine control, and negatively impact immune function. There is overwhelming support for the view that decrements in vigilance can negatively impact performance. Advances in neuroscience provide a foundation for the sea change in public and legal perspectives that now regard a sleep-deprived individual as impaired.

ANESTHESIOLOGY has a major stake in understanding the impact of sleep on clinical performance and career sustainability.[1–9] Vigilance is part of the logo of the American Society of Anesthesiologists, and sleep deprivation impairs vigilance[10] and neurocognitive function.[11] There is overwhelming support for the view that decrements in vigilance can negatively impact performance.[1,2,12–16] Demanding call schedules, increasing numbers of patients, and a shortage of caregivers further reinforce the relevance of fatigue for medical practice. A growing body of human data suggest that recurrent sleep restriction can contribute to significant neuroendocrine disruption.[17,18] The publication by the U.S. Institute of Medicine,[19] attributing as many as 98,000 deaths per year to medical errors, has further encouraged efforts to understand the regulation of vigilance and management of fatigue.

The clinical significance of sleep-dependent changes in autonomic control[20] has contributed to the development of sleep disorders medicine.[21,22] Advances in sleep medicine are being incorporated into anesthesiology practice.[23–32] The developing interaction between anesthesiology research and sleep research indicates the need for a review that highlights aspects of sleep neurobiology of particular relevance for anesthesiology. This article provides an update on the neurobiology of arousal state control by selectively reviewing (1) sleep phenomenology; (2) the regulation of arousal states by multiple brain regions; (3) the cholinergic model of rapid eye movement (REM) sleep; (4) the regulation of traits that define arousal states; and (5) neurochemical modulation of arousal states by acetylcholine, adenosine, γ-aminobutyric acid (GABA), monoamines, and hypocretin/orexin. The article concludes by identifying gaps in existing knowledge that provide opportunities for anesthesia research.

Sleep Is Temporally Organized, Homeostatically Regulated, and Actively Generated by the Brain

In 1953, it was shown for the first time that humans have a unique phase of sleep during which the cortical electroencephalogram is activated. The Chicago laboratory responsible for this discovery also noted the presence of disconjugate eye movements, for which this state was named rapid eye movement, or REM, sleep.[33] REM sleep accounts for approximately 20% of a normal night of sleep, whereas the remaining 80% is comprised of non–rapid eye movement (NREM) sleep. Sleep is not merely the passive loss of wakefulness. Sleep states are actively generated by the central nervous system (CNS). Sleep is homeostatically regulated and temporally organized into distinct phases. During a normal sleep interval, there is a regular and periodic oscillation between the REM and NREM phases. This periodicity also illustrates that sleep, similar to breathing, is actively generated by the nervous system. Sleep deprivation is normally followed by an increase in sleep. This rebound increase demonstrates the homeostatic regulation of sleep.[34]

Normal sleep exhibits a dynamic architecture, and that temporal organization must be preserved if sleep is to produce the subjective experience of being restful and refreshing.[22,35] Any number of physiologic signs could

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have been chosen to name the two major phases of sleep. For example, REM sleep also is characterized by the presence of an activated cortical electroencephalogram. The activated electroencephalogram is comprised of fast-frequency, low-amplitude waves. This activated electrographic pattern has given rise to descriptions of REM sleep as "active" sleep and to the NREM phase of sleep as "quiet" sleep. It is interesting to note that the cortical electroencephalogram during REM sleep is similar to the electroencephalogram of alert wakefulness. This similarity likely arises, in part, from cerebral metabolic and hemodynamic characteristics of REM sleep. Measures of cerebral blood flow and glucose utilization show that the brain is as metabolically active during REM sleep as it is during wakefulness.[36–39] This activation of the cortical electroencephalogram fits well with the fact that cognitive changes and the mental experience of dreaming occur during REM sleep.[40] To French investigators, the electroencephalographic similarity between wakefulness and REM sleep gave rise to the term *sommeil paradoxical*, or paradoxical sleep.[41] Therefore, the terms REM sleep, active sleep, and paradoxical sleep all refer to the same state. Human sleep is consolidated into bouts of 6–8 h.[22,35] The daily drive to sleep is modulated by the hypothalamic suprachiasmatic nuclei that coordinate circadian (24-h) rhythms. The time at which we experience the desire to sleep is regulated by both circadian and ultradian rhythms. Individuals who live to age 70 yr will have spent more than 20 yr sleeping. Mathematical and conceptual models of sleep cycle control have operationally defined this circadian modulation as *process C* and a homeostatic process, modeled by spectral analysis of the electroencephalogram, as *process S*.[34] During a normal night of sleep, the brain actively generates an ultradian ($<<$ 24 h) rhythm of NREM and REM sleep. The human NREM–REM period duration is approximately every 90 min. Pioneering studies postulated that the NREM–REM cycle was generated, in part, by the interaction between cholinergic and monoaminergic neurons.[42,43] Subsequent mathematical and cellular models provided support for the view that the NREM–REM cycle resulted from the reciprocal interaction between cholinergic and monoaminergic neurons.[44] Much of research in sleep neurobiology continues to confirm, refute, and refine postulates of the reciprocal interaction model and the two-process model of sleep cycle control.[45–47] The emerging appreciation that sleep comprises a significant portion of the human condition continues to generate enthusiasm for efforts to understand the neurobiology of arousal state control.

Multiple Brain Regions Generate Arousal States

For more than 20 yr, anesthesiologists have asserted that there is no single mechanism causing states of anesthesia.[48] There is now good agreement that a single

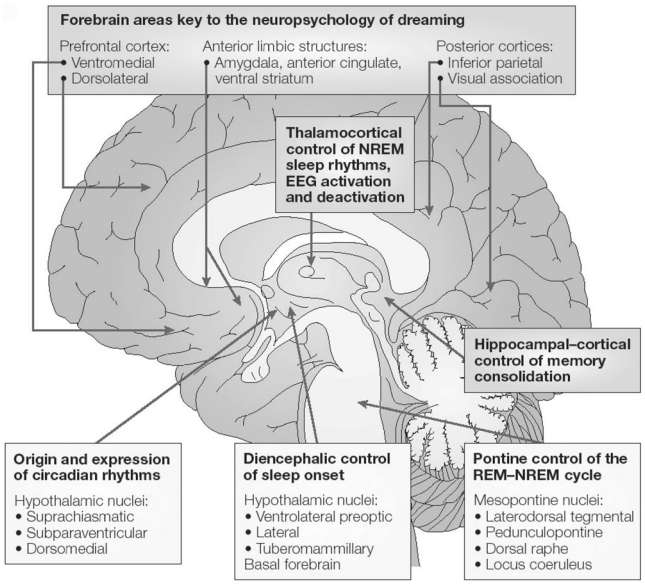

Fig. 1. Sagittal schematic drawing of the human brain illustrating regions that contribute to the regulation of sleep and wakefulness. The diagram emphasizes regulation of physiologic traits and arousal states by neural circuits that are distributed throughout the brain. EEG = electroencephalographic; REM = rapid eye movement; NREM = non–rapid eye movement. From Hobson and Pace-Schott;[77] used with permission from *Nature* (http://www.nature.com/).

mechanism of anesthetic action cannot account for the physiologic and behavioral traits used to define anesthetic states.[49–52] Anesthesia and sleep are different states sharing some remarkably similar physiologic and behavioral traits. As noted elsewhere,[53] anesthesia and sleep have so many trait similarities that patients are often told that anesthesia will put them to sleep. Sleep is a comforting metaphor[54] for an altered arousal state caused by toxic molecules, many of which have startling similarities between their ED_{50} and their LD_{50}. There is good agreement between clinical and preclinical research that spontaneously occurring states of arousal are generated by anatomically distributed and chemically heterogeneous neurons.[22,35,52,55] The hypothesis that neuronal networks which evolved to regulate naturally occurring sleep preferentially modulate traits that define states of sedation and anesthesia[49,56,57] has received consistent support.[58–70]

More than 150 yr of clinical neurology underlie the idea that specific neural functions are localized to specific brain regions.[71] Efforts to understand the mechanisms by which sleep and anesthesia eliminate wakefulness must confront the complexity that multiple brain regions contribute to the regulation of arousal states.[55] An overview of the multiple brain regions contributing to arousal state control is schematically illustrated in figure 1. Recent reviews provide detailed information and multiple perspectives regarding numerous brain regions regulating sleep and wakefulness.[22,55,72–78] The negative effects of sleep deprivation on performance and

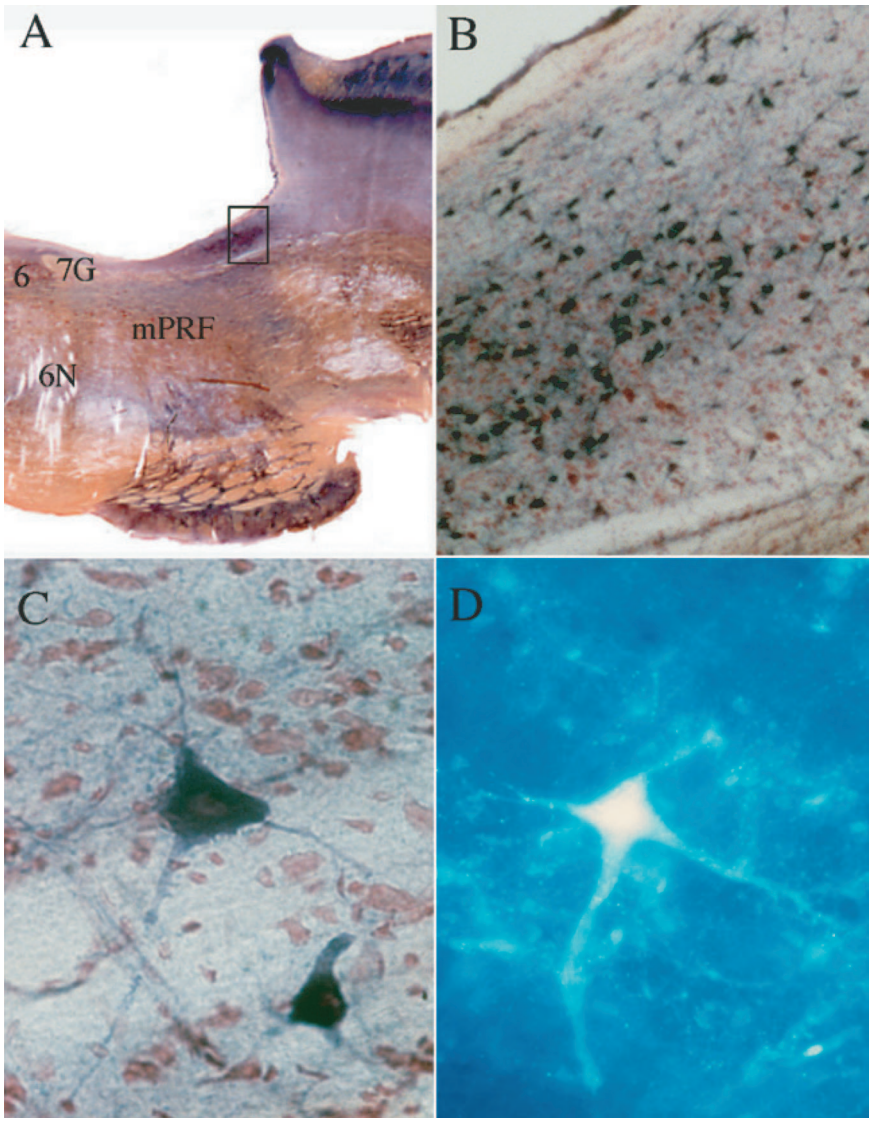

Fig. 2. Cholinergic and cholinoceptive regions of the medial pontine reticular formation (mPRF) contribute to the regulation of sleep and wakefulness. (*A*) Sagittal view of cat pons. For orientation, this section identifies at the caudal (*left*) margin the abducens (*6*) nucleus and ventral to the genu of the facial nerve (*7G*), the sixth cranial nerve (*6N*). The mPRF corresponds, in part, to the gigantocellular tegmental field.[480] The mPRF contains muscarinic cholinergic receptors[99,100,111] and is therefore referred to as being cholinoceptive. Cells that produce acetylcholine (*black rectangle* in *A*) are located in the laterodorsal and pedunculopontine tegmental (LDT/PPT) nuclei.[87] The region of the *black box* is enlarged (*B*) to show cells staining positively for NADPH-diaphorase (*black cells*). In the LDT/PPT, 100% of the cholinergic neurons stain positively for NADPH-diaphorase.[90] Cholinergic LDT/PPT neurons (*C*) project to the mPRF and can be labeled by mPRF injection of fluorescent tracers (*D*) and other retrograde tracing molecules.[88,89] Acetylcholine release from LDT/PPT neurons contributes to the brain activation characteristic of rapid eye movement sleep and wakefulness.

the state-dependent changes in neuronal excitability documented by preclinical studies fit well with brain region–specific alterations in brain metabolism and blood flow elucidated by advances in the functional neuroimaging of sleep.[39,79]

This review focuses on the role of the pons in the regulation of arousal states. The primacy of the pontine reticular formation (fig. 2) as a region contributing to arousal state control originated with Jouvet's[80] discovery that the surgically isolated pontomedullary brain stem was sufficient for generating REM sleep. The conclusion that the pons plays a key role in REM sleep generation is further supported by basic[81] and clinical[75,82–86] evidence showing that pontine lesions disrupt REM sleep.

