128

BASIC MECHANISMS OF SLEEP: NEW EVIDENCE ON THE NEUROANATOMY AND NEUROMODULATION OF THE NREM-REM CYCLE

EDWARD F. PACE-SCHOTT
J. ALLAN HOBSON

The 1990s brought a wealth of new detail to our knowledge of the brain structures involved in the control of sleep and waking and in the cellular level mechanisms that orchestrate the sleep cycle through neuromodulation. This chapter presents these new findings in the context of the general history of research on the brainstem neuromodulatory systems and the more specific organization of those systems in the control of the alternation of wake, non–rapid eye movement (NREM), and REM sleep.

Although the main focus of the chapter is on the our own model of reciprocal aminergic-cholinergic interaction, we review new data suggesting the involvement of many more chemically specific neuronal groups than can be accommodated by that model. We also extend our purview to the way in which the brainstem interacts with the forebrain. These considerations inform not only sleep-cycle control *per se,* but also the way that circadian and ultradian rhythms resonate to regulate human behavior including the intensity and form of conscious awareness.

RECIPROCAL INTERACTION AND ITS RECENT MODIFICATIONS

Behavioral State–Dependent Variations in Neuromodulation

A paradigm shift in thinking about sleep-cycle control was forced by the discovery of the chemically specific neuromodulatory subsystems of the brainstem (for reviews, see refs. 1 to 4) and of their differential activity in waking (noradrenergic, serotonergic, and cholinergic systems on), NREM sleep (noradrenergic, serotonergic, and cholinergic systems damped), and REM sleep (noradrenergic and serotonergic systems off, cholinergic system undamped) (1–4).

Original Reciprocal Interaction Model: An Aminergic-Cholinergic Interplay

The model of reciprocal interaction (5) provided a theoretic framework for experimental interventions at the cellular and molecular level that has vindicated the notion that waking and REM sleep are at opposite ends of an aminergically dominant to cholinergically dominant neuromodulatory continuum, with NREM sleep holding an intermediate position (Fig. 128.1). The reciprocal interaction hypothesis (5) provided a description of the aminergic-cholinergic interplay at the synaptic level and a mathematic analysis of the dynamics of the neurobiological control system. In this section, we review ongoing recent findings of the essential roles of both acetylcholine (ACh) and the monoamines serotonin (5-HT) and norepinephrine (NE) in the control of the NREM-REM cycle as well as work that has led to the alteration (Fig. 128.2) and elaboration (Fig. 128.3) of the original reciprocal interaction model.

Although there is abundant evidence for a cholinergic mechanism of REM-sleep generation centered in the pedunculopontine (PPT) and laterodorsal tegmental (LDT) nuclei of the mesopontine tegmentum (for reviews, see refs. 2 to 4 and 6 to 8), not all PPT-LDT neurons are cholinergic (9–12), and cortical ACh release may be as high during wakefulness as during sleep (13).

Recently, reciprocal interaction (5) and reciprocal inhibition (14) models for control of the REM-NREM sleep cycle by brainstem cholinergic and aminergic neurons have been questioned (10). Specifically, the hypothesized self-stimulatory role of ACh on those mesopontine neurons associated with the characteristic pontogeniculooccipital (PGO) waves

Edward F. Pace-Schott and J. Allan Hobson: Laboratory of Neurophysiology, Department of Psychiatry, Harvard Medical School. Boston, Massachusetts.

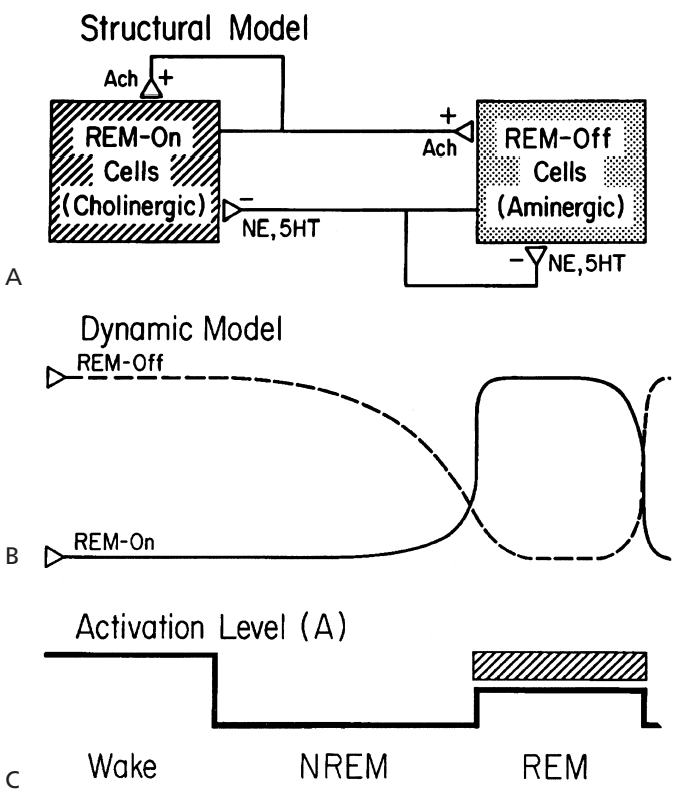


FIGURE 128.1. The original reciprocal interaction model of physiologic mechanisms determining alterations in activation level. **A:** Structural model of reciprocal interaction. REM-on cells of the pontine reticular formation are cholinoceptively excited or cholinergically excitatory (ACH+) at their synaptic endings. Pontine REM-off cells are noradrenergically (NE) or serotonergically (5-HT) inhibitory (−) at their synapses. **B:** Dynamic model. During waking, the pontine aminergic system is tonically activated and inhibits the pontine cholinergic system. During NREM sleep, aminergic inhibition gradually wanes, and cholinergic excitation reciprocally waxes. At REM sleep onset, aminergic inhibition is shut off, and cholinergic excitation reaches its high point. **C:** Activation level. As a consequence of the interplay of the neuronal systems shown in **A** and **B,** the net activation level of the brain **(A)** is at equally high levels in waking and REM sleep and at about half this peak level in NREM sleep. (From Hobson JA, Stickgold R, Pace-Schott EF. The neuropsychology of REM sleep dreaming. *Neuroreport* 1998;9:R1–R14, with permission.)

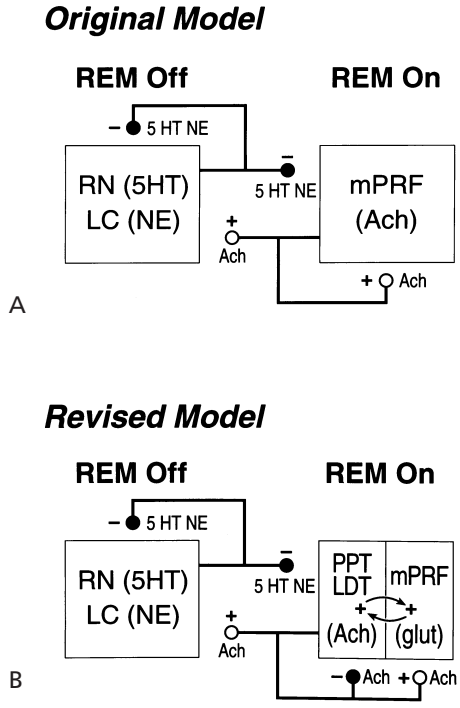


FIGURE 128.2. Synaptic modifications of the original reciprocal interaction model based on recent findings. **A:** The original model proposed by McCarley and Hobson (5). **B:** Synaptic modifications of the original reciprocal interaction model based on recent findings of self-inhibitory cholinergic autoreceptors in mesopontine cholinergic nuclei and excitatory interactions between mesopontine cholinergic and noncholinergic neurons (Fig. 128.3 and 128.4C, for more detail and references). The exponential magnification of cholinergic output predicted by the original model *(A)* can also occur in this model with mutually excitatory cholinergic-noncholinergic interactions taking the place of the previously postulated, mutually excitatory cholinergic-cholinergic interactions. In the revised model, inhibitory cholinergic autoreceptors would contribute to the inhibition of laterodorsal tegmental nucleus (LDT) and pedunculopontine tegmental nucleus (PPT) cholinergic neurons that is also caused by noradrenergic and serotonergic inputs to these nuclei. Therefore, the basic shape of reciprocal interaction's dynamic model (Fig. 128.1B) and its resultant alternation of behavioral state (Fig. 128.1C) could also result from the revised model. *Open circles,* excitatory postsynaptic potentials; *closed circles,* inhibitory postsynaptic potentials; Ach, acetylcholine; glut, glutamate; 5-HT, serotonin; LC, locus ceruleus; mPRF, medial pontine reticular formation; NE, norepinephrine; RN, dorsal raphe nucleus. (From Hobson JA, Stickgold R, Pace-Schott EF. The neuropsychology of REM sleep dreaming. *Neuroreport* 1998;9:R1–R14, with permission.)

of REM sleep has not been confirmed in *in vitro* slice preparations of the rodent brainstem (10). For example, ACh has been shown to hyperpolarize cell membranes in slice preparations of the rodent parabrachial nucleus (15), LDT (16), and PPT (10). Similarly, those LDT-PPT neurons with burst discharge properties most like those hypothesized to occur in PGO-burst neurons ("type I" neurons) may not be cholinergic (9). Much evidence remains, however, that the reciprocal interaction model accurately describes essential elements of REM-NREM sleep-cycle control even though a few assumptions in its detailed synaptic mechanisms and connectivity are heuristic (see Figs. 128.2 and 128.3).