Pontine cholinergic neurons (fig. 2) are located in the laterodorsal and pedunculopontine tegmental (LDT/PPT) nuclei.[87] Neurons in the medial pontine reticular formation (mPRF) do not synthesize acetylcholine and receive their cholinergic input from LDT/PPT nuclei.[55,75,88–90] Cholinergic neurons are present in regions of human pons that are homologous to LDT/PPT in nonhuman animals.[91]

Laterodorsal and pedunculopontine tegmental neurons contribute significantly to control of ascending arousal-promoting input and descending motor output.[92] LDT/PPT neurons regulate acetylcholine release within the mPRF,[93] and REM sleep is enhanced by LDT/PPT electrical stimulation.[94] Microdialysis data show that acetylcholine release in the pontine dorsal tegmental field[95] and in the medial pontine reticular formation[96,97] is significantly greater during spontaneous REM sleep than during wakefulness or non-REM sleep. Microdialysis data also demonstrate significant enhancement of acetylcholine release in the mPRF during the cholinergically induced REM sleep–like state compared with waking levels.[98] Taken together, these data demonstrate that pontine cholinergic neurotransmission participates in generating the activated brain state of REM sleep.

Receptor mapping studies have demonstrated muscarinic cholinergic receptors localized to the mPRF of

cats[99] and homologous oral pontine reticular nucleus of rats.[100] Many studies have attempted to specify the role of the five muscarinic receptor subtypes in the regulation of sleep and wakefulness. A challenge for such studies is the existence of only relatively subtype selective muscarinic antagonists and the lack of subtype selective muscarinic receptor agonists.[101,102] There is good evidence from animal studies that in the pontine reticular formation, muscarinic receptors of the M2 subtype are important for REM sleep generation.[103] Functional data indicate that M2 muscarinic autoreceptors modulate acetylcholine release in the mPRF of cats[104] and oral pontine reticular nucleus of C57BL/6J mice.[105] Cholinergically activated signal transduction cascades in the pontine reticular formation contribute to REM sleep generation. All muscarinic receptors are coupled to guanine nucleotide binding (G) proteins, and in many brain regions M2 and M4 muscarinic receptor subtypes are linked to inhibitory G proteins (Gi). Therefore, activation of M2 or M4 muscarinic receptors inhibits adenylyl cyclase, cyclic adenosine monophosphate, and protein kinase A.[101] Pertussis toxin catalyzes the adenosine diphosphate ribosylation of the α-subunit of Gi proteins[106] and thereby inhibits intracellular signaling mechanisms normally caused by activating Gi proteins. Cholinergic REM sleep enhancement is blocked by administration of pertussis toxin into the pontine reticular formation of cats[107] and C57BL/6J mice.[108] These data are consistent with G-protein mediation of REM sleep. This interpretation is supported by additional signal transduction studies demonstrating cholinergic REM sleep modulation by mPRF adenylate cyclase, 3′,5′-cyclic adenosine monophosphate, and protein kinase A.[109,110] Direct measurement of G proteins reveals activation by carbachol and inactivation by atropine in the pontine reticular formation of rats[111] and C57BL/6J mice,[65] further supporting a role for pontine M2 and possibly M4 muscarinic receptors in REM sleep generation. The muscarinic receptor subtypes mediating REM sleep in humans remain to be identified.

The Cholinergic Model of Arousal State Control: A Tool for Causal Hypothesis Testing

All efforts to understand the neurobiology of arousal state control must be able to differentiate cellular and molecular events that cause changes in arousal states from events that are merely correlated with a particular state. Forty years of sleep research concur that administering acetylcholine or cholinergic agonists into the pontine reticular formation of intact, unanesthetized animals causes a REM sleep–like state.[103,112–116] The ability to cause physiologic and behavioral traits resembling REM sleep has provided an important experimental tool for overcoming the limitations of merely correlating physiologic traits with different arousal states. The cholinergic model of REM sleep shares many of the physiologic and behavioral features of spontaneous REM sleep, such as tonic motor atonia, phasic muscle twitches, rapid eye movements, and activation of the cortical electroencephalogram (fig. 3). Neuropharmacologic evocation of the REM sleep–like state is concentration dependent,

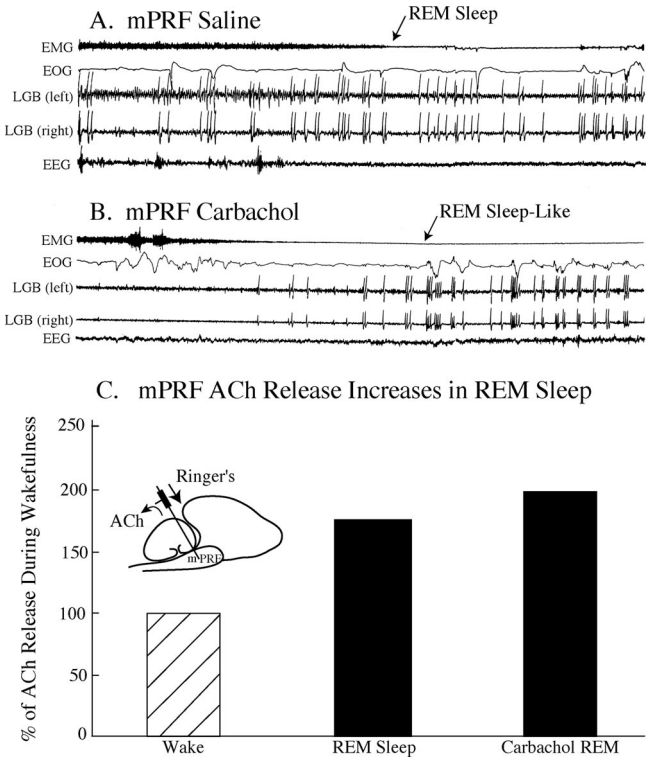

Fig. 3. The electrographic features of rapid eye movement (REM) sleep are elicited by microinjection of cholinergic agonists (*e.g.*, carbachol) or acetylcholinesterase inhibitors into medial regions of the pontine reticular formation (mPRF). The traces in *A* illustrate 80 s of recording from an intact, unanesthetized cat during the transition from non-REM sleep to REM sleep (*arrow*) after saline (control) microinjection into the medial pontine reticular formation. Note the onset of muscle atonia in the electromyogram (EMG). The cortical electroencephalogram (EEG) shows the normal transition from the high-amplitude waves of non-REM sleep to the low-amplitude, fast-frequency waves of REM sleep. Recordings from depth electrodes placed in the left and right lateral geniculate bodies (LGB) reveal the onset of field potentials that comprise a state-specific marker of REM sleep. These potentials are named *PGO waves* for the brain locations (pons, geniculate, occipital cortex) from which they can be recorded.[481] Microinjecting nanogram amounts of carbachol (*B*) into the mPRF causes a REM sleep–like state characterized by the same electrographic features of REM sleep (*A*). One difference is that microinjection of cholinomimetics into the mPRF causes onset of a REM sleep–like state to occur directly from wakefulness, with no intervening non-REM sleep (*B*). EOG = electrooculogram. From Baghdoyan *et al.*;[116] modified with permission. *C* indicates that, compared with wakefulness, acetylcholine (ACh) release in the mPRF (see *inset*) significantly increases during both REM sleep and during the cholinergically evoked REM sleep–like state (Carbachol REM). From Leonard and Lydic[97] and Lydic *et al.*;[98] modified with permission. These findings demonstrate a role for pontine cholinergic transmission in the generation of REM sleep.

significantly dependent on the site of pontine microinjection, and blocked by muscarinic antagonists such as atropine,[72,103,117] indicating mediation by muscarinic cholinergic receptors. The cholinergically evoked REM sleep–like state also is blocked by drugs that disrupt the vesicular packaging of acetylcholine.[118]

Five major factors have contributed to advances in understanding arousal state control resulting from the cholinergic model of REM sleep. First, pontine administration of cholinomimetics causes the short latency onset of multiple physiologic and behavioral traits that are not significantly different from those observed during REM sleep without drug administration (fig. 3). Therefore, the model is ideally suited to testing causal rather than merely correlational hypotheses. Second, efforts to understand how arousal states are generated must identify specific brain regions (fig. 2) and receptor systems (muscarinic cholinergic) regulating arousal states. Third, parallel experiments can be conducted using intact, spontaneously sleeping animals. This makes it possible to determine how the cholinergically induced REM sleep–like state is similar to and different from naturally occurring REM sleep. For example, figure 3C shows that acetylcholine release in the medial pontine reticular formation increases during both REM sleep and the cholinergically induced REM sleep–like state. Fourth, these experiments permit quantitative comparisons of multiple physiologic traits (*e.g.*, electroencephalogram, electromyogram, breathing) during cholinergically induced and spontaneously occurring states. When inferential statistics reveal lack of a significant difference between a dependent variable quantified during REM sleep and during the cholinergic model, one may assign a quantitative probability to having identified a common control mechanism. Fifth, from the perspective of comparative biology, there is compelling evidence that cholinergic neurotransmission modulates arousal.[119] Many laboratories have shown that administering a cholinergic agonist to homologous pontine regions of rats also causes a REM sleep–like state.[120–127] Neural networks generating physiologic traits of REM sleep can be cholinergically activated even in anesthetized rats[128] and cats.[129] Pontine reticular formation microinjection of neostigmine also has been shown to cause a REM sleep–like state accompanied by REM sleep–like alterations in breathing in B6 mice.[108,130] In humans, intramuscular administration of the cholinergic antagonist scopolamine significantly delays REM sleep onset.[131] Intravenous injection of cholinergic agonists or acetylcholinesterase inhibitors shortens latency to onset and increases duration of human REM sleep.[132,133] Intravenous administration of the acetylcholinesterase inhibitor physostigmine increases REM sleep in cats.[119] Systemic administration of physostigmine enhances breathing in some obstructive sleep apnea patients[134] and reverses propofol-induced unconsciousness.[135] Finally, there is good agreement from human studies that the pontine reticular formation plays an essential role in regulating arousal[37,38,136,137] and attention.[138] The excellent agreement between human and nonhuman data demonstrates that basic studies of brain acetylcholine are relevant to problems of clinical interest.[27,28,30]

The data reviewed above show that the ability to test causal hypotheses regarding the neurochemical regulation of arousal states and physiologic traits has been significantly advanced by the cholinergic model of REM sleep. The cholinergic model has helped elucidate pontine cholinergic neurotransmission as a causal factor contributing to arousal state control. The following section reviews state-dependent modulation of muscle tone, awareness and memory, nociception, and respiratory control and highlights the role of pontine acetylcholine in producing these traits.

Multiple Traits Define Arousal States

The success of sleep neurobiology has been derived, in part, from deconstructing states into their component traits and then characterizing the mechanisms regulating those traits. Those data, and the lack of support for a unitary hypothesis of anesthesia,[51,52] make clear that characterizing the mechanisms generating anesthetic traits provides a powerful paradigm for gaining insight into the regulation of anesthetic states. The desirable anesthetic state is a constellation of reversible traits that include analgesia, amnesia, unconsciousness, blunted sensory and autonomic reflexes, and skeletal muscle relaxation.[139] In addition to the characteristic of reversibility, another goal of anesthesia is the temporal coordination of the foregoing five traits. Ideally, the onset of these drug-induced traits occurs at approximately the same time. Undesirable anesthetic complications often are characterized by temporal dissociations in the offset of drug-induced traits, such as failure of a seemingly awake, postanesthetic patient to maintain upper airway patency. As with successful anesthesia, normal sleep also requires the temporal coordination of multiple traits. In fact, the nosology of many sleep disorders is characterized by the intrusion of sleep traits into the state of wakefulness (*e.g.*, onset of motor atonia during a narcoleptic attack) or the expression of waking traits during sleep (*e.g.*, somnambulism).

In the following subsections, attention is focused on the REM phase of sleep because REM sleep is accompanied by significant perturbations in the regulation of cardiovascular function,[20,78,140–147] motor control,[148,149] neuroendocrine function,[150] host response to infection,[151–154] cognitive processing,[40] and nociception.[155–157]

Traits Defining States: Muscle Tone

The reversible, active inhibition of motor tone is essential for the integrity of both anesthesia and sleep. The

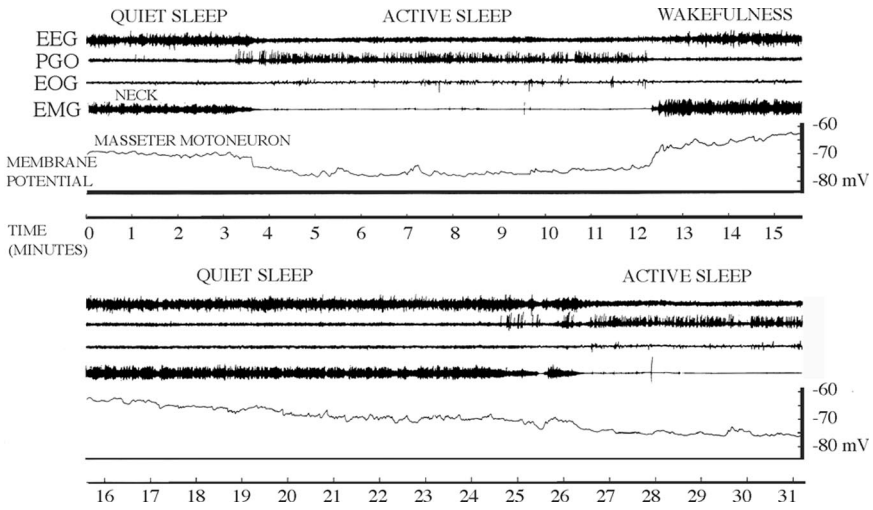

Fig. 4. Motoneuron hyperpolarization during the rapid eye movement (REM; active) phase of sleep. Recordings of electroencephalogram (EEG), ponto-geniculo-occipital (PGO) waves from the thalamus, electrooculogram (EOG), and neck muscle electromyogram (EMG) show transitions between non-REM (quiet) sleep, REM (active) sleep, and wakefulness during 31 min (*abscissa*). Intracellular recording (membrane potential) of a jaw-closure (masseter) motoneuron shows the beginning of hyperpolarization (toward −80 mV) at approximately 3.5 min, during the transition from non-REM sleep to REM sleep. During the active sleep phase (REM sleep), there was an increase in eye movement potentials (electrooculogram) and a decrease in neck muscle electromyographic activity. Note at 12.5 min the membrane depolarization (toward −60 mV) with the spontaneous arousal. At approximately 25.5 min, there was a resumption of REM (active) sleep and again a hyperpolarization of the motoneuron. This recording illustrates the temporal coordination between onset and offset of skeletal motor inhibition and the other electrographic traits of REM sleep, including electroencephalographic activation, PGO waves, and rapid eye movements. Disruptions in the temporal coordination of these traits contribute to pathophysiologic states. From Chase and Morales;[149] used with permission.

development of muscle-relaxing drugs is recognized as one of the major advances in anesthesiology.[158,159] Disrupting the neuromuscular transmission characteristic of wakefulness is essential for maintaining states of anesthesia. Without peripheral neuromuscular blockade, anesthetized or sedated patients can exhibit purposive movements in response to nociceptive stimulation. Maintenance of normal sleep also requires muscle tone suppression. Within a sleep interval, the loss of wakefulness is followed by NREM sleep. During the NREM phase of sleep, there is onset of hypotonia in antigravity muscles. The REM phase of sleep normally develops out of NREM sleep, and postural muscles are actively inhibited during REM sleep. The electromyographic recordings shown in figures 3 and 4 illustrate the gradual development of motor atonia seen during the onset of normal REM sleep. With the resumption of wakefulness from sleep, motor tone returns (fig. 4).

Volatile anesthetics have been reported to inhibit nicotinic receptors and decrease patient requirement for muscle relaxants (reviewed in Dilger).[160] The exact spinal mechanisms by which anesthetics cause immobility are not clear and vary with different inhalation agents.[161] Preclinical studies report that administration of muscarinic and nicotinic antagonists does not alter immobility produced by isoflurane.[162] In addition to peripheral mechanisms of motor inhibition, anesthetic drugs are likely to alter muscle tone *via* CNS actions. The remainder of this section selectively highlights advances regarding CNS mechanisms that actively generate the motor hypotonia and atonia of natural sleep. The CNS mechanisms causing motor atonia during sleep are relevant to anesthesiology for at least three reasons. First, potent agents, intravenous anesthetics, and opioids all have actions on the medullary and pontine neurons regulating state-dependent changes in muscle tone. Second, some of the negative motor effects after prolonged administration of neuromuscular blocking agents in the intensive care environment are likely to be CNS mediated. Finally, pontomedullary systems that actively inhibit motor tone may comprise a target for future anesthetic drug development.

The current appreciation that REM sleep is present in all placental, terrestrial mammals[163] grew from the discovery that, similar to humans, cats have regularly occurring episodes of REM sleep[164] accompanied by skeletal muscle atonia.[165] There is excellent homology between human and nonhuman animals for the trait of state-dependent atonia. This homology has made it possible for preclinical studies to significantly advance efforts to understand human disorders of motor control. This homology provides another good example of basic research advancing the understanding and treatment of human pathophysiology. Inability to generate the normal REM sleep atonia can permit the expression of complex motor acts during sleep.[166]

Specific brain stem regions are now known to regulate state-dependent motor control (reviewed in Lai and Siegel[148] and Chase and Morales).[149] Early studies showed that the medullary reticular formation contains a neuronal network that inhibits skeletal muscle tone.[167] Pioneering recordings of single cell discharge revealed a REM sleep–dependent suppression of both flexor and extensor muscle activity.[168] Extracellular recordings from brain stem neurons provided evidence for control of muscle tone by monoamine-containing nuclei such as the locus coeruleus and midline dorsal raphe nucleus.[148,169,170] The significant influence of sleep on monosynaptic reflex control came from studies which used the jaw-closure reflex as a model system.[171] These studies made the important discovery that evocation of the

jaw-closure reflex was facilitated during wakefulness and absent during REM sleep.

Studies of state-dependent changes in cellular excitability require the technically daunting feat of intracellular recordings from brain stem neurons across states of sleep and wakefulness. The first reports of intracellular recordings from motoneurons during sleep were made in 1978 (reviewed in Chase and Morales).[149] Intracellular recordings of membrane potential were obtained from the motor nucleus of the fifth cranial nerve (trigeminal) of intact, unanesthetized cats across spontaneous cycles of sleep and wakefulness. While these recordings were maintained, the mesencephalic nucleus was stimulated electrically to evoke the jaw-closure reflex. Electrical stimulation of the pontine reticular formation with another electrode facilitated the jaw-closure reflex during wakefulness and NREM sleep, but the reflex was abolished during REM sleep.[172] This ability of REM sleep to reverse the monosynaptic reflex is referred to as *reflex response reversal*. The key point is that the sign (excitation or inhibition) of the reflex was reversed as a function of sleep. One implication of these important discoveries is the potential for synaptically mediated events to underlie the disruptions in autonomic control, such as upper airway hypotonia, that are characteristic of REM sleep.

Figure 4 illustrates motoneuron hyperpolarization during REM sleep. The discovery of reflex response reversal encouraged efforts to understand the cellular and molecular mechanisms mediating REM sleep–dependent atonia. These studies required the development of techniques for maintaining long-term intracellular recordings from spinal cord neurons. The first intracellular recording from spinal motoneurons across states of sleep and wakefulness[173] began to provide insights into the cellular mechanisms causing the atonia of REM sleep. Studies of spinal motoneurons during sleep are directly relevant to research characterizing anesthetic actions on spinal neurons.[174] During REM sleep, motoneurons are bombarded with inhibitory postsynaptic potentials (IPSPs).[149] These IPSPs are suprasegmental in origin and comprise one mechanism contributing to the atonia of REM sleep. Pontine administration of cholinergic agonists causes a REM sleep–like state which includes the trait of skeletal muscle atonia.[103,175] Relative to the cholinergic model of REM sleep (fig. 3), it should be clear that the intracellular recordings from lumbar motoneurons revealed that pontine administration of cholinergic agonists caused IPSPs that were indistinguishable from IPSPs recorded during natural REM sleep.[176] These α motoneuron IPSPs are glycinergically mediated.[149] The implication of such an observation is that pontine cholinergic neurotransmission comprises one link in the causal chain of events causing the motor atonia of REM sleep. Microinjection of carbachol into pontine reticular regions known to enhance REM sleep causes increased medullary and spinal levels of glycine and GABA.[177] Altering pontine cholinergic neurotransmission also can cause upper airway hypotonia, described below in the section about state-dependent alterations in respiratory control.

In addition to the trait of tonic motor atonia, REM sleep is characterized by phasic myoclonic contractions. These limb jerks or twitches of REM sleep occur most often in conjunction with intense rapid eye movement activity and ponto-geniculo-occipital waves (fig. 3A). At the spinal motoneuron level, these intervals of intense rapid eye movements reveal membrane depolarization and cell discharge. These phasic increases in motoneuron excitability seem to be mediated by the amino acid transmitter glutamate and by non–*N*-methyl-D-aspartate receptors.[149]

At the level of the pons, multiple neurotransmitters and neuromodulators can induce muscle atonia. The relation between acetylcholine and state-dependent atonia is demonstrated by microdialysis data that document increased acetylcholine release in dorsal[95] and medial[97] regions of the pontine reticular formation during REM sleep (fig. 3A), during the REM sleep–like state caused by administration of carbachol into the mPRF (fig. 3B),[98] and during episodes of cataplexy in the canine model of narcolepsy.[178] As discussed above, the mPRF receives cholinergic projections from the LDT/PPT nuclei (reviewed in Steriade and McCarley).[90] Electrical stimulation of LDT/PPT increases acetylcholine release in the mPRF while causing hypotonia and respiratory rate depression.[93] Corticotropin-releasing factor, glutamate, kainic acid, and quisqualic acid have been shown to induce muscle atonia when microinjected into the mPRF of cats or homologous regions of rats referred to as pontine reticular nucleus, oral part.[148] The PPT also receives γ-aminobutyric acid–mediated (GABAergic) projections from the basal ganglia, which contribute to the regulation of skeletal muscle tone.[179] Cholinergic REM sleep enhancement also activates cells in the dorsolateral pontine cuneiform nucleus. This nucleus expresses nitric oxide synthase and, when stimulated, suppresses motor tone and somatic reflexes.[180] The intertrigeminal region is located more ventrally in the pons, and lesions of the intertrigeminal area depress respiratory motor activity.[181]

There is good agreement that the principle mechanism for REM sleep atonia is postsynaptic inhibition.[149] Future studies are needed to differentiate the extent to which active inhibition and disfacilitation (*i.e.*, the loss of excitatory input) contribute to motor atonia caused by general[160] and local[182] anesthetics. Such studies also will be important for specifying the mechanisms by which anesthetics acting at the spinal cord can alter brain arousal.[183,184]

Traits Defining States: Unconsciousness and Amnesia

The absence of a satisfactory definition of consciousness in relation to sleep[185] and anesthesia[186,187] is well

appreciated. The challenge of operationally differentiating consciousness, arousal, vigilance, and alertness has been thoughtfully reviewed.[188] Cognitive activity occurs during sleep in the form of dreams,[40] and the mental activity of dreaming is characteristically bizzare.[189] The discovery of the REM phase of sleep noted reports of vivid mental activity.[33] Relevant for efforts to identify similarities and differences between states of sleep and anesthesia, dreaming during anesthesia was reported in only 6% of the patients included in a large, multicenter study.[190] Dreaming occurs during REM sleep, and deprivation of REM sleep causes a rebound increase in dreaming,[191] consistent with the view that REM sleep is a homeostatically regulated, fundamental need. Given favorable circumstances, dream recall can be elicited from virtually all intact, healthy humans.[192] Even allowing for variance in research methodology, these comparisons suggest significant difference in mental activity during sleep and anesthesia. Differences in cholinergic neurotransmission during sleep and anesthesia account, in part, for differences in mental activity.[30]

In the operating room and the intensive care unit,[193] amnesic drugs are desirable for preventing recall, and benzodiazepines routinely are used to produce anterograde amnesia. The significant sleep disturbances of intensive care unit patients has been reviewed elsewhere,[194] and the potential clinical benefit of continuous intensive care unit sedation is not supported by available data.[195,196] Imperfect pharmacology and patient diversity force anesthesiologists to a margin between undertreatment—with the risk of patient recall—and potential complications secondary to excessively deep or prolonged unconsciousness. Analyses of closed claims data in the United States indicate a 300% increase since the 1970s in cases of patients' recall of events while undergoing general anesthesia.[197] Data from a multicenter study suggest that awareness during anesthesia may occur with an incidence of 1–2 per 1,000 patients, resulting in 26,000 cases each year in the United States.[190]