New Findings Supporting the Cholinergic Enhancement of REM Sleep

Numerous findings confirm the hypothesis that cholinergic mechanisms are essential to the generation of REM sleep and its physiologic signs (for reviews, see refs. 1 to 4, 6 to

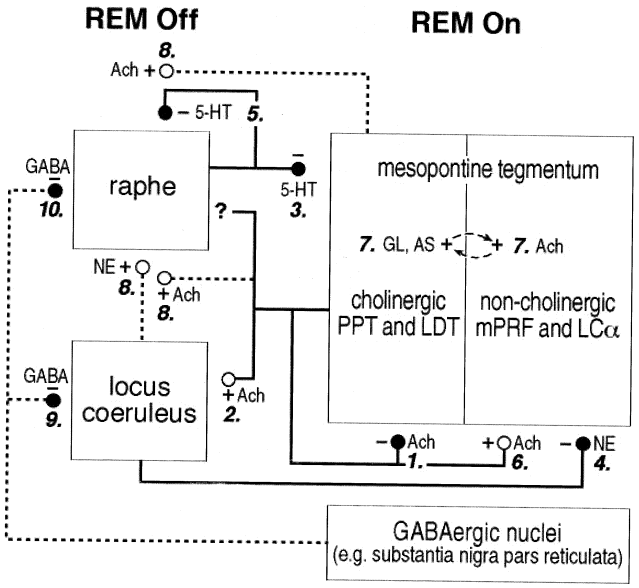


FIGURE 128.3. Additional synaptic details of the revised reciprocal interaction model shown in Fig. 128.2B derived from data reported *(solid lines)* and hypothesized relationships suggested *(dotted lines)* in recent experimental studies (numbered on figure and below). See the text for a discussion of these findings. Additional synaptic details can be superimposed on the revised reciprocal interaction model without altering the basic effects of aminergic and cholinergic influences on the REM sleep cycle. Excitatory cholinergic-noncholinergic interactions using acetylcholine (Ach) and the excitatory amino acid transmitters enhance firing of REM-on cells *(6* and *7),* whereas inhibitory noradrenergic *(4),* serotonergic *(3),* and autoreceptor cholinergic *(1)* interactions suppress REM-on cells. Cholinergic effects on aminergic neurons are excitatory *(2),* as hypothesized in the original reciprocal interaction model, and they may also operate through presynaptic influences on noradrenergic-serotonergic as well as serotonergic-serotonergic circuits *(8).* GABAergic influences *(9* and *10),* as well as other neurotransmitters such as adenosine and nitric oxide (see text), may contribute to the modulation of these interactions. *Open circles,* excitatory postsynaptic potentials; *closed circles,* inhibitory postsynaptic potentials; AS, aspartate; glut, glutamate; 5-HT, serotonin; LCa, peri–locus ceruleus α; LDT, laterodorsal tegmental nucleus; mPRF, medial pontine reticular formation; NE, norepinephrine; PPT, pedunculopontine tegmental nucleus. (For the specific references corresponding to the interactions numbered *1* to *10,* please refer to ref. 2.)

8, 11 to 13, 14, 17, and 18). A selection of the many recent examples follows.

Experimental REM Sleep Induction and Suppression

Microinjection of cholinergic agonist (e.g., carbachol) or cholinesterase inhibitors into many areas of the paramedian pontine reticular formation (PRF) of the cat induces REM sleep (for reviews, see refs. 6 to 8). The endogenous ACh released into these areas originates in neurons of the mesopontine tegmentum (6). In addition to these short-term REM induction sites, carbachol injection into a more lateral pontine site in the caudal peribrachial area has been shown to induce long-term (more than 7 days) REM enhancement (19) and long-term PGO enhancement but without REM enhancement (20). *In vivo* cholinergic REM enhancement and a specific carbachol-sensitive site in the dorsal locus subceruleus of rats have been described (21).

In addition to the well-known suppression of REM by muscarinic antagonists (1), presynaptic anticholinergic agents have also been shown to block REM (22). Activation of muscarinic M2 receptors (M2AChR) in the pontine reticular formation has been shown to be the primary mechanism for REM induction with carbachol, and such activation has been shown to increase G-protein binding in brainstem nuclei associated with ACh release in the PRF and REM sleep (7, 23).

Cholinergic Neurons and REM Sleep

As reviewed by Semba (6), studies have demonstrated a physiologically meaningful heterogeneity among mesopontine neurons both *in vivo* and *in vitro.* In behaving cats and rats, separate populations of REM-and-wake-on, REM-on, and PGO wave–associated neurons can be identified in the LDT and PPT with strong evidence that a subset of these are cholinergic (6). In rodent brainstem slices, mesopontine neurons can be divided according to their membrane current characteristics into types I, II and III, with types II and III being cholinergic and projecting to the thalamus (6).

Many recent experimental findings associate REM sleep generation with mesopontine cholinergic neurons. For example, although type I bursting neurons are noncholinergic, cholinergic type II and III PPT-LDT neurons have firing properties that make them well suited for the *tonic* maintenance of REM (9). Three supportive experimental studies by Robert McCarley's group at Harvard (reviewed in ref. 2) are as follows: (a) PPT-LDT neurons specifically show immediate-early gene (e.g., *c-fos*) immunoreactivity after carbachol-induced REM sleep; (b) low-amplitude electrical stimulation of the LDT enhances subsequent REM sleep; and (c) electrical stimulation of the cholinergic LDT evokes excitatory postsynaptic potentials in PRF neurons that can be blocked by scopolamine. Finally, the excitatory amino acid, glutamate, when microinjected into the cholinergic PPT, increases REM sleep in a dose-dependent manner (24).

Acetylcholine Release and REM Sleep

Microdialysis studies show enhanced release of endogenous ACh in the medial PRF during natural REM sleep (25). Moreover, stimulation of the PPT causes increased ACh release in the PRF (26). Thalamic ACh concentration of mesopontine origin is higher in both wake and REM than

in NREM (27), and a REM-specific increase of ACh in the lateral geniculate body (LGB) has also been observed (28). Both muscarinic and nicotinic receptors participate in the depolarization of thalamic nuclei by the cholinergic brainstem (29).

Cholinergic Mediation of Specific REM Signs: PGO Waves, Muscle Atonia, Cortical Desynchronization, and Hippocampal Theta

PGO input to the LGB of the thalamus is cholinergic (12), and it can be antidromically traced to pontine PGO-burst neurons (30). In turn, stimulation of mesopontine neurons induces depolarization of cortically projecting thalamic neurons (29). Notably, retrograde tracers injected into the thalamus label 50% or more of cholinergic PPT-LDT neurons (31). Neurotoxic lesions of pontomesencephalic cholinergic neurons reduce the rate of PGO spiking (32), and PGO waves can be blocked by cholinergic antagonists (8). A long history of microinjection studies has shown that, at the level of the pons, cholinergic mechanisms at a variety of sites participate in the suppression of muscle tone accompanying REM (for review, see ref. 33). In addition to brainstem-mediated cholinergic mediation of PGO waves and atonia, cholinergic basal forebrain (BF) nuclei control other distinctive signs of REM including cortical desynchronization and hippocampal theta (see the section on the BF). It may therefore not be an exaggeration to state that the evidence of cholinergic REM sleep generation is now so overwhelming and so well accepted that this tenet of the reciprocal interaction model is an established principle.