In elderly patients, pharmacologic manipulation of GABA or cholinergic neurotransmission can contribute to the undesirable side effect of postoperative delirium. Recent compendia indicate an incidence of postoperative delirium in 2–50% of nondemented, older patients.[198] Although it is cautioned that most of the research on postoperative delirium in the elderly is "purely descriptive or anecdotal," postoperative delirium is associated with delayed recovery, increased time in the hospital, and increased morbidity.[198] The central anticholinergic syndrome can contribute to delirium and prolonged anesthetic recovery,[199] and cholinergic agents can activate the cortical electroencephalogram by reversing the actions of isoflurane.[67]

The foregoing points illustrate the need for systematic research on sedation, postoperative delirium, and brain mechanisms regulating states of sleep and anesthesia. It is relevant to note that current clinical guidelines for sedating children are based on the degree and definition of sedation, rather than on the pharmacologic agent administered.[200] Preclinical studies investigating the relation between sleep and prolonged propofol sedation suggest that sedation caused no evidence of sleep deprivation.[60] Prolonged sedation, however, potentiated the onset and duration of loss of righting reflex induced by propofol and isoflurane.[61] Objective measures of drive to sleep in human volunteers show that sleep tendency is increased for up to 8 h after drugs used for ambulatory surgery.[26] The importance and clinical relevance of studies such as this[26] is emphasized by the fact that more than 60% of all surgeries in the United States are performed in an ambulatory environment.[201]

The term *conscious sedation* describes a pharmacologically induced arousal state that is similar to but different from physiologic sleep. The term *sleep* provides a convenient metaphor[54] for an assortment of altered arousal states caused by sedative–hypnotic drugs. Authors focusing on the sleep-like traits of sedation describe this altered arousal state as "light sleep."[202] More recent anesthesia textbooks note that "the terms sleep, hypnosis, and unconsciousness are used interchangeably in anesthesia literature to refer to the state of artificially induced (i.e., drug-induced) sleep."[203] There are also important differences between sleep and sedation. A key criterion for successful sedation is depression of sensory input. Although sleep is characterized by diminished sensory processing, nociceptive input disrupts sleep. Intervals of sleep do not terminate with vomiting, but there is a positive correlation between level of sedation and amount of nausea and vomiting.[204] Motor atonia, as outlined above, is a characteristic of REM sleep. In contrast, conscious sedation is a dissociated state comprised of waking traits, such as the ability to follow verbal commands, and traits similar to sleep, such as memory impairment and autonomic depression.

Objective criteria for accurately distinguishing between sedation and natural sleep are relevant to practice guidelines for monitoring levels of consciousness during sedation.[205–207] The distinct differences between the NREM and REM phases of sleep reviewed above illustrate the potential for inaccurate arousal state classification when obtunded states of arousal are all described as "sleep." Pharmacologically induced states of sedation are superimposed on a patient's endogenous level of arousal, and endogenously generated arousal states "can oscillate rapidly, resulting in bizarre and important clinical syndromes."[208] For example, children given ketamine–midazolam have been described as "asleep but arousable,"[209] but this arousal state can change to one of confusional hyperarousal. After oral, intravenous, or rectal administration of midazolam, paradoxical excitement has been reported in up to 10% of children in recovery

or after discharge.[210] The mechanisms causing paradoxical excitement are unknown. Determining the causes of this altered arousal state represent an important research opportunity.

Traits Defining States: Nociception

There is a reciprocal relation between sleep and pain.[211,212] Preclinical studies from the laboratory of Pompeiano[168] demonstrated for the first time that ascending spinal pathways were suppressed during REM sleep. Single cell recordings from dorsal spinocerebellar tract and spinoreticular tract neurons show that spontaneous and evoked neuronal responses are depressed during REM sleep, relative to wakefulness and NREM sleep.[155] This cellular depression results from both presynaptic and postsynaptic inhibitory processes. Additional data show that REM sleep–dependent sensory neuron suppression also may vary as a function of sensory modality and afferent fiber diameter. In humans, REM sleep depresses the Babinski and plantar flexion reflexes[213] and reduces the excitability of spinal polysynaptic nociceptive reflexes.[214] Studies using human volunteers indicate that the ability to process nociceptive input is present during all stages of sleep.[215] The reduction of human thermal pain sensation during sleep[216] may be mediated by sleep-dependent inhibition of spinoreticular tract neurons, which convey pain and tactile input to rostral brain regions.[156] Little attention, however, has been given to the question of how spinal nociceptive mechanisms interact with supraspinal systems known to generate states of sleep and wakefulness. The remainder of this section highlights evidence that pontine cholinergic networks long known to regulate states of consciousness[42] also modulate nociceptive processing. The data reviewed below imply that a better understanding of supraspinal cholinergic antinociception may lead to the development of adjunctive therapies than can diminish pain without the unwanted side effect of sleep disruption.[217,218]

Many clinical and preclinical studies have demonstrated the enhancement of pain threshold *via* epidural, spinal, or intrathecal administration of cholinergic agonists and acetylcholinesterase inhibitors.[219–224] Preclinical studies administering opioids directly into the brain stem have produced systematic maps for understanding the supraspinal sites and mechanisms of opioid analgesia (*cf.* table 3 in[225]). These pioneering mapping studies did not investigate medial pontine reticular formation regions known to regulate sleep and wakefulness. Data demonstrating cholinergic generation of REM sleep and antinociception led to examination of the hypothesis that the medial pontine reticular formation contributes to supraspinal antinociception.[59]

Figure 5 shows the time course of antinociceptive behavior cholinergically evoked from the medial pontine reticular formation. The key finding was that microinjection of the cholinergic agonist carbachol and the acetylcholinesterase inhibitor neostigmine caused a significant and prolonged enhancement of antinociceptive behavior. This behavior is measured as the latency with which an animal flicks its tail to avoid a thermal stimulus. In contrast, morphine administered directly into the same medial pontine reticular formation site did not increase tail flick latency. These data showed that regions of the pontine reticular formation known to generate REM sleep can also modulate antinociceptive behavior.[59]

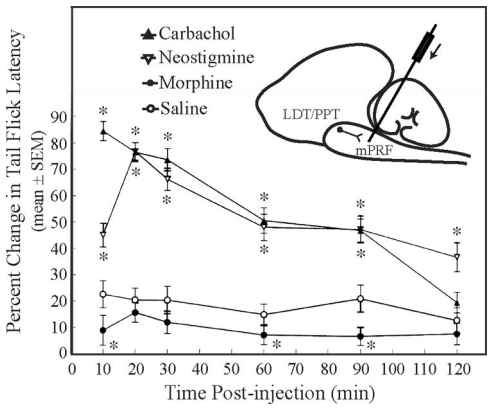

Fig. 5. Time course of antinociceptive behavior after medial pontine reticular formation (mPRF) microinjection of carbachol, neostigmine, morphine, or saline (control). Tail flick latency is expressed on the ordinate as mean ± SEM percent change from baseline. Time after drug delivery into the mPRF is shown on the *abscissa*. Note the significant enhancement of tail flick latency after mPRF microinjection of carbachol, neostigmine, or both. Morphine, similar to saline, had no antinociceptive actions after administration into the mPRF. * Significant increases in cholinergically elicited antinociceptive behavior compared with saline, or significant decreases induced by morphine. These findings imply that cholinergic stimulation of the mPRF may contribute to rapid eye movement sleep–dependent suppression of sensory input. LDT/PPT = laterodorsal and pedunculopontine tegmental. From Kshatri *et al.*;[59] used with permission.

Figure 6 illustrates the finding that cholinergic drugs enhance REM sleep[103] whereas opioids inhibit REM sleep[226,227] when microinjected into the medial pontine reticular formation. Sleep cycle disruption by opioids is recognized in the substance abuse literature, and clinical data implicate opioids as a potential contributor to postoperative sleep disruption.[218,228] Postoperative sleep disruption has been shown to be followed by a rebound increase in REM sleep.[229,230] After lower abdominal surgery, patients who receive morphine also have poor sleep quality.[27] Multiple brain mechanisms contribute to sleep disruption caused by opioids. For example, the basal forebrain provides cholinergic projections to the cortex that are essential for maintaining normal activation of the electroencephalogram and behavioral arousal. Morphine acts at the level of the basal forebrain to decrease acetylcholine release in the prefrontal cortex, disrupt activation of the electroencephalogram, and blunt arousal.[231] REM sleep is also an activated brain state. Acetylcholine is essential for REM sleep genera-

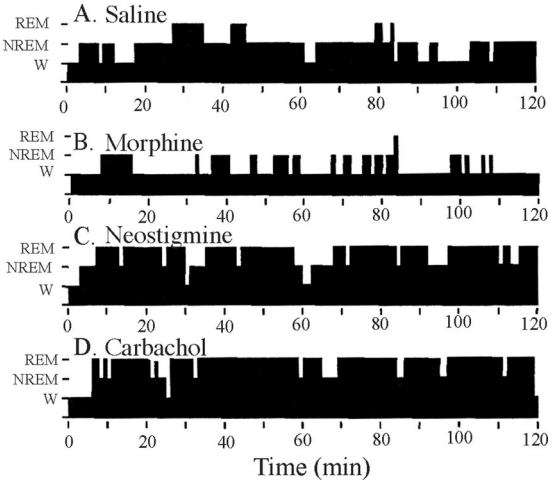

Fig. 6. Time spent in wakefulness (W), non–rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep after injection of saline (*A*), morphine (*B*), neostigmine (*C*), or carbachol (*D*) into the medial pontine reticular formation. These plots represent the minute-by-minute scoring of polygraphically confirmed states of arousal. Note the enhancement of REM sleep caused by neostigmine or carbachol, and the inhibition of REM sleep caused by morphine. These data are consistent with the interpretation that the decrease in REM sleep caused by systemically administered opioids is mediated, at least in part, at the level of the mPRF. From Kshatri *et al.*;[59] used with permission.

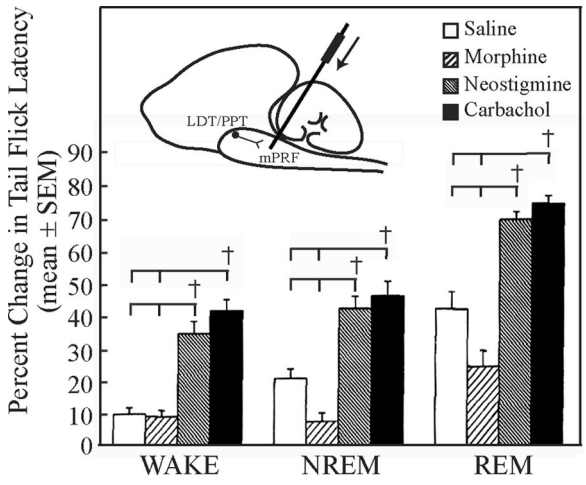

Fig. 7. Nociception is altered by sleep and wakefulness. In every arousal state, medial pontine reticular formation (mPRF) microinjection of neostigmine and carbachol caused greater antinociceptive behavior than mPRF administration of saline or morphine. The state-dependent increase in tail flick latency is evident from a rank ordering of latencies showing that for each of the microinjection treatments, tail flick latency in wakefulness < non–rapid eye movement (NREM) sleep < rapid eye movement (REM) sleep. Therefore, cholinergic stimulation of the mPRF may contribute to the REM sleep-dependent increase in antinociceptive responsiveness. LDT/PPT = laterodorsal and pedunculopontine tegmental. From Kshatri *et al.*;[59] used with permission.

tion, and opioids decrease acetylcholine release in pontine regions generating REM sleep.[232,233] In these same pontine brain regions, opioids inhibit REM sleep *via* μ-opioid receptor mechanisms.[226] The cellular and molecular mechanisms causing postoperative REM sleep rebound remain poorly understood. Preclinical data recently indicate that after 24 h of sleep deprivation, rats anesthetized for 6 h with propofol recovered sleep to the same degree as rats allowed to sleep for 6 h.[69]

Results of tail flick latency experiments conducted across polygraphically recorded states of wakefulness, NREM sleep, and REM sleep made clear that in every sleep/wake state, neostigmine and carbachol produced significantly greater antinociceptive behavior than saline (vehicle control) or morphine when microinjected into the medial pontine reticular formation (fig. 7). This finding of cholinergic antinociception evoked from the medial pontine reticular formation[59] is not limited to cats. Delivery of cholinergic agonists into homologous regions of rat pontine reticular formation also enhances antinociception,[234,235] and chronic opioid administration inhibits sleep.[236]

The medial pontine reticular formation is not considered to be a component of pain pathways. The data reviewed here, however, demonstrate that pontine regions known to regulate sleep also contribute to supraspinal cholinergic antinociception. At the level of the intralaminar thalamus, preclinical studies also demonstrate antinociceptive mechanisms *via* muscarinic mechanisms.[237] Modulation of nociception may be another function subserved by peptides that alter levels of arousal. For example, hypocretin-1 (also called orexin A) activates G proteins in the medial pontine reticular formation[238,239] and is antinociceptive in mice and rats.[240] As with the other traits characterizing anesthetic states, the trait of antinociception is modulated by multiple brain stem regions[241] and neurotransmitters.[155,242]

Traits Defining States: Respiration

Sleep apnea comprises one of the most prevalent and poorly understood sleep disorders.[243] The apneic episodes illustrated by figure 8 are more frequent and of longer duration during REM sleep.[140,141] Anesthesia depresses upper airway muscle function,[244] and this depressant action is more severe in the upper airway than on the phrenic nerve.[245] These data make sleep apnea directly relevant for efforts to maintain airway patency before and after intubation associated with anesthesia or sedation.[246–248]

The causal relation between states of consciousness and breathing is bidirectional, and changes in breathing can also alter levels of consciousness. For example, the arousal response to airway obstruction is blunted by sleep apnea,[249] but sleep deprivation exacerbates sleep apnea.[250] Asthmatic attacks can be accompanied by feelings of panic, and the conscious awareness of respiratory effort contributes to the dysphoric aspects of dyspnea.[251] Even small restrictions in airflow can disrupt states of sleep.[252] Surgical pain is arousing and therefore is a respiratory stimulant that antagonizes respiratory depression caused by opioids or potent agents.[253] Elim-

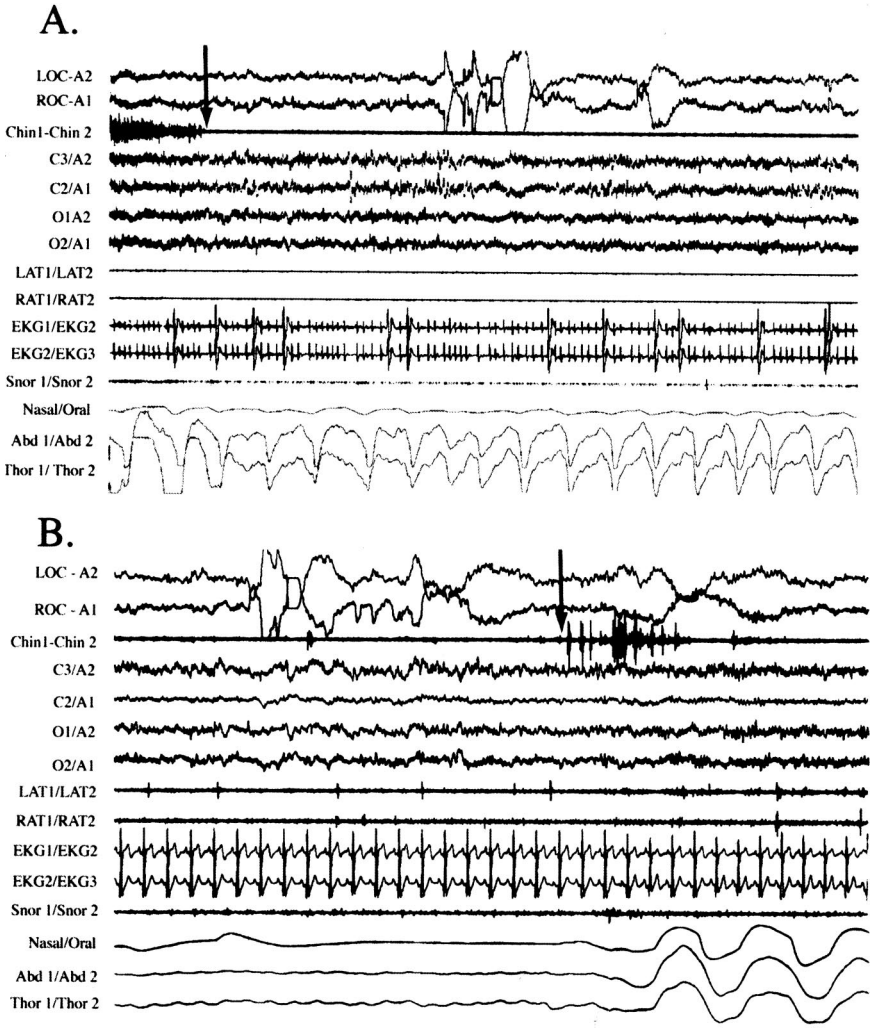

Fig. 8. Polygraphic recording of human sleep and breathing. *A* shows a transition into rapid eye movement sleep. The *arrow* marks the loss of muscle tone (Chin 1-Chin 2) with the onset of rapid eye movement sleep. This 1-min record also illustrates the decrease in respiratory airflow (Nasal/Oral trace) due to airway obstruction. Respiratory effort was maintained (Abd1/Abd2, Thor1/Thor2), indicating an obstructive (*vs.* central) apneic episode. Percent oxygen saturation reached a minimum of 76 and averaged only approximately 85. *B* shows a 30-s record obtained from a patient during a prolonged apnea. Note the cessation of nasal/oral airflow and the prolonged interval of hypopnea. During an arousal (*arrow*), muscle tone (Chin 1-Chin 2), respiratory effort (Abd and Thor), and airflow (Nasal/Oral) resumed. This recording illustrates the point that individuals with sleep apnea must awaken to terminate an airway obstruction and successfully breathe. Abd 1/2 = respiratory effort—abdomen; C3/A2 = left central electroencephalogram; EKG1/2 = electrocardiogram; Snor1/2 = snoring sensor; LAT1/2 = left anterior tibialis electrocardiogram; LOC-A2 = left outer canthus/right ear lobe electrooculogram placement; Nasal/Oral = airflow from nasal/oral cavity; O1/A2 = left occipital electroencephalogram; RAT1/2 = right anterior tibialis electrocardiogram; ROC-A2 = right outer canthus/right ear lobe electrooculogram placement; Thor1/2 = respiratory effort—chest.

inating the unwanted opioid side effect of respiratory depression would significantly advance clinical care.

Most patients with obstructive sleep apnea (OSA) remain undiagnosed and untreated.[254–256] This is of interest to anesthesiologists because OSA patients require special care for anesthetic management of the upper airway.[24,31,246,257] The need for special airway care is consistent with the fact that neuromuscular blocking agents[258] and general anesthesia[245] cause greater depression of upper airway muscles than of the diaphragm. The long-standing finding that OSA patients tend to be hypertensive[259,260] has been supported by recent prospective[261] and community-based[262] studies. The frequency and severity of OSA increases during the REM phase of sleep, but obstructive events also occur during NREM sleep.[23] Individuals with OSA have a peak in sudden cardiac death during sleeping hours.[263] There is evidence that OSA causes impaired cognitive function, likely *via* alterations in normal function of the prefrontal cortex.[264] The prefrontal cortex also contributes to cardiopulmonary control. Preclinical data show that rate of breathing increases with increasing levels of acetylcholine in the prefrontal cortex,[265] and muscarinic cholinergic autoreceptors regulate acetylcholine release in mouse prefrontal cortex.[266–268]

Childhood OSA is a common disease estimated to occur in approximately 2% of young children[269] and is associated with diminished cognitive function.[270] Children with OSA have a high incidence of respiratory complications associated with postoperative opioid administration.[271] In a group of 46 children averaging 43 months of age, oxygen desaturation associated with OSA also has been associated with reduced opioid requirement for analgesia.[29] The mechanisms causing an association between increased frequency of oxygen desaturation and increased sensitivity to opioids remain speculative and may include developmental changes in opioid receptors,[272] pontine cholinergic neurons,[92] or both.

The foregoing clinical data reinforce the need for elucidating the neurochemical mechanisms underlying state-dependent respiratory control. Mouse models also make clear the importance of genetics for respiratory control,[273] even with analyses that quantify breathing as a function of arousal state.[274] Such basic studies also are needed to unmask the cellular and molecular mecha-

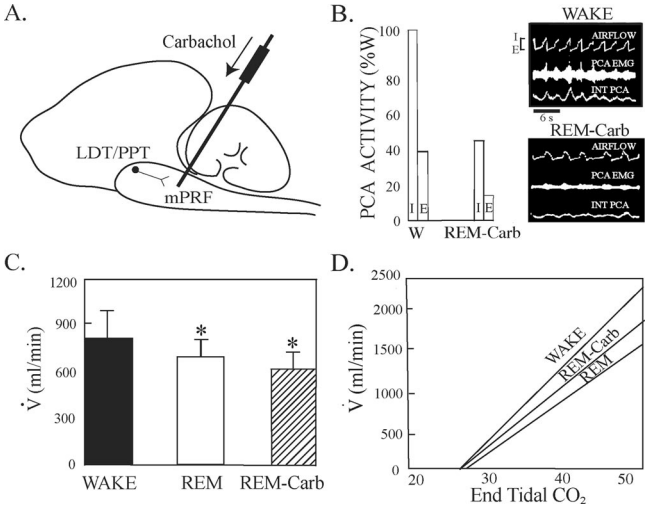

Fig. 9. Examples of depressed breathing caused by microinjecting cholinomimetics into the medial pontine reticular formation (mPRF). The brain has no pain receptors, and *A* indicates that cholinomimetics such as carbachol can be microinjected directly into the mPRF of an awake animal. LDT/PPT = laterodorsal and pedunculopontine tegmental. *B* shows electromyographic (EMG) discharge of the laryngeal abductor, the posterior cricoarytenoid (PCA) muscle, during inspiration (I) and expiration (E). The *bar graph* shows the decrease in PCA discharge during the carbachol-induced rapid eye movement sleep–like state (REM-Carb) compared with wakefulness (W). The *right portion* of *B* shows PCA muscle tone (electromyogram) during wakefulness and the PCA hypotonia during the REM sleep–like state caused by mPRF injection of the cholinomimetic carbachol. From Lydic *et al.* [278]; used with permission. *C* shows minute ventilation during wakefulness, REM sleep, and REM-Carb. * Significant decrease below waking levels. From Lydic and Baghdoyan;[277] used with permission. *D* shows arousal state-dependent changes in the hypercapnic ventilatory response. During spontaneous or carbachol-induced REM sleep, there is a significant decrease in the ventilatory response to hypercapnia compared with the waking hypercapnic ventilatory response. From Lydic *et al.*;[482] used with permission.

nisms through which different drugs alter breathing during sleep[275] and sedation.[200] This section is limited to considering evidence that pontine cholinergic systems known to modulate arousal also alter upper airway muscles, ventilation, and the ventilatory response to hypercapnia. Interested readers are referred elsewhere[22,276] for recent reviews of breathing during sleep.

An overview of sleep-dependent depression of skeletal muscle tone was provided earlier in this review. Pontine administration of cholinergic agonists causes IPSPs in spinal motoneurons that are indistinguishable from IPSPs recorded during natural REM sleep.[149] This finding stimulated efforts to determine whether pontine cholinergic neurotransmission also alters upper airway function. Figure 9A schematizes injection of the cholinergic agonist carbachol into the feline medial pontine reticular formation. Microinjections were made while recording electromyographic activity from upper airway muscles of intact, sleeping animals.[277,278] Microinjection of cholinergic agonists into the medial pontine reticular formation caused upper airway muscle hypotonia (fig. 9B). These data were of interest because they demonstrated significant respiratory modulation from medial regions of the pontine reticular formation regulating sleep but containing no respiratory neurons.[279] Respiratory depression caused by microinjecting cholinergic agonists into the pons was subsequently shown to occur in decerebrate and/or anesthetized animals.[128,280] In intact sleeping animals, microinjection of cholinergic agonists into the medial pontine reticular formation also increases acetylcholine release[98] and significantly decreases minute ventilation (fig. 9C). The cholinergically induced decrease in minute ventilation results primarily from a decrease in frequency of breathing. Human posterior cricoarytenoid muscles also become hypotonic during natural sleep.[281]

Human chemosensitivity is decreased during sleep[22] and anesthesia.[282] Central chemosensitivity now is known to involve many brain regions in addition to the ventrolateral surface of the medulla.[283,284] Enhancing cholinergic neurotransmission in medial pontine reticular formation regions regulating states of consciousness depresses the hypercapnic ventilatory response (fig. 9D). Considered together, the data summarized by figure 9 showed for the first time that many REM sleep–dependent changes in breathing are caused by enhancing cholinergic neurotransmission in the medial pontine reticular formation. The power of the cholinergic model for providing mechanistic insights into the state-dependent respiratory control also is apparent during anesthesia.[280] The implication of these findings is that endogenous acetylcholine in the pontine reticular formation contributes to the respiratory changes characteristic of sleep. Neuroimaging studies of patients with multiple system atrophy suggest that deficits in cholinergic projections from the pons may contribute to their OSA.[285]