New Findings Supporting the Serotonergic and Noradrenergic Suppression of REM Sleep

Aminergic Inhibition of the Cholinergic REM Generator

At the heart of the reciprocal interaction concept is the idea that cholinergic REM sleep generation can only occur when the noradrenergic and serotonergic mediators of waking release their inhibitory constraint of the cholinergic REM generator. The evidence for such inhibitory serotonergic and noradrenergic influences on cholinergic neurons and REM sleep is also now quite strong. (For reviews, see refs. 18, 34, and 35 for 5-HT and ref. 36 for NE.)

Serotonin in Natural REM Sleep

Serotonergic neurons from the dorsal raphe (DR) have been shown to synapse on LDT-PPT neurons (37). Extracellular levels of 5-HT are higher in waking than in NREM and higher in NREM than REM in the brainstem and cortex of rats (38) and the DR (39) and medial PRF (40) of cats. Moreover, reduced extracellular 5-HT concentration in REM sleep has been demonstrated in the human amygdala, hippocampus, orbitofrontal cortex, and cingulate cortex (41).

There is also strong evidence that specific physiologic signs of REM sleep are inhibited by endogenous 5-HT (34). For example, in sleeping cats, the firing of DR neurons is inversely correlated with the occurrence of PGO waves (34). Similarly, hippocampal theta activity, another specific sign of REM sleep, is suppressed by serotonergic activity of the median raphe nucleus (42).

Experimental Serotonergic Suppression of Cholinergic Systems and REM Sleep

Numerous experimental findings have shown that 5-HT and its agonists inhibit mesopontine cholinergic cells as well as REM sleep itself. For example, 5-HT has been shown both to hyperpolarize rat cholinergic LDT cells *in vitro* (10) and to reduce REM sleep percentage *in vivo* (43). Experimentally administered 5-HT has also been shown to suppress specific physiologic signs of REM. For example, 5-HT has been shown to counteract the REM-like carbachol-induced atonia of hypoglossal motor neurons (44).

Microinjection of the 5-HT agonist 8-OH-DPAT into the peribrachial region impedes PGO waves and REM sleep initiation in cats (45). Simultaneous unit recording has shown that microinjection of 8-OH-DPAT selectively suppressed the firing of REM-on but not REM-and-wake-on cells of the cholinergic LDT-PPT (46). *In-vivo* microdialysis of 5-HT agonists into the dorsal raphe nucleus (DRN) decreased DRN levels of serotonin (presumably by 5-HT autoreceptors on DRN cells) which, in turn, increased REM sleep percentage (47). Mesopontine injection of a 5-HT agonist depressed ACh release in the lateral genicolate body (28).

Such findings conclusively show brainstem involvement in the serotonergic suppression of REM sleep. However, localization of this effect solely to the brainstem has been challenged in favor of an amygdala-pontine interaction (48).

Suppression of REM by Endogenous Norepinephrine and Its Agonists

Much recent evidence also implicates NE in the inhibitory control of REM sleep. For example, locus ceruleus (LC) neurons have been shown to become quiescent during REM in the monkey (49), as well as in the cat and rat (1). Electrical stimulation of the pons in the vicinity of the (noradrenergic) LC reduced REM sleep in rats (50), and the noradrenergic antagonist idazoxan increases REM when injected into the PRF of cats (51).

Combined Effects of Serotonin and Norepinephrine on REM Sleep

The REM suppressive effects of 5-HT and NE are likely to be additive. This is suggested by the finding that reuptake

inhibitors targeting primarily either 5-HT or NE transporters all suppress REM sleep in humans (52). Unlike the other brainstem monoamines, the REM sleep effects of dopamine (DA) are more complex (see later).

Therefore, like cholinergic enhancement, aminergic suppression of REM sleep is now an established principle. The 5-HT_{1A} receptor may be of the greatest importance in the inhibition of cholinergic firing in the cat PPT (45) and LDT (53), and mesopontine postsynaptic 5-HT_{1A} receptors may be the active site for serotonergic inhibition of REM (35). Although 5-HT_2 receptors may also be involved in modulating the REM-NREM cycle, their roles are unclear because both 5-HT_2 agonists and 5-HT_2 antagonists suppress REM, whereas 5-HT_2 agonists suppress but 5-HT_2 antagonists increase slow-wave sleep (SWS) (35). Both α_1 (54) and α_2 receptors (55) may be sites of adrenergic REM suppression.

Modification of the Original Reciprocal Interaction Hypothesis to Accommodate New Findings

Modifications of simple reciprocal inhibition or interaction models, which are consonant with recent findings, have been proposed for the brainstem control of REM sleep. For example, Leonard and Llinas suggested in regard to the McCarley and Hobson (5) model that " . . . 'indirect feedback' excitation via cholinergic inhibition of an inhibitory input or cholinergic excitation of an excitatory input or some combination of the two could replace direct feedback excitation in their model" (10). Mutually excitatory or mutually inhibitory interactions between REM-on cholinergic and REM-on noncholinergic mesopontine neurons have also been proposed in the cat (11). Similarly, Semba suggested that naturally occurring REM sleep is instigated when cholinergic LDT-PPT neurons increase their cholinergic stimulation of PRF networks known to be associated with carbachol-induced REM (6). In turn, Semba suggested that PRF neurons may provide a glutamatergic, excitatory feedback to cholinergic neurons in the LDT-PPT thereby maintaining REM sleep (6). Representative hypothetical cholinergic-noncholinergic mechanisms are illustrated in Figs. 128.2B, 128.3, and 128.4C-a. [**Please note** that, with regard to Fig. 128.4A–C, neuronal interactions will be identified in the subsequent main body of the text with *lowercase letters* (e.g., 128.4C-a) that also designate the corresponding excitatory or inhibitory synaptic interaction in the figure itself as well as designating this same interaction in the corresponding figure legend. The illustration of a particular synaptic interaction in a schematic of a particular behavioral state (i.e., Fig. 128.4A-wake, Fig. 128.4B-NREM sleep, and Fig. 128.4C-REM sleep), is not meant to imply that this interaction only occurs in this behavioral state. For example, many of the subcortical excitatory interactions associated with ascending forebrain arousal are shared by both waking and REM sleep (6).]

Other suggested modifications have invoked the contribution of inhibitory neuromodulators such as γ-aminobutyric acid (GABA) in the control of the REM-NREM cycle (for review, see ref. 56). For example, from *in vivo* microdialysis studies of GABA in the cat, Nitz and Siegel (57) suggested that GABA suppresses noradrenergic LC neurons during REM (Figs. 128.3 and 128.4C-b). Similarly, other investigators have suggested that GABAergic inhibition is responsible for the quiescence of serotonergic DR neurons during REM (34). The role of GABA in the suppression of aminergic neurons during REM sleep is strengthened by findings that natural concentrations of 5-HT in the DR during REM are decreased, thereby arguing against serotonergic DR self-inhibition by 5-HT_{1A} somatodendritic autoreceptors (35).

Still other modifications have caused investigators to postulate a role for presynaptic autoreceptors and heteroreceptors. For example, *in vitro* studies in the rat suggested the following modification of reciprocal interaction (58) (Fig. 128.3). During waking, presynaptic nicotinic facilitation of excitatory LC noradrenergic inputs to the DR enhances serotonergic firing. During REM, when the LC is silent, this same presynaptic nicotinic input may facilitate serotonergic self-inhibition by raphe neurons themselves. Notably, all such modifications retain one or both of the major tenets of the reciprocal interaction model: cholinergic facilitation and adrenergic inhibition of REM.

Many of the studies questioning reciprocal interaction or reciprocal inhibition (9,10,15,16) have been carried out on *in vitro* rodent models, and the relation of these findings to findings on the *in vivo* generation of REM sleep signs in the cat is only in its early stages (11). Moreover, the hyperpolarization by ACh of cholinergic cells (9–11,16,28, 59) (Fig. 128.3) may result from recently identified ACh M2 autoreceptors that contribute to the homeostatic control of cholinergic activity (7,59).

In contrast to the hyperpolarization of some mesopontine cholinergic neurons by cholinergic agonists, many medial PRF neurons are depolarized by carbachol (6). This finding suggests that the exponential self-stimulatory activation that can be triggered by cholinergic stimulation in diverse mesopontine and medial pontine sites (1–4) may involve noncholinergic excitatory intermediary neurons. Such cholinergic self-regulation, combined with cholinergic-noncholinergic mutual excitation, is illustrated in Figs. 128.2B, 128.3, and 128.4C-a.