Opioids continue to serve as the analgesic drug of choice despite the potential side effect of respiratory depression and being a leading cause of postoperative nausea and vomiting.[286] Administering morphine intrathecally to humans causes a dose-dependent respiratory depression[287] and a centrally mediated depression in the ventilatory response to hypoxia.[288] A number of studies have focused on efforts to identify the brain regions and neurotransmitters through which opioids cause state-dependent respiratory depression. For example, microinjection of opioids into the medial pontine reticular formation causes a μ receptor–mediated inhibition of the REM phase of sleep, decreases acetylcholine release in the medial pontine reticular formation, and significantly increases respiratory apneas (reviewed in Lydic *et al.*).[289] The tongue muscle is believed to block the upper airway in many cases of OSA.[290,291] This observation has encouraged efforts to understand the respiratory role of the medullary hypoglossal nucleus.[292,293] Many studies aim to clarify the interaction between pontine regions regulating sleep and the hypoglossal nucleus.[294–298] Microinjection of carbachol into the medial pontine retic-

ular formation increases release of the inhibitory neurotransmitters GABA and glycine in the hypoglossal nucleus.[177] The hypoglossal nucleus contains neurons that synthesize acetylcholine,[299] and hypoglossal motor neurons are stimulated by nicotine[300] and innervated by nitric oxide containing fibers.[301]

Additional neurotransmitters and neuromodulators that alter breathing and states of consciousness include serotonin,[302] hypocretin,[303] and GABA.[304,305] As reviewed elsewhere,[289] serotonin can facilitate respiratory drive to upper airway muscles, and activation of α_2 adrenoreceptors can depress respiratory neurons and the ability to respond to hypercapnia. In human volunteers, the genioglossus muscle is stimulated by a selective serotonin reuptake inhibitor.[306] Hypocretin excites serotonergic neurons in the dorsal raphe nucleus of rat,[307] suggesting a respiratory-facilitatory role for hypocretin. GABAergic systems also have been shown to facilitate or to depress respiratory function. The complexity of state-dependent respiratory control is illustrated by evidence that GABAergic modulation varies as a function of brain region involved[308] and even arousal state. Delivery of a γ-aminobutyric acid type A ($GABA_A$) receptor antagonist to the brain stem hypoglossal nucleus causes increases in genioglossus muscle activity during NREM sleep but not during the REM phase of sleep.[309] The foregoing breathing data illustrate the difficulty of developing drugs that will eliminate wakefulness without depressing respiratory control. The next section highlights the role of acetylcholine, adenosine, GABA, monoamines, and hypocretin in regulating states of arousal.

Arousal States Are Regulated by Multiple Neurotransmitters and Neuromodulators

Acetylcholine

Cholinergic neurotransmission is known to modulate cortical and behavioral levels of arousal. Anesthesiologists were among the first investigators to report the positive correlation between cortical cholinergic neurotransmission and arousal.[310] General anesthetics produce unconsciousness, in part, by disrupting central cholinergic neurotransmission.[49,135,311–313] As noted above, REM sleep also is referred to as paradoxical sleep because the electroencephalographic activation of REM sleep is similar to the electroencephalographic activation of wakefulness. The finding that cortical acetylcholine release is greater during wakefulness and REM sleep than during NREM sleep[314–316] or anesthesia fits well, therefore, with the electroencephalographic activation characteristic of wakefulness and REM sleep. Cortical acetylcholine is essential for maintaining behavioral arousal and normal cognition. Consistent with the clinical effect of opioids to blunt arousal and impair cognition are preclinical data showing that opioids decrease acetylcholine release in brain regions that promote cortical and behavioral arousal.[231–233]

Intravenous and volatile anesthetic drugs disrupt cholinergic neurotransmission in multiple brain regions. Opioids[233] and ketamine[317] decrease acetylcholine release in pontine reticular formation regions that play a role in generating normal REM sleep. Halothane and isoflurane also depress release of acetylcholine in the pontine reticular formation[58] and electrophysiologic studies show that sevoflurane blocks cholinergic synaptic transmission.[318] Propofol administration to rats decreases cortical acetylcholine release,[319] and in human volunteers, propofol-induced unconsciousness can be reversed with physostigmine.[135] These propofol data are consistent with long-standing preclinical evidence that the acetylcholinesterase inhibitor eserine (physostigmine) causes activation of the cortical electroencephalogram[320] and that intravenous physostigmine enhances the electrographically activated state of REM sleep.[132] Clinical studies demonstrate that cholinomimetics significantly reduce latency to REM sleep onset in normal, human volunteers.[133]

Cholinergic brain stem neurons (LDT/PPT) that project to the thalamus and cortex produce an activated cortical electroencephalogram during wakefulness or REM sleep.[321–323] During the NREM phase of sleep and during halothane anesthesia, decreased pontine cholinergic neurotransmission contributes to deactivation of the cortical electroencephalogram, including spindle generation. Figure 10A illustrates cortical electroencephalographic recordings characteristic of wakefulness, NREM sleep, REM sleep, and halothane anesthesia. In addition to illustrating the similarity in the activated electroencephalogram of wakefulness and REM sleep, figure 10 shows that spindles in the electroencephalogram caused by halothane anesthesia have the same appearance and frequency as NREM sleep spindles. The cellular and molecular bases for electroencephalographic spindle generation are being elucidated to include cholinergic projections from brain stem to centromedian and reticular nuclei of the thalamus.[323–325] During NREM sleep, there is a slowing of discharge in cholinergic neurons that project to thalamus. Functional imaging studies of human brain during anesthesia report that halothane causes a significant decrease in glucose metabolism in the thalamus.[326]

Halothane anesthesia has been shown to cause spindles in the cortical electroencephalogram while decreasing acetylcholine release from pontine cholinergic neurons.[58] The causal, rather than merely correlational, nature of the relation between pontine cholinergic neurotransmission and halothane-induced spindles in the electroencephalogram is illustrated by figure 10B. These data show that the enhanced spindle frequency during halothane anesthesia is significantly reduced by administration of a cholinergic agonist into pontine reticular

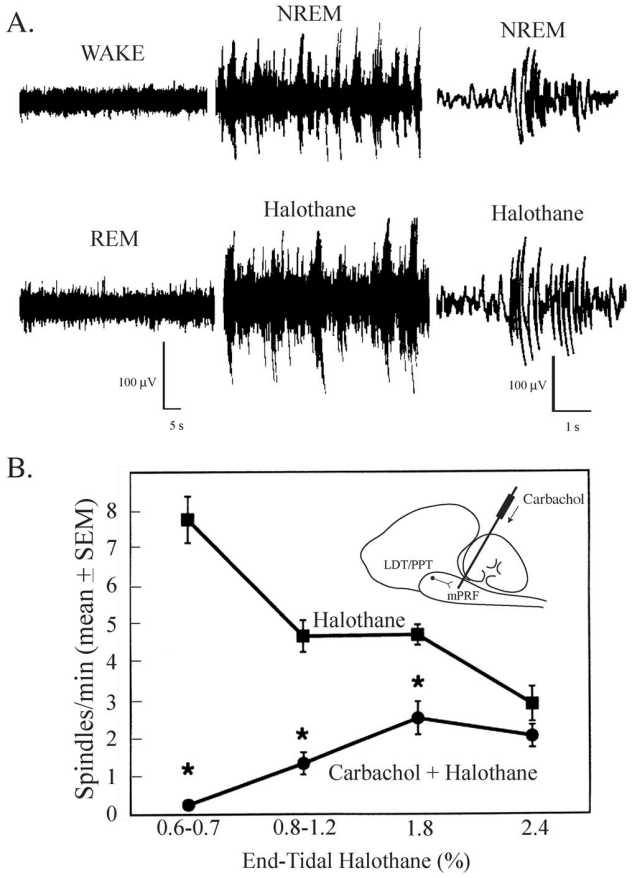

Fig. 10. Cholinergic activation of the cortical electroencephalogram during halothane anesthesia. (*A*) Electroencephalogram recorded from cat during wakefulness (WAKE), non–rapid eye movement (NREM) sleep, rapid eye movement (REM) sleep, and halothane anesthesia. *Left upper and lower traces* illustrate the similarity in electroencephalogram between wakefulness and REM sleep. *Middle upper and lower traces* show the similar bursts in the electroencephalogram recorded during NREM sleep and halothane anesthesia. *Right upper and lower traces* show electroencephalographic recordings at a faster sweep speed to illustrate that waves in the 8- to 14-Hz frequency, referred to as *spindles*, characterize the cortical electroencephalogram during NREM sleep and halothane anesthesia. Therefore, although NREM sleep and halothane anesthesia are different states of consciousness, both states exhibit similar electroencephalographic traits. This trait similarity suggests that an understanding of the neuronal mechanisms generating the electroencephalogram of NREM sleep can help to elucidate neuronal mechanisms regulating the electroencephalogram during anesthesia. (*B*) Microinjection of carbachol into the medial pontine reticular formation (mPRF) inhibits halothane-induced spindles in the electroencephalogram. *Inset* illustrates microinjection site for delivery of the cholinergic agonist carbachol into the mPRF. The mPRF receives cholinergic input from the laterodorsal and pedunculopontine tegmental (LDT/PPT) nuclei. *Graph* plots number of spindles in the electroencephalogram *versus* end-tidal halothane measured from cat. The two functions show number of spindles in the electroencephalogram during halothane alone and after carbachol microinjection into the mPRF during halothane anesthesia. The key point is that the cortical electroencephalogram is activated by enhancing cholinergic input to the mPRF. During REM sleep and wakefulness, cholinergic output from the LDT/PPT is increased to suppress spindles in the electroencephalogram.[483] These preclinical studies suggest one mechanism potentially underlying the clinical finding[135] that physostigmine can reverse the loss of consciousness produced by propofol. From Keifer *et al.*;[58] used with permission.

formation regions known to activate the cortex and to generate REM sleep. As described in detail elsewhere,[323] the synaptic hyperpolarization of thalamocortical neurons and spindles in the electroencephalogram effectively disconnect the cortex from afferent input, thus helping to maintain states of sleep or anesthesia. This blockade of sensory input at the level of the thalamus helps to explain why arousal thresholds from NREM sleep are higher than from REM sleep. There also are developmental differences in arousal threshold. Children require a greater stimulus to elicit arousal, and this fact has clinical relevance for children with OSA[269] and may relate to the decreased opioid requirement for these children.[29]

This review is focused on pontine cholinergic networks, but it should be noted that basal forebrain cholinergic neurons also contribute to the regulation of arousal[327] and breathing.[328] Microdialysis data indicate that acetylcholine release in the substantia innominata region of the basal forebrain is significantly decreased below waking levels during NREM sleep and increased above waking levels during the cortical activation of REM sleep.[329] Basal forebrain acetylcholine release is significantly enhanced by dialysis delivery of a nitric oxide synthase inhibitor, suggesting that endogenous nitric oxide can modulate basal forebrain levels of acetylcholine.[330]

Consciousness and memory associated with states of sleep and anesthesia are modulated by muscarinic cholinergic receptors.[28,30] Muscarinic receptors of the M1 subtype are located throughout the cortex.[331] Intracellular recordings from cortical neurons during NREM sleep, REM sleep, and wakefulness indicate long-lasting hyperpolarization during NREM sleep, suggesting disfacilitation of thalamocortical synapses by low cholinergic activity.[332] Such disfacilitation would impair higher cortical function. Normal working memory and the regulation of attention and arousal require an intact prefrontal cortex.[333] Sleep deprivation is deleterious to both anesthesiologist and patient because memory and arousal functions subserved by prefrontal cortex are especially vulnerable to sleep deprivation[137,334–336] and anesthesia.[337,338] Muscarinic receptors modulate acetylcholine release and activation of the prefrontal cortical electroencephalogram.[265–268]

Adenosine

Dephosphorylation of adenosine triphosphate produces adenosine, and all cellular activities that increase metabolic demand will increase adenosine. There is good evidence that the accumulation of adenosine during wakefulness contributes to the drive for sleep[339] and the slow-wave activity in the electroencephalogram that is characteristic of NREM sleep.[340] Adenosine increases REM sleep when injected into the pontine reticular formation of rats[124] and decreases wakefulness when delivered by dialysis into feline LDT/PPT.[341] Adenosine has

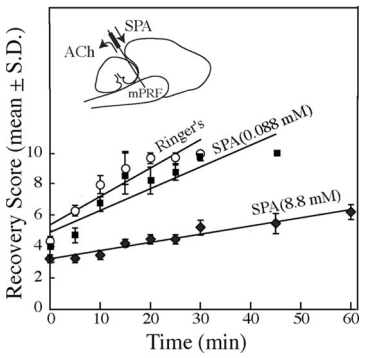

Fig. 11. Recovery from halothane anesthesia in the cat is delayed by administering an adenosine A_1 receptor agonist into the medial pontine reticular formation (mPRF). The three functions plot the time course of recovery from halothane anesthesia during control dialysis (Ringer's) and microdialysis delivery of two levels of the adenosine A_1 receptor agonist N^6-p-sulfophenyladenosine (SPA). Simultaneous measures revealed that SPA also decreased acetylcholine (ACh) release (not shown). The study from which these data are taken support the interpretation that adenosine A_1 receptors in mPRF regions known to modulate sleep also contribute to generating halothane anesthesia. From Tanase *et al.*;[63] used with permission.