Conclusions Regarding the Current Status of Reciprocal Interaction

We conclude that the two central ideas of the reciprocal interaction model are strongly supported by subsequent research: (a) noradrenergic and serotonergic influences enhance waking and impede REM by anticholinergic mechanisms; and (b) cholinergic mechanisms are essential to REM sleep and come into full play only when the serotonergic and

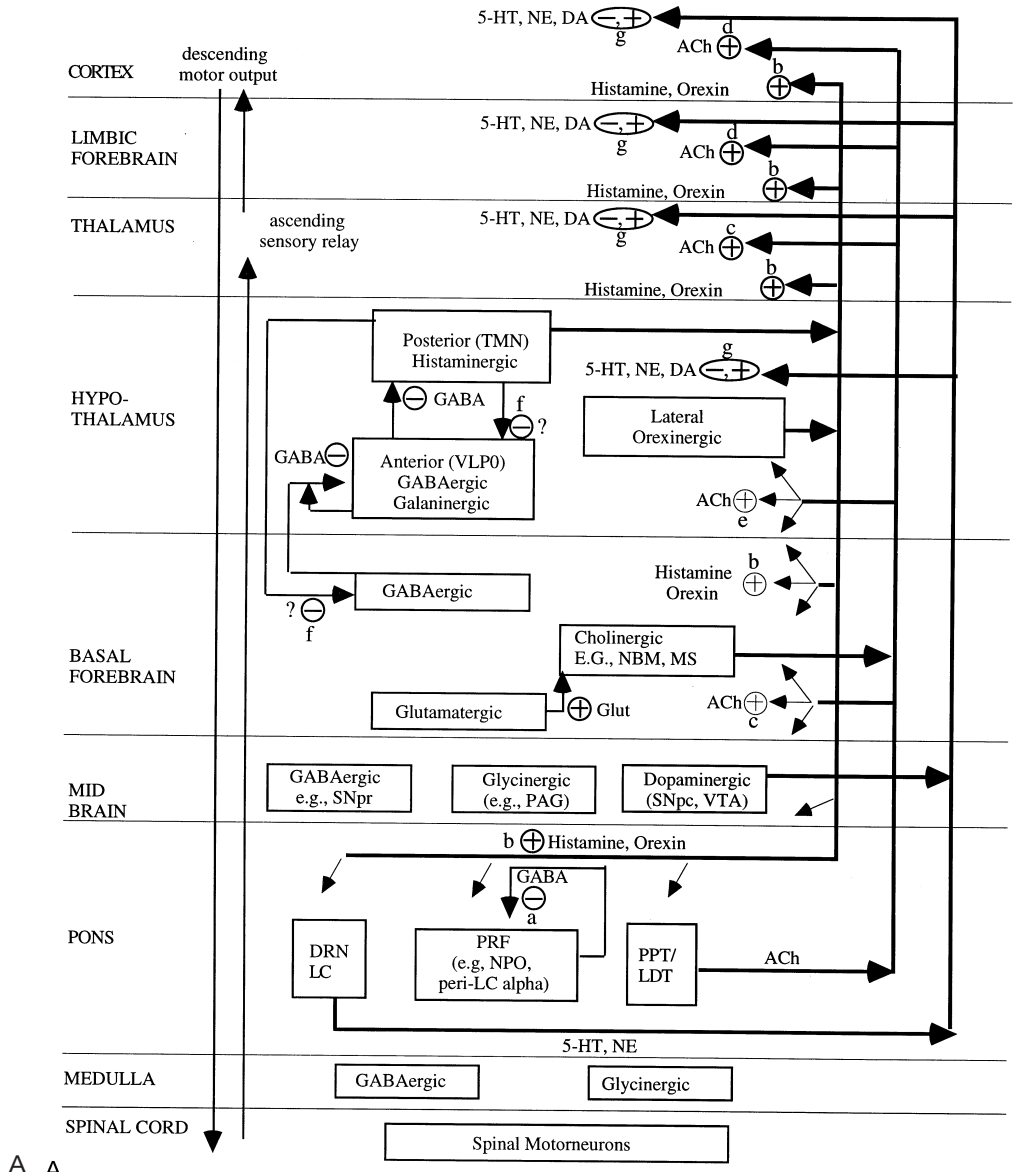
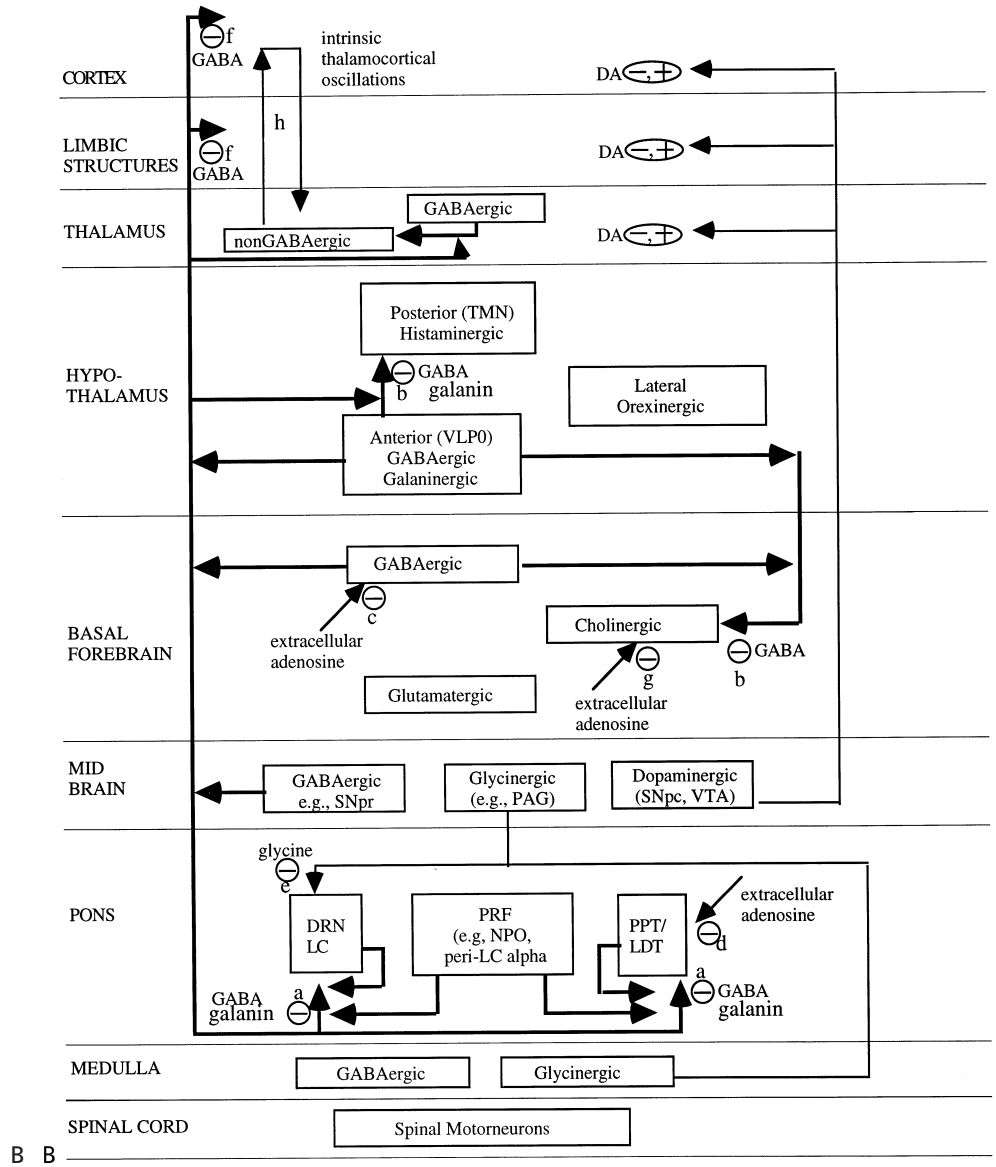


FIGURE 128.4. Critical neuromodulatory systems for the initiation and maintenance of the behavioral states of wake **(A),** NREM sleep **(B),** and REM sleep **(C).** Illustrated circuits are those hypothesized to play executive roles in state initiation or maintenance or to mediate cardinal physiologic signs of that state (e.g., REM atonia). The major defining neuromodulatory features of each state are described, and the most important of these are depicted with the *heaviest lines* in diagrams. The exclusion of particular circuits in individual state diagrams does not imply that circuit's inactivity during that state, and illustration of a particular synaptic interaction in a particular behavioral state is not meant to imply that this interaction only occurs in this behavioral state. For example, much of the sleep-associated GABAergic neuronal inhibition illustrated in NREM **(B)** is probably maintained in REM **(C).** Similarly, many of the subcortical excitatory interactions associated with ascending forebrain arousal are shared by both waking and REM sleep (6). Potentially influential peptidergic neuromodulation (e.g., VIP), and behavioral state–related changes in basal ganglia activity (see text) are left out for the sake of clarity. Finally, neuromodulatory changes occurring with the alternations of substages within NREM sleep are not illustrated. Details of neuronal interactions are provided in the text and are cross-referenced using lower-case letters appearing adjacent to the excitatory or inhibitory synaptic interaction illustrated in **A–C.** These neuronal interactions are also summarized at the end of each sublegend with a representative citation.