been postulated to function as an endogenous sleep-promoting factor[342] and to facilitate the ability of sleep to restore brain energy metabolism.[343] Blocking local adenosine triphosphate synthesis within the basal forebrain causes an increase in NREM sleep.[344] *N*-methylated xanthine molecules such as caffeine, theobromine, and theophylline all promote arousal. Caffeine increases latency to sleep onset and reduces delta power in the electroencephalogram characteristic of NREM sleep.[345] Four adenosine receptors (A_1, A_{2a}, A_{2b}, A_3) have been cloned and the availability of agonists and antagonists have made it possible to begin to specify how these receptors contribute to the regulation of arousal states.[346]

Figure 11 shows that microdialysis delivery of an adenosine A_1 agonist to medial regions of the pontine reticular formation delays recovery from halothane anesthesia while decreasing acetylcholine release.[63] Exogenous adenosine also can enhance the hypnotic effect of intravenous anesthetics. The figure 11 data identify a specific site within the pons[63] where administering an adenosine A_1 agonist delays recovery of wakefulness after anesthesia.[347] The acetylcholine release data are consistent with electrophysiologic evidence showing that adenosine A_1 receptors cause presynaptic disfacilitation[348] and postsynaptic inhibition[349] of cholinergic LDT/PPT neurons. These findings are consistent with the suggestion that activation of adenosine A_1 receptors contributes to isoflurane anesthesia.[350] When rats are deprived of sleep, the anesthesia-induced loss of righting reflex is significantly enhanced.[61] The sleep deprivation–induced shortening of loss of righting was partially blocked by administering adenosine A_1 and A_2 receptor antagonists.[70] These findings are consistent with the hypothesis that adenosinergic mechanisms modulating sleep also may alter responsiveness to some anesthetics. Depriving children of sleep in hopes of facilitating conscious sedation for therapeutic or diagnostic procedures, however, has not been successful.[289]

Prolonged wakefulness increases rat brain levels of adenosine,[351] and caffeine ingestion by humans increases latency to sleep onset and reduces the electroencephalographic delta power of NREM sleep.[345] Methylxanthines such as theophylline and caffeine are competitive inhibitors of adenosine A_1 and A_2 receptors; therefore, the arousal-promoting action of methylxanthines is consistent with adenosine increasing the drive to sleep. Adenosine inhibits neurons that promote arousal, and systemic administration of adenosine agonists increases NREM sleep.[342,346]

The role of adenosine in pain mechanisms recently has been reviewed.[352] Adenosine also provides a tool for pain management,[353,354] with few side effects when administered intrathecally.[355,356] The mechanisms of adenosine's antinociceptive actions are complex and depend on the type of pain, the location of adenosine administration, and the subtype of adenosine receptor activated. Adenosine decreases opioid and anesthetic requirement.[357,358] Preclinical studies discovered that administering an adenosine A_1 agonist into pontine reticular formation regions regulating sleep also causes antinociception.[62] The small dose of adenosine A_1 agonist injected into the pontine reticular formation caused a surprisingly long duration antinociceptive effect. Site-specific neurochemistry is a recurring theme in this review, and the antinociceptive actions of a systemically administered adenosine A_1 agonist are diminished by spinal cord transection.[359] Adenosine A_1 receptors are coupled to G proteins, which amplify synaptic signaling in the time domain. *In vitro* studies show that G proteins in REM sleep generating regions of the pontine reticular formation are activated by an adenosine A_1 agonist.[360]

GABA

Many anesthetic and sedating drugs act by increasing conductance at $GABA_A$ receptors.[52,361] Results regarding the presynaptic actions of general anesthetics on amino acid neurotransmitter uptake have been inconsistent. *In vitro* data show that isoflurane and propofol did not alter uptake, binding, or transport of GABA and glutamate.[362] Isoflurane and propofol, however, have been shown to inhibit glutamate and GABA release evoked from cortical synaptosomes.[363] $GABA_A$ and $GABA_C$ receptors are coupled to chloride ion channels, and the $GABA_B$ subtype is a G protein–coupled receptor.[364] Memory depends on normal hippocampal function, and volatile anesthetics accentuate $GABA_A$ transmission in rat hippocampus.[365] GABA agonists have been shown to disrupt synaptic function in developing rat brain, leading to memory and performance impairments.[366] Injection of a $GABA_A$ agonist into rat hippocampus decreased the amount of an-

esthetic needed to induce a loss of righting reflex or motoric response to tail pinch.[367] *In vitro* data show that propofol depresses excitability of hippocampal CA1 neurons by enhancing tonic inhibition mediated by $GABA_A$ receptors.[368] Ketamine, chloral hydrate, halothane anesthesia, and NREM sleep all decreased the firing rate of wake-active GABAergic neurons in the ventral tegmental area.[369]

Sleep can be enhanced by selectively increasing inhibitory GABAergic neurotransmission in brain regions that generate arousal, such as the posterior hypothalamus, locus coeruleus, and dorsal raphe nucleus (reviewed in Baghdoyan and Lydic[72] and Mallick *et al.*).[370] In the basal forebrain, blocking $GABA_A$ receptors significantly increases acetylcholine release.[371] This finding is consistent with data showing that direct administration of a $GABA_A$ agonist into the basal forebrain of rats increases NREM sleep and inhibits wakefulness and REM sleep.[372]

γ-Aminobutyric acid–mediated transmission in the medial preoptic area of the hypothalamus modulates arousal. Propofol is thought to act by enhancing GABAergic neurotransmission,[361] and microinjecting propofol into the medial preoptic area of rat hypothalamus leads to an increase in NREM sleep.[373] The sleep-enhancing effects of propofol are blocked by coadministration of the benzodiazepine receptor antagonist flumazenil.[374] Multiple neurotransmitters have been shown to interact with GABAergic systems regulating arousal. For example, the sleep-inducing effects of adenosine microinjected into the medial preoptic area are blocked by flumazenil.[375] Administering the cholinergic agonist carbachol into the medial preoptic area of rats promotes arousal,[376] and the sedative–hypnotic effects of propofol are, in part, cholinergically modulated.[377]

In humans, systemic administration of sedative hypnotics that enhance the actions of GABA increase NREM sleep and decrease REM sleep.[378] Animal studies have shown that the effects of GABAergic drugs on sleep are site dependent with the brain. In rats, microinjecting a $GABA_B$ receptor agonist, but not agonists for $GABA_A$ or $GABA_C$ receptors, into the pedunculopontine tegmental nuclei caused a significant increase in the REM phase of sleep.[379] In regions of the pontine reticular formation that regulate arousal (fig. 2), microinjecting a $GABA_A$ antagonist enhanced REM sleep, and administering a $GABA_A$ agonist decreased REM sleep.[380] Microinjection of $GABA_B$ antagonists and agonists also enhanced and blocked, respectively, REM sleep, but the changes in sleep and wakefulness were of a lesser magnitude than the effects produced by $GABA_A$ antagonists and agonists.[381] These data, combined with evidence that cholinergic neurotransmission is a contributor to arousal state control (figs. 2, 3, 6, and 7), suggest an interaction between GABA and acetylcholine in the regulation of arousal. The potential for this interaction was demonstrated by data showing that microdialysis delivery of the

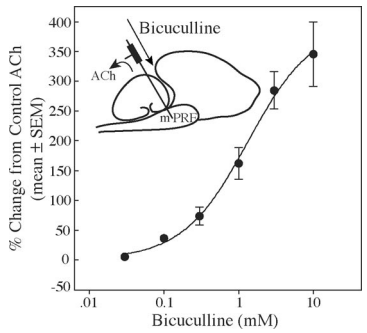

Fig. 12. Microdialysis delivery of the γ-aminobutyric acid type A receptor antagonist bicuculline to medial regions of the pontine reticular formation (mPRF) of halothane-anesthetized cat causes a concentration-dependent increase in acetylcholine (ACh) release. Similar studies using intact, unanesthetized animals showed that bicuculline also caused a significant increase in rapid eye movement sleep. From Vazquez and Baghdoyan;[382] used with permission.

$GABA_A$ receptor antagonist bicuculline to medial regions of the pontine reticular formation caused a concentration-dependent increase in acetylcholine release (fig. 12) that was blocked by the $GABA_A$ receptor agonist muscimol.[382] Microdialysis delivery of bicuculline to the pontine reticular formation of intact, unanesthetized animals also enhanced REM sleep.[382] These results support the interpretation that $GABA_A$ receptors in the pontine reticular formation modulate levels of arousal, in part, by altering acetylcholine release. Recent microinjection data also provide strong support for the regulation of arousal by a GABAergic–cholinergic interaction in the pontine reticular formation.[305] The REM sleep–like state evoked by pontine microinjection of carbachol was blocked by pretreatment with muscimol, but the REM sleep–like state evoked by microinjection of bicuculline was not blocked by pretreatment with scopolamine.[305] Taken together, these microinjection and microdialysis data suggest that GABAergic transmission in the pontine reticular formation promotes wakefulness by inhibiting cholinergically activated REM sleep-promoting neurons.[305,382]

The foregoing results demonstrate that the effects of GABAergic drugs on states of arousal vary significantly as a function of the brain region into which GABAergic drugs are administered. These data provide yet another line of support for the view that the mechanisms of drug action on arousal states must be characterized in a brain region–specific manner. Studies aiming to understand the mechanisms through which anesthetic drugs alter arousal or nociception must also be conducted in a site-specific manner. For example, *in vitro* data indicate that in thalamic neurons amobarbital alters specific and restricted membrane ionic currents gated by $GABA_A$ receptors.[383]

Monoamines

As reviewed elsewhere,[22,55,90,384,385] raphe and locus coeruleus neurons discharge maximally during wakeful-

ness, discharge more slowly during NREM sleep, and stop firing during REM sleep. These neuronal activity patterns support the interpretation that serotonin (5-HT)–containing neurons in the midline raphe nuclei and noradrenergic neurons in locus coeruleus contribute to the generation of wakefulness and the inhibition of REM sleep.[72] A REM sleep inhibitory role for serotonin is supported by data showing that knockout mice lacking either 5-HT_{1B} receptors[386] or 5-HT_{1A} receptors[387] have significantly more REM sleep than wild-type mice. Consistent with these findings are data showing that mice lacking a serotonin transporter gene have decreased REM sleep.[388] These preclinical findings provide an interpretation for the REM sleep reduction caused by antidepressants functioning as serotonin selective reuptake inhibitors.[388]

Rather than exerting a unitary control of wakefulness or sleep, serotonergic neurons are postulated to enhance arousal secondary to promoting motor activity and sensory processing.[389] There is also evidence that 5-HT_2 receptors may modulate the sleep-promoting effects of the cytokine interleukin 1.[390] The potential clinical relevance of serotonergic receptors is illustrated by basic studies showing that selective activation of 5-HT4(a) receptors can prevent fentanyl-induced respiratory depression without loss of analgesia.[391]

Consistent with the sleep-dependent firing rate of locus coeruleus neurons, norepinephrine levels in the locus coeruleus progressively decrease during the transitions from wakefulness, to NREM sleep, and NREM sleep to REM sleep.[385,392] The three groups of adrenergic receptors and (subtypes) are comprised of α_1 (1a, 1b, 1d), α_2 (2a, 2b, 2c), and β adrenoceptors (1, 2, 3).[393] The α_2 agonist dexmedetomidine has a sedative–hypnotic action that is mediated by the locus coeruleus,[394] consistent with its utility in clinical anesthesia.[395] Neurons are hyperpolarized by many anesthetic agents,[396] and inhibiting the discharge of wake-promoting neurons results in the loss of wakefulness. There is good evidence that noradrenergic transmission contributes to the generation of general anesthesia and sleep.[397] The sedative actions of dexmedetomidine are diminished by lesions of hypothalamic regions contributing to NREM sleep,[398] consistent with norepinephrine being relevant for both sleep and anesthesia.[64] The complexity of multiple transmitters interacting to modulate states of arousal is again demonstrated by the finding that α_1 and α_2 adrenoceptors in the pontine dorsal raphe nucleus modulate the release of serotonin.[399] In mice, targeted disruption of the gene for dopamine β-hydroxylase, the enzyme converting dopamine to norepinephrine, caused decreases in brain-activated states of wakefulness and REM sleep. These results are consistent with the view that noradrenergic neurotransmission contributes to the generation of wakefulness and REM sleep.[400]

A large body of evidence supports a role for histamine in the maintenance of wakefulness.[401] Similar to serotonergic and noradrenergic neurons described above, histaminergic neurons within the posterior hypothalamus have long been known to show a selective, wake-on/REM-off discharge pattern.[402,403] These histaminergic neurons project to many arousal-promoting nuclei and excite other monoaminergic and cholinergic neurons by activating H1, H2, and H3 receptors. For example, microinjecting an H1 receptor agonist into the LDT decreases cortical slow wave activity and increases wakefulness.[404] Knockout mice lacking the synthetic enzyme for histamine show an increase in REM sleep and a slowing of the electroencephalogram during wakefulness.[405]

Multiple lines of evidence illustrate the importance of dopamine for regulation of arousal and affective states. For example, substance abuse is a significant occupational hazard for anesthesiologists.[406–408] Dopaminergic reward circuits underlie both addiction[409,410] and the pharmacologic treatment of drug withdrawal.[411] Dopamine agonists enhance vigilance and performance.[412] To date, five subtypes of G protein–coupled dopamine receptors (D1–D5) have been identified.[413] In rats, wakefulness is enhanced by systemic[414] or intracerebroventricular[415] administration of dopamine D1 and D2 receptor agonists.