A: Wake: diverse ascending activation. During the wake state, the full complement of ascending arousal systems classified by Saper et al. (76) actively modulates the forebrain with the chemical products of their respective brainstem and diencephalic nuclei *(heavy lines in diagram),* including: *serotonin* (5-HT) from the dorsal raphe (DRN) nucleus of the pons innervating the entire forebrain; *norepinephrine* (NE) from the locus ceruleus (LC) of the pons innervating the entire forebrain; *(Figure continues.)*



B B

FIGURE 128.4. *Continued. dopamine* (DA) from the ventral tegmental area (VTA) and substantia nigra pars compacta (SNpc) of the midbrain innervating the entire forebrain; *acetylcholine* (ACh) from the mesopontine laterodorsal tegmental and pedunculopontine nuclei (LDT-PPT), which chiefly modulates the diencephalon; and ACh from the magnocellular cholinergic cells of the basal forebrain that innervate limbic forebrain (e.g., medial septal area or MS to hippocampus) and the cortex (nucleus basalis of Meynert or NBM); *histamine* from the posterior hypothalamus, especially the tuberomamillary nucleus (TMN), which both promotes arousal of the entire forebrain and facilitates other ascending arousal systems in the brainstem; and *orexin* from the lateral hypothalamus that promotes arousal of the forebrain and brainstem arousal systems in a manner similar to histamine. *Selected neuronal interactions: a,* GABAergic inhibition promoting wakefulness versus REM (77); *b,* histaminergic and orexinergic activation of forebrain and brainstem (83, 86); *c,* cholinergic activation of diencephalon (see also e) by mesopontine nuclei (6); *d,* cholinergic activation of limbic forebrain and cortex by basal forebrain nuclei (69); *e,* cholinergic innervation of hypothalamic structures by mesopontine nuclei (6); *f,* reciprocal inhibition by wake-promoting posterior hypothalamus of sleep-promoting anterior hypothalamic and basal forebrain nuclei (83); *g,* serotonergic, noradrenergic, and dopaminergic arousal of diencephalon, limbic forebrain, and neocortex by aminergic brainstem nuclei by both inhibitory and excitatory synapses; and *h,* GABAergic inhibition of sleep-promoting anterior hypothalamic ventrolateral preoptic area (VLPO) cells by basal forebrain and other anterior hypothalamic cells (83).

B: NREM sleep: widespread GABAergic inhibition. The attenuation of wake-associated arousal of the brainstem, diencephalon, limbic forebrain, and neocortex by ascending and descending cholinergic, noradrenergic, serotonergic, histaminergic, and orexinergic systems allows inhibitory GABAergic systems *(Figure continues.)*

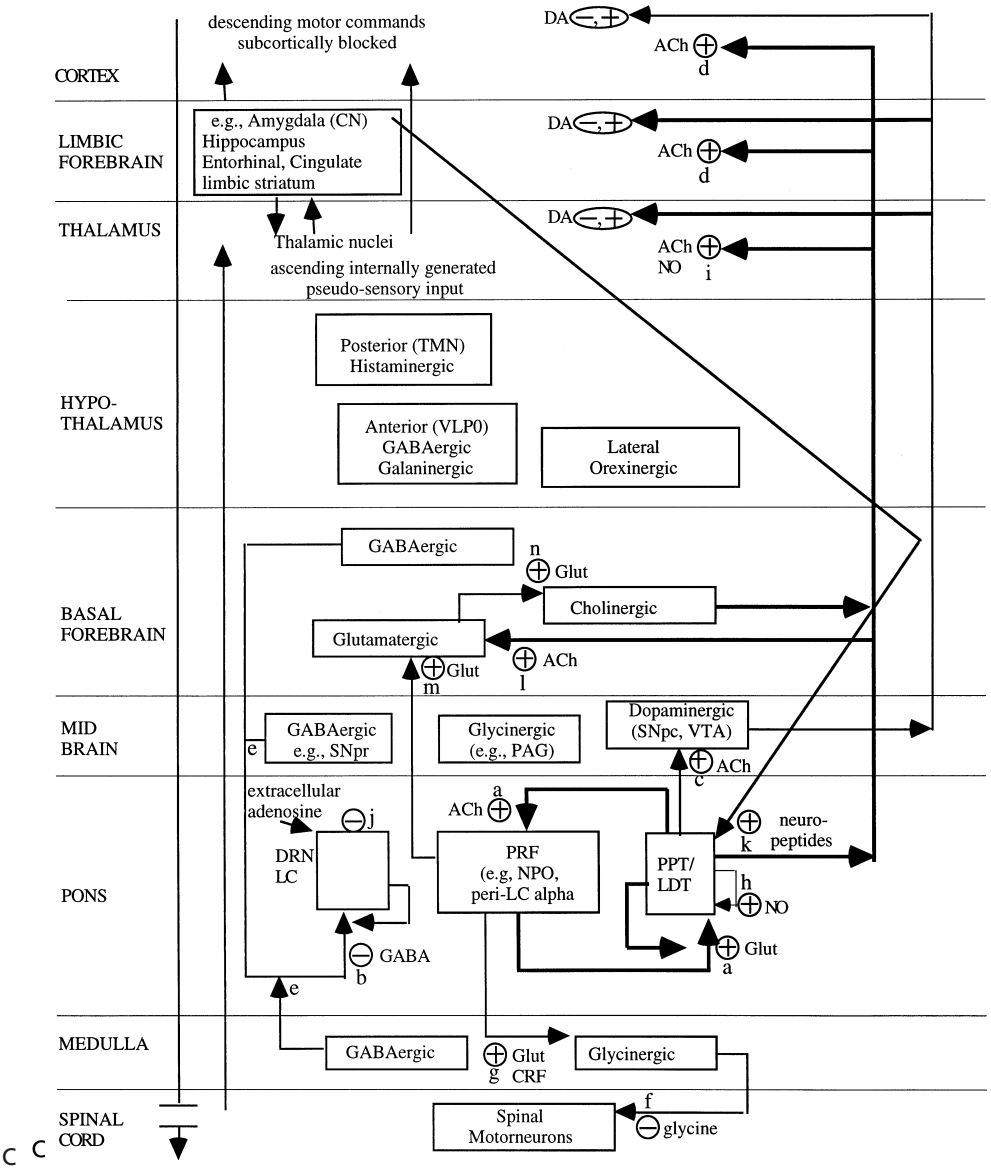


FIGURE 128.4. *Continued. (heavy lines)* to become prominent at various levels of the neuraxis. Maintained dopaminergic activation of the forebrain (61,62) is insufficient to maintain arousal sufficient to support wakefulness or REM sleep. At the thalamocortical level, such inhibition allows emergence of intrinsic oscillatory rhythms characterized in the EEG by sleep spindles, delta waves, and very slow (less than 1 Hz) oscillations (108). *Selected neuronal interactions: a,* GABAergic and galaninergic inhibition by the anterior hypothalamus (e.g., VLPO) of brainstem aminergic and cholinergic ascending arousal systems (195); *b,* GABAergic and galaninergic inhibition by the anterior hypothalamus (e.g., VLPO) of diencephalic aminergic (especially the histaminergic TMN) and cholinergic ascending arousal systems (83); *c,* high levels of extracellular adenosine accumulated during waking trigger sleep onset by inhibiting specific GABAergic basal forebrain cells that have, in turn, been inhibiting sleep-associated VLPO neurons during waking (83); *d,* extracellular adenosine accumulated during waking inhibits mesopontine cholinergic ascending activating systems (18); *e,* glycinergic midbrain and medullary cells exert tonic inhibition over pontine aminergic ascending activating systems (56); *f,* GABAergic inhibition of limbic and neocortical forebrain (56); *g,* extracellular adenosine accumulated during waking inhibits basal forebrain cholinergic ascending activating systems (18); and *h,* aminergic demodulation and GABAergic inhibition allows emergence of intrinsic thalamocortical oscillations (108).

C: REM sleep: selective cholinergic activation: During REM sleep, cholinergic activation of the forebrain from the brainstem (mesopontine) and basal forebrain ascend ing cholinergic systems is reinstated *(heavy lines)* in the absence of the aminergic (5-HT, NE, histamine) and orexinergic activation present during waking. Such selective cholinergic activation favors the distinctive forebrain-brainstem interactions of REM sleep in which internally generated ascending pseudosensory signals (e.g., pontogeniculooccipital or PGO waves) impinge on thalamocortical relay circuits and descending cortical and subcortical motor commands are blocked (3). Specific brainstem and basal forebrain circuits promoting the *(Figure continues.)*

noradrenergic systems are inhibited. Because many different synaptic mechanisms could mediate these effects, we now turn our attention to some intriguing possibilities.

OTHER NEUROTRANSMITTER SYSTEMS

Beyond the originally proposed cholinergic and aminergic neuronal populations, many additional neurotransmitter systems may participate in the neuromodulation of REM and NREM sleep. Since 1975, significant progress has been made in the identification of other chemically specific neuromodulatory systems showing differential activation with particular behavioral states or with specific physiologic signs within a behavioral state. These other neuromodulatory systems may interact with aminergic and cholinergic systems in the generation of REM sleep and its signs. We now discuss these new findings and the ways that they modify and extend the reciprocal interaction model, first in terms of the chemically specific systems and then in terms of the neuroanatomic networks subserving this physiology. In the following sections, we also address current findings on the diencephalic neuromodulation of NREM sleep and the wake-sleep transition.

Dopaminergic Systems

Given the key role of the other monoamines in the control of behavioral state and the powerful alerting effects of dopaminergic drugs, the potential role of DA in the control of the sleep-wake and the REM-NREM cycle has also been examined (see ref. 60 for review). DA release does not vary dramatically in phase with the natural sleep cycle as do 5-HT, NE, and ACh (61,62). However, REM sleep deprivation appears to enhance DA levels and DA receptor sensitivities (63).

Experimental manipulation of dopaminergic systems also gives varying results. For example, a DA agonist reduced REM sleep at low doses but enhanced it at higher ones (64), whereas a DA reuptake inhibitor had the opposite effect (65). In addition, although many human studies report REM suppression by DA reuptake inhibitors and indirect agonists (52,66), a DA-enhancing agent, bupropion, has been shown to human enhance REM sleep (67). Moreover, studies on the administration of dopaminergic drugs have suggested that DA may play a role in the induction or intensification of nightmares (60). Therefore, the effects of DA on sleep appear to be variable and are in much need of further study.

As is the case with many other neuromodulators, the sleep effects of DA may be mediated by dopaminergic effects on the aminergic and cholinergic systems involved in the executive control of the REM-NREM cycle. For example, DA has been shown to enhance cortical ACh release (68), whereas cholinergic mesopontine neurons have been shown to enhance mesolimbic DA release (31) (Fig. 128.4C-c). Such mutual facilitation between cholinergic and dopaminergic systems may serve to maintain or intensify REM sleep, especially given DA neurons' continued activity during REM (61,62) (Fig. 128.4C-c).

GABAergic Systems

Numerous findings have implicated GABA, the most ubiquitous central nervous system inhibitory neurotransmitter,

FIGURE 128.4. *Continued.* distinctive physiological features of REM sleep (cholinergic forebrain activation, PGO waves, skeletal muscle atonia, and rapid eye movements) are detailed in the text and are summarized here. *Selected neuronal interactions: a,* exponentially increasing activity of mesopontine PPT-LDT cholinergic neurons results in part from positive feedback *(heavy lines)* involving cholinergic excitation of pontine reticular formation (PRF) cells by the PPT-LDT and reciprocal glutamatergic excitation of the PPT-LDT by the PRF (6); *b,* GABAergic inhibition of pontine aminergic nuclei withdraws their inhibitory influence on PPT-LDT cholinergic cells (56) (see also *e*); *c,* cholinergic stimulation from the PPT-LDT enhances activity of midbrain dopaminergic cells (31), which, in turn, enhance cortical release of ACh (68); *d,* cholinergic activation of the limbic and neocortical forebrain by the basal forebrain occurs (69); *e,* additional inhibition of pontine aminergic (REM-off) nuclei by midbrain and medullary GABAergic neurons occurs (56); *f,* inhibition of spinal motor neurons by medullary glycinergic neurons is primary source of REM atonia (33); *g,* medullary glycinergic neurons are, in turn, activated by pontine glutamatergic and corticotropin-releasing factor (CRF)–ergic neurons (33); *h,* nitric oxide (NO) co-released from cholinergic cells facilitates self-activation of LDT-PPT (80); *i,* cholinergic activation of the thalamus by the LDT-PPT is facilitated by co-released NO (81); *j,* extracellular adenosine accumulated during waking provides additional inhibition of pontine aminergic (REM-off) nuclei (18); *k,* descending signals from the limbic forebrain may contribute to the initiation of REM by neuropeptidergic efferent projections to the mesopontine tegmentum from central nucleus (CN) of the amygdala (104); *l,* the LDT-PPT cholinergically stimulates basal forebrain glutamatergic cells, which, in turn, excite cholinergic basal forebrain neurons projecting to the limbic and neocortical forebrain (6); *m,* PRF glutamatergic neurons excite basal forebrain glutamatergic cells, which, in turn, excite cholinergic basal forebrain neurons projecting to the limbic and neocortical forebrain (6); and *n,* intrinsic basal forebrain glutamatergic cells excite cholinergic basal forebrain neurons projecting to the limbic and neocortical forebrain (69). SNpr, substantia nigra pars reticulata.

in the control of the sleep-wake and the REM-NREM cycle (8,17,56,57,69,70) (for reviews, see refs. 56 and 71). GABAergic inhibition has been hypothesized to play both REM-facilitory and REM-inhibitory roles in its mediation of executive circuits controlling the REM-NREM cycle. In addition, during NREM sleep, GABA has been hypothesized to play key roles in the deactivation of wake-related arousal systems and in the generation of intrinsic thalamocortical oscillations such as the slow oscillations of NREM sleep (see the later section on the thalamus).

REM-facilitory roles of GABA include inhibition of those aminergic neurons, which, in turn, exert tonic suppression of pontine cholinergic REM-generation networks. For example, during REM, GABA may suppresses noradrenergic LC (57) and serotonergic DR neurons (34, 72) (Fig. 128.4C-b). In addition, iontophoretic injection of GABA antagonists into the LC induced increased LC neuronal activity in all behavioral states, with an especially dramatic rise seen during REM (56). GABA may regulate specific elements of REM activation such as PGO wave activity. For example, in the initial stages of PGO wave generation, GABAergic and glycinergic cells may inhibit aminergic cells and thus may release the cholinergic PGO-triggering or transmitting cells (8,17,56,57,71,72) (Fig. 128.4C-b).

The REM-inhibitory roles of GABA may include direct inhibition of these same pontine cholinergic REM-generation networks. More specifically, GABAergic afferents to the PPT and LDT originating in the substantia nigra pars reticulata or in GABAergic neurons of the mesopontine tegmentum itself may exert direct inhibitory influences on PGO-related cells of these nuclei (3,8,17) (Fig. 128.4B-a). For example, the spike-bursting pattern in pontine PGO-burst cells may be the result of excitatory signals impinging on cells that are tonically inhibited by GABA (70). Such excitatory signals may include corollary discharge from ocular premotor neurons commanding REMs (70).

GABAergic inhibition is also important in sleep-promoting dysfacilitation of the brainstem and diencephalic arousal networks that maintain wakefulness and prevent NREM sleep. For example, GABAergic cells of the BF may inhibit hypothalamic and brainstem arousal systems (73) (Fig. 128.4B-b), whereas GABAergic input from a variety of brainstem nuclei may be responsible for decreased activity of the LC and DR during SWS (56) (Fig. 128.4B-a). Similarly, sleep-active GABAergic cells of the VLPO of anterior hypothalamus may maintain or initiate sleep by inhibiting histaminergic arousal networks in the posterior hypothalamus (74–76) (Fig. 128.4B-b) as well as in the LC and DR (56) (Fig. 128.4B-a). Luppi et al. (56) proposed that although VLPO GABAergic neurons inhibit the LC and DR during SWS, a second population of GABAergic cells in midbrain and medulla are recruited to accomplish more complete LC-DR inhibition of REM (Fig. 128.4C-e).