Dopamine contributes to the regulation of sleep through mechanisms that have not yet been elucidated. Approximately two thirds of patients with Parkinson disease have excessive daytime sleepiness, parasomnias, or difficulty initiating and maintaining sleep.[416] The Standards of Practice Committee of the American Academy of Sleep Medicine notes that restless legs syndrome and periodic limb movement disorder are most successfully treated with dopaminergic drugs.[417]

Dopamine levels are modulated by presynaptic dopamine autoreceptors and by a dopamine transporter. In mice, deletion of the dopamine transporter gene caused increased wakefulness, decreased NREM sleep, and rendered these mice unresponsive to the arousal-promoting actions of methamphetamine and modafinil.[418] The drug modafinil has U.S. Food and Drug Administration approval for treating the excessive daytime sleepiness of narcolepsy. The mechanisms of action of modafinil remain unknown, and the pharmacologic profile of modafinil differs from sympathomimetic amines. Recent studies report that modafinil significantly enhances wakefulness after general anesthesia.[32]

The specific brain nuclei and synaptic mechanisms by which dopamine alters sleep and enhances arousal are not yet clear.[419] Studies which used early immediate gene (c-fos) expression as an index of neural activity, combined with immunostaining for tyrosine hydroxylase, report that dopamine neurons in the ventral tegmental nucleus revealed greatest Fos expression during recovery from REM sleep deprivation.[420] Microdialysis measures of dopamine from locus coeruleus and amyg-

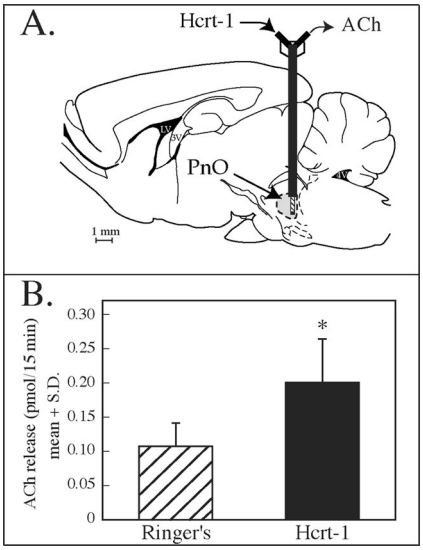

Fig. 13. Acetylcholine (ACh) release in the pontine reticular formation of isoflurane-anesthetized rat is increased by microdialysis delivery of the peptide hypocretin-1 (Hcrt-1). (*A*) Sagittal schematic of rat brain (rostral to left) illustrating placement of a microdialysis probe into the pontine reticular nucleus, oral part (PnO). (*B*) Endogenously released acetylcholine was measured during dialysis delivery of hypocretin-1. These results are consistent with the possibility that hypocretin modulates arousal, in part, by altering acetylcholine release in the pontine reticular formation. Data in *B* are from Bernard *et al.*;[239] used with permission.

dala across the feline sleep cycle found no significant alterations in dopamine release.[392] However, in rat prefrontal cortex, basal levels of dopamine are greater during the dark phase (when rats are active) than during the light phase (when rats spend more time sleeping).[421]

Hypocretin/Orexin

The discovery that hypocretin-1 and hypocretin-2 (also known as orexin A and orexin B) are arousal-promoting peptides produced by lateral hypothalamic neurons has stimulated efforts to specify the role of hypocretins in motor control.[422,423] These efforts are based on findings suggesting that defects in the hypocretin system may play a causal role in human and animal narcolepsy.[424–427] Pontine administration of hypocretin has been shown to alter muscle tone in decerebrate rats.[428] Microinjection of hypocretin into the trigeminal motor nucleus or hypoglossal nucleus of decerebrate cats increased muscle activity in the masseter and genioglossus muscles, respectively.[429] The locus coeruleus receives the most prominent extrahypothalamic hypocretinergic innervation of all brain regions studied,[422,423] and descending projections from locus coeruleus enhance motoneuron excitability.[430] In decerebrate rats, muscle tone was increased when hypocretin was administered into locus coeruleus, and muscle tone decreased when hypocretin was administered into pontine reticular formation.[428] *In vitro* studies of rat cortex indicate that norepinephrine release is increased by hypocretin-1 and hypocretin-2.[431]

Many studies are evaluating the potential relevance for arousal state control of the hypocretin peptides. Administering hypocretin-1 into the locus coeruleus[432] or basal forebrain of rats increases wakefulness,[433] and intraventricular administration of hypocretin-1 caused activation of the electroencephalogram in rats anesthetized with isoflurane.[434] Additional data suggest that hypocretinergic neurons may contribute to the mechanisms underlying barbiturate anesthesia.[435] Relevant to the topic of pontine cholinergic modulation of arousal, figure 13 shows that hypocretin-1 enhances acetylcholine release in the pontine reticular formation of rats.[239] This finding fits with evidence that hypocretin-1 facilitates synaptic activity in the pontine reticular formation[303] and is consistent with the possibility that hypocretin may promote arousal, in part, by enhancing cholinergic neurotransmission.

Conclusions: Gaps in Knowledge as Opportunities for Research

The U.S. National Institutes of Health has made available a plan for accelerating medical discovery and improving health.† The National Institutes of Health plan places special emphasis on translating basic research into clinical application. The neurobiology of arousal state control is a crosscutting research theme directly relevant for sleep disorders medicine and anesthesiology. The concluding sections highlight three areas where gaps in knowledge magnify the disease burden and, by definition, provide opportunities for translational research.

Information Systems and Functional Genomics of Arousal State Control

The ability to create in real time a complete, digital, anesthesia record offers a powerful tool for translational research. The large amount of human physiologic information that can be synthesized by digital information systems has the potential to provide anesthesiology with unique patient data for phenotyping comorbidities.‡ These information systems also give anesthesiology a special opportunity for developing a functional genomics that can link genetic factors to anesthesia outcome.[436]

Developing a functional genomics of arousal state control will depend on a viable dialogue between basic and clinical research. Anesthesiology has successfully used the ability of preclinical models to unmask basic mechanisms that can be translated into clinical relevance.[437] The power of mouse models for characterizing genetic regulation of anesthetic susceptibility was appreciated many years ago.[438] Those pioneering studies presaged the recent sequencing of the mouse genome. The mouse

† www.nih.gov/news/pr/oct2004/od-04.htm. Accessed December 5, 2004.

‡ www.gasnet.org/aims/oreilly.php. Accessed December 5, 2004.

genome was first published in December 2002 and revealed a 99% homology with the human genome.[439] This homology means that preclinical studies using mice can significantly advance understanding of human disease.[440,441] The foregoing factors have led to the view that the mouse is "the most important animal model in biomedical research."§ Sleep varies significantly among mouse strains[442–444] and, given the high degree of genetic homology, it is not surprising that human sleep is a heritable phenotype.[445,446] Inbred strains of mice exhibit significant variability in response to anesthesia,[447] and human perioperative outcome varies significantly as a function of genotype.[436] The importance of genetic factors regulating sleep is illustrated by the finding that a single gene mutation in fruit flies produces a short-sleeping phenotype with a reduced lifespan.[448] Multiple studies now indicate that pontine cholinergic neurotransmission is a lower level phenotype modulating the higher level phenotype of sleep[105,108] and sleep-dependent alterations in breathing.[130,449] Ideally, patient data gleaned from automated information systems can be used to plan preclinical studies seeking to elucidate mechanisms regulating arousal states and contributing to state-dependent pathophysiology.

Sleep and Anesthesia in Elderly Patients

Elderly patients will comprise an increasing caseload for anesthesiology. In the United States, the number of persons aged 65 yr and older was estimated at 33.5 million in 1995, 34.7 million in 2000, and 79 million (20% of the population) by 2050.[450] From midlife to the eighth decade of life, total sleep time decreases by an average of 27 min/decade.[451] One cross-sectional study showed that more than one third of the elderly had sleep problems.[452] Sleep disorders have been described as one of the most pervasive and poorly addressed problems of aging.[453] Postoperative delirium is common in older patients,[454,455] even in the absence of neurodegenerative disorders.[456] Postoperative delirium is known to be associated with medical comorbidity, increased mortality, and decreased ability to live independently after discharge.[457] Delirium can have many causes,[458] resulting in a wide rage of altered arousal states.[208]

The foregoing clinical data have prompted basic studies aiming to understand the contribution of cholinergic neurotransmission to the regulation of cortical arousal. Prefrontal cortex contributes to regulation of arousal and orientation (fig. 1). Studies in mice show that presynaptic and postsynaptic muscarinic cholinergic receptors help to regulate excitability of prefrontal cortex.[266–268] Additional mouse data show that pontine cholinergic neurotransmission significantly alters breathing and cortical acetylcholine release during anesthesia.[265] The National Institutes of Health maintains a colony of aged mice that can be acquired by extramural investigators. Characterizing age-related changes for multiple neurotransmitters across multiple arousal states will help to clarify changes in sleep and responsiveness to anesthetics observed in older patients.

Obesity Alters Arousal and Autonomic Control

Obesity is directly relevant for sleep, anesthesiology, and the regulation of arousal states. The ongoing obesity epidemic has prompted both the World Health Organization and the National Institutes of Health to develop task forces to identify causes and countermeasures for obesity.[459] Obesity is a disease[460] with adverse health effects, and the American Society for Bariatric Surgery estimated that in 2003, more than 100,000 patients elected stomach reduction surgery in an effort to treat their obesity. Some of the clinical features and implications of obesity for anesthesia and intensive care unit patients have been reviewed.[461] In young adults, obesity is associated with short sleep duration, and short sleep duration is a risk factor for diabetes and heart disease.[462] Obesity also increases the likelihood of OSA,[463] and upper airway muscle function is particularly sensitive to depression by anesthetic agents.[464] There is a significant interaction between sleep and the immune system,[152,153,465,466] and obesity is a risk factor for surgical site infection.[467] In 2003, U.S. medical expenditures attributed to obesity and associated chronic disease were estimated at $75 billion.[468] Poor physical fitness is a modifiable risk factor, and exercise capacity has been shown to be a powerful predictor of mortality.[469]

Brain regions controlling appetite also contribute to the regulation of sleep and state-dependent changes in autonomic control. Appetite is regulated, in part, by a group of hormones that feed back to the arcuate nucleus of the hypothalamus to control food intake. Leptin is an adipocyte-derived cytokine that normally functions to decrease food intake and maintain energy homeostasis.[470] There is good agreement between clinical and preclinical data showing a relation among leptin, sleep, and breathing.[17] Patients with OSA have higher levels of serum leptin,[471] but common human obesity is associated with leptin resistance.[472] Epidemiologic data reveal a relation between the apnea–hypopnea index and serum leptin levels, consistent with the possibility that sleep apnea may suppress leptin secretion.[473] Considerable data support the hypothesis that sleep apnea may be a manifestation of a feed-forward metabolic syndrome in which visceral obesity increases insulin resistance and inflammatory cytokines.[18] Rats selectively bred for low aerobic capacity do score high on risk factors for the metabolic syndrome.[474] Studies of mutant mice reveal a transcription factor (*Clock*) that modulates the circadian distribution of sleep and may also contribute to obesity and metabolic syndrome.[475]

Leptin-deficient mice are obese, have diminished mo-

§ www.genome.gov/10005831. Accessed December 5, 2002.

tor activity, and have a depressed ability to generate an appropriate ventilatory response to hypercapnia.[476] Sleep exacerbates the depressed breathing of these obese mice, and chronic leptin replacement reduces food intake, increases tidal volume and respiratory rate during REM sleep, and increases the ventilatory response to carbon dioxide challenge.[477] Interestingly, the arousal promoting peptide hypocretin is down-regulated in the hypothalamus of obese mice.[478] Obese leptin-deficient mice also have a different ventilatory and sleep response to pontine administration of neostigmine compared with C57BL/6J mice.[449] The brain sites and neurotransmitters through which leptin modulates breathing are currently unknown.[479]

The data highlighted in this review provide a rationale for translational research focused on endogenous molecules that regulate arousal and energy homeostasis. Anesthesia patients routinely give investigators the ability to sample serum and cerebrospinal fluid. Ready access to blood and cerebrospinal fluid provides the potential for targeted assays of arousal-regulating molecules. Ultimately, relational databases linking molecular profiles to patient data will contribute to a molecular characterization of anesthetic states and sleep disorders.

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