In contrast to the foregoing sleep-promoting effects of GABAergic transmission in the diencephalon, it has been reported that a specific GABAergic mechanism in the nucleus pontis oralis of the cat PRF promotes wakefulness versus REM sleep (77) (Fig. 128.4A-a). Such opposing sleep effects highlight the regional heterogeneity of roles for GABAergic inhibition in modulating behavioral states.

Glycinergic Systems

Glycine, another inhibitory neurotransmitter, has also been shown to influence the neural mechanisms underlying the sleep-wake and REM-NREM cycles (8,56,78). As in the case of GABA, glycine may provide tonic inhibition of LC and DR neurons during all behavioral states; however, increased GABAergic inhibition of the LC may be more important in progressive deactivation during NREM (56). Like GABA, glycine may regulate specific physiologic manifestations of REM. For example, medullary glycinergic cells are responsible for the postsynaptic inhibition of somatic motor neurons during REM atonia (33,79) (Fig. 128.4C-f), and glycinergic inhibition may play a regulatory role in the premotor functions of the pons (79).

Glutamatergic Systems

Glutamate, the most ubiquitous central nervous system excitatory neurotransmitter, has also been shown to influence the sleep-wake and the REM-NREM cycles (3,11,24,33). Semba (6) summarized evidence for excitatory glutamatergic input to the mesopontine tegmentum from the medial prefrontal cortex, from co-release by mesopontine cholinergic neurons themselves, from the PRF, and from the subthalamic nucleus (Fig. 128.4C-a). As described earlier in the section on modification of the original reciprocal interaction hypothesis, such glutamatergic excitation (Figs. 128.2B, 128.3, and 128.4C-a) may widely interact with cholinergic and cholinoceptive neurons to generate the exponential increase of mesopontine and pontine reticular activity associated with REM sleep activation (2,6,11). Pontine glutamatergic cells may transmit REM sleep atonia-related signals to medullary sites (Fig. 128.4C-g), where they may then activate inhibitory glycinergic as well as GABAergic cells, which, in turn, suppress somatic motor neurons (3,33,79).

Nitroxergic Systems

The diffusible gaseous transmitter nitric oxide (NO) has been widely implicated in sleep-cycle modulation (for review, see ref. 80). NO is hypothesized to function primarily as an intercellular messenger capable of diffusing into and producing a wide variety of physiologic effects on neighboring cells including enhanced synaptic transmission through enhanced release of neurotransmitter (80). One such neuro-

transmitter is ACh (80). NO is co-produced by all cholinergic neurons of the LDT and PPT (80), and inhibition of the NO synthesizing enzyme in the PRF both decreased ACh release and attenuated both natural and ACh-agonist–induced REM sleep (80). Leonard and Lydic (80) suggested that pontine NO thereby serves an important role in maintaining the cholinergically mediated REM sleep state (Fig. 128.4C-h).

Both natural and experimentally increased activity of mesopontine cholinergic neurons results in increased NO release in the thalamus (81) (Fig. 128.4C-i). NO has been shown to enhance capillary vasodilation (80), and, given its co-release with ACh, this has important implications for cholinergically mediated changes in regional blood flow during REM (see later).

Histaminergic Systems

The histaminergic arousal system, originating in neurons of the posterior hypothalamus, is fully discussed in terms of its role in the hypothalamic mediation of the sleep-wake cycle in the following neuroanatomic section. In brief, projections of this system innervate the entire forebrain (Fig. 128.4A-b) and have reciprocal projections to brainstem regions known to be involved in behavioral state control such as the mesopontine tegmentum (82). Histamine is a wake-promoting substance, and experimental lesions of histaminergic nuclei in the posterior hypothalamus such as the tuberomamilary nucleus (TMN) result in hypersomnolence (83). Moreover, microinjection of histamine or histamine agonist into the mesopontine tegmentum results in an increase in waking (82). In turn, there exists strong evidence that, during sleep, wake-active posterior hypothalamic histaminergic neurons are themselves tonically inhibited by GABAergic and galaninergic projections from the anterior hypothalamus and adjacent BF (75,76,83) (for reviews on histaminergic influences in sleep, see refs. 76 and 83) (Fig. 128.4A-b).

Adenosinergic Systems

Adenosine has received much experimental attention as a probable physiologically important endogenous somnogen (84). Adenosine has been shown to exert multiple effects on behavioral state (18,84). For example, adenosine may exert tonic inhibition over the glutamatergic excitatory inputs to the cholinergic cells of the LDT and PPT (18,85) (Fig. 128.4B-d), and it may contribute to the REM-related suppression of serotonergic raphe neurons (18) (Fig. 128.4C-j). In addition, adenosine may exert tonic inhibition over BF cholinergic neurons (18). Finally, as noted, extracellular buildup of adenosine may constitute the sleep-promoting factor associated with prolonged wakefulness (18,84) (Fig. 128.4B-c).

Neuropeptidergic Systems

Many different neuropeptides have been implicated in regulation of the sleep-wake and REM-NREM cycles. These include galanin (75,76) (Fig. 128.4B-b), orexin (86,87) (Fig. 128.4A-b), vasoactive intestinal polypeptide (VIP), and numerous hormones (33,48,88) (Fig. 128.4C-g) (for reviews, see ref. 89 for the cytokines, ref. 90 for hormonal influences, and ref. 88 for VIP).

Many such neuropeptides have, like adenosine, been proposed to be endogenous sleep substances whose accumulation over prolonged waking promotes sleep onset (for review, see ref. 89). As noted by Kreuger and Fang (89), there is especially strong evidence for specific promotion of NREM by tumor necrosis factor, interleukin 1, growth hormone–releasing hormone, and prostaglandin D_2 as well as for promotion of REM by VIP and prolactin. Other neuropeptides such as atriopeptin, bombesin, corticotropin-releasing factor, and substance P are released from mesopontine cholinergic terminals, and these may, in turn, modify the sleep regulatory effects of co-released ACh (reviewed in ref. 6).

Three findings highlight the importance of neuropeptides in the regulation of sleep. The first is that inhibitory neurons in the VLPO of the hypothalamus, a specifically sleep-active area (74), use galanin as well as GABA to inhibit ascending arousal systems such as the LC (75,76) (Fig. 128.4B-a). As noted by Shiromani et al. (83), the association of galanin with NREM is particularly significant because this neuropeptide also stimulates release of growth hormone from the pituitary and may therefore play an important role in the pulsatile release of growth hormone specifically associated with NREM SWS. The second is the demonstration that corticotropin-releasing factor participates in the pontomedullary control of REM atonia (33) (Fig. 128.4C-g). The third finding has come from studies on the genetic basis of narcolepsy using animal models. The neuropeptide orexin (or hypocretin), produced only by neurons in the lateral hypothalamus, may play a key role in sleep regulation by its modulation of ascending cholinergic and monoaminergic arousal systems (86,87) (Fig. 128.4A-b).

Second Messengers and Intranuclear Events

As in much of neuroscience, research on behavioral state control is now beginning to extend its inquiry beyond the neurotransmitter and its receptors to the roles of intracellular second messengers (7), as well as intranuclear events (91). Results of the molecular genetic approach to sleep research include the discovery of the role of orexin in sleep regulation (see earlier) and the discovery that choline acetyltransferase mRNA levels show behavioral state dependency in the rat (92). As noted by Shiromani et al. (83), the experimental observation of behavioral state dependent immediate early

gene expression in hypothalamic cells indicates that intranuclear events must participate in the control of sleep-wake cycles.

NEUROANATOMY OF REM-NREM CONTROL SYSTEMS

At the same time that sleep studies have probed more and more deeply, to the cell membrane and beyond, efforts to understand the mechanisms of state control at a more global and regional level have continued. The picture that we are attempting to sketch is designed to provide an integrating framework for the analytic studies just reviewed. A major breakthrough in the regional brain research effort has been provided by the explosive growth of imaging studies of the human brain. This work provides still another bridge for integration: Now for the first time, we can begin to relate the cellular and molecular-level data from animals to the regional data in humans. This comparison is of particular relevance to dream theory and psychopathology.

Brainstem Executive Control of the REM-NREM Cycle

In the pons, cholinergic, serotonergic, noradrenergic, glutamatergic, and GABAergic neurotransmission among the LDT and PPT (containing cholinergic cells), the DRN (mainly serotonergic), and the LC (mainly noradrenergic) forms the core circuits for the executive control of the REM-NREM cycle (for reviews, see refs. 1 to 4, 6, 8, and 17) (Fig. 128.4B and C).

In the EEG-aroused states of REM and waking, the LDT and PPT provide a large proportion of the excitatory cholinergic input to both the thalamus and the BF (Fig. 128.4A-c), which then activate limbic structures and the cortex (6) (Fig. 128.4A-d). Expression of the physiologic signs of REM is, however, modifiable at diverse sites both rostral and caudal to these executive networks, as detailed later. For example, in addition to inputs from the DRN and LC, the LDT-PPT also receives projections from limbic forebrain structures (6) and the basal ganglia (93) (Fig. 128.4C-k). Moreover, in the control of sleep onset, the physiologic features of NREM sleep, and circadian control of the sleep-wake cycle, diencephalic structures come to be of primary importance (Fig. 128.4A and B).

Other Brainstem Structures

Many different brainstem structures in addition to LDT-PPT cholinergic cells and the LC and raphe nuclei are crucially involved in the modulation of REM sleep and its distinctive physiologic signs. These include noncholinergic areas within the PPT-LDT as well as peribrachial areas caudal to the LDT and PPT in the cat (8), diverse cholinoceptive areas in the medial pontine reticular system such as the nucleus pontis oralis of the rat (33), and the gigantocellular tegmental field and LC α of the cat (7,14). Adding to the functional complexity of mesopontine cholinergic areas are its important roles in functions other than behavioral state control such as motor control (106).

Structures rostral and caudal to the pons such as the ventrolateral periaqueductal gray (56,94) and the medulla (33,79) also play key roles in the transmission and modulation of the physiologic signs of REM sleep. For example, sleep-associated inhibition of LC and DR by glycinergic input originates in the periaqueductal gray, the midbrain reticular formation, and various medullary sites (e.g., raphe magnus, gigantocellular α, paragigantocellular nuclei) (Fig. 128.4B-e), whereas GABAergic inhibition originates in an even more diverse set of brainstem and diencephalic regions (56) (Fig. 128.4B-a). Similarly, REM-associated postural atonia involves brainstem networks extending rostrally from midbrain areas such as the periaqueductal gray, through the mesopontine PPT, through the pontine inhibitory area and peri-LC areas to the medullary nucleus magnocellularis, and thence to spinal motor neurons caudally (33) (Fig. 128.4C-f,g). Brainstem structures rostral to the pons could facilitate brainstem-limbic interactions in REM sleep (see later) such as those also hypothesized to contribute to REM-related atonia (33).

Figure 128.4A to C schematizes major neuromodulatory systems involved in the generation and maintenance of the three cardinal behavioral states at different levels of the central nervous system. (For reviews on the functional neuroanatomy of brainstem control of sleep cycles, see refs. 1 to 4, 6, 8, 14, 17, 56, and 79.)

Forebrain Structures

Other important contemporary research now extends the study of sleep-wake and REM sleep control mechanisms rostrally from the pontine brainstem to diencephalic structures in a manner consistent with connectivity studies (48). In addition to the well-described brainstem-thalamus-cortex axis, subcortical sleep control mechanisms intercommunicate with each other and with the cortex through an interconnected network of structures extending rostrally from the brainstem RAS to the hypothalamus, BF, and limbic system.

Saper et al. (76) classified three ascending arousal systems: the brainstem cortical projection system (including DR serotonergic, LC noradrenergic, and LDT-PPT cholinergic elements), the cholinergic BF projection system, and the histaminergic hypothalamic cortical projection system. The BF system projects to topographically specific cortical areas, whereas the other systems project diffusely to widespread areas of the forebrain.

We now briefly summarize recent findings on this ex-

tended subcortical system that are pertinent to sleep-wake and REM sleep control. We focus here on findings in the hypothalamus, BF nuclei, amygdala, thalamus, and basal ganglia.

Hypothalamus

Histaminergic neurons originating in the posterior hypothalamus innervate virtually the entire brain including brainstem structures such as the mesopontine tegmentum (82) (Fig. 128.4A-b). These brainstem regions, in turn, innervate both anterior and posterior hypothalamus (82,83) (Fig. 128.4A-e).

Anterior portions of the hypothalamus (preoptic area and adjacent BF) are known to be essential to promoting sleep (73,76,82,83). In contrast, tonic firing of histaminergic neurons in the posterior hypothalamus play an important role in cortical arousal and the maintenance of wakefulness (for reviews, see refs. 76 and 83) (Fig. 128.4A-b). The TMN plays a particularly important role in this posterior hypothalamic histaminergic arousal system, and these neurons have been shown to decrease their firing during sleep (74,76,83).

Sherin et al. (74) proposed that a monosynaptic pathway in the hypothalamus may constitute a ''switch'' for the alternation of sleep and wakefulness. Using immediate early gene (*c-fos*) techniques, these workers identified a group of GABAergic and galaninergic neurons in the VLPO, which are specifically activated by sleep (74) and have since been shown to be selectively sleep active using electrophysiology (83). These GABAergic and galaninergic VLPO neurons constitute the main source of innervation to the histaminergic neurons of the TMN (Fig. 128.4B-b) and may therefore specifically inhibit histaminergic neurons of the TMN to preserve sleep (74–76).

One study demonstrated extensive histaminergic innervation of the mesopontine tegmentum including the LDT (82) (Fig. 128.4A-b). Suppression of slow-wave activity and an increase in waking followed microinjection of histamine and histamine agonist into these areas (82). Histaminergic projections from the TMN to areas of the BF involved in sleep-wake control (Fig. 128.4A-b) were also demonstrated in the cat (95). VLPO neurons were also shown to innervate other components of ascending arousal systems such as the monoaminergic nuclei of the brainstem (Fig. 128.4B-b), and there they may also exert a sleep-promoting inhibitory influence (75,95). An important finding is that the orexinergic cells of the lateral hypothalamus also innervate most of the brainstem and diencephalic ascending arousal systems (Fig. 128.4A-b), and, therefore, these may also play a modulatory role in the sleep-wake cycle (86,87).

Combining the foregoing findings with evidence of the somnogenic effects of adenosine, Shiromani et al. (83) proposed the following model for the control of the wake-NREM transition and its link to the ultradian REM-NREM cycle, detailed here and illustrated in Fig. 128.5:

Figure 128.5I: During prolonged wakefulness, accumulating adenosine inhibits specific GABAergic anterior hypothalamic and BF neurons that have been inhibiting the sleep-active VLPO neurons during waking (Fig. 128.4A-h). During waking, TMN neurons may also reciprocally inhibit sleep-active neurons of the anterior hypothalamus and BF (Fig. 128.4A-f).

Figure 128.5II: The thus disinhibited sleep-active GABAergic neurons of the VLPO and adjacent structures then inhibit the wake-active histaminergic neurons of the TMN as well as those of the pontine aminergic (DR and LC) and cholinergic (LDT-PPT) ascending arousal systems, thereby initiating NREM sleep.

Figure 128.5III: Forebrain activation by these ascending arousal systems (Fig. 128.4A-b,c,g) is thus dysfacilitated.

Figure 128.5IV: Once NREM sleep is thus established, the executive networks of the pons initiate and maintain the ultradian REM-NREM cycle described by reciprocal interaction.

Tying the hypothalamus to the pons in this dynamic manner may provide a critical link between the circadian clock in the suprachiasmatic nucleus and the NREM-REM sleep cycle oscillator (83). The circadian control of sleep by the suprachiasmatic nucleus is beyond the scope of this review but constitutes a key influence not only on the sleep wake alternation but also on shorter-period oscillations such as the ultradian REM-NREM alternation (96). (For a comprehensive review of circadian rhythms and the suprachiasmatic nucleus in sleep-wake regulation, see ref. 97.)

Basal Forebrain

BF nuclei have anatomic connections with the LC, raphe, and pontine nuclei (69,73) and, in turn, project to more rostral structures such as the cortex, thalamus, and limbic systems (69,98). In addition to its brainstem and cortical connectivity, the BF also has anatomic connections with the anterior and posterior hypothalamus, the amygdala, and the thalamus (73). (For reviews of BF connectivity see refs. 69 and 73.)

Neurochemically, ACh plays a major role in BF control of behavioral state chiefly by its activating effects on the cortex and other forebrain structures (69). Magnocellular cholinergic cells of the BF nuclei promote the activation of those cortical and limbic structures to which they project (69,73,98) (Fig. 128.4A-d). For example, cholinergic cells of the nucleus basalis of Meynert activate topographically distinct areas of the cortex (69,73,98), and cholinergic activity of the medium septum and vertical limb of the diagonal band of Broca mediates hippocampal theta rhythm (42).

There are extensive functional interactions between the brainstem structures (LC, raphe nuclei, LDT-PPT) and the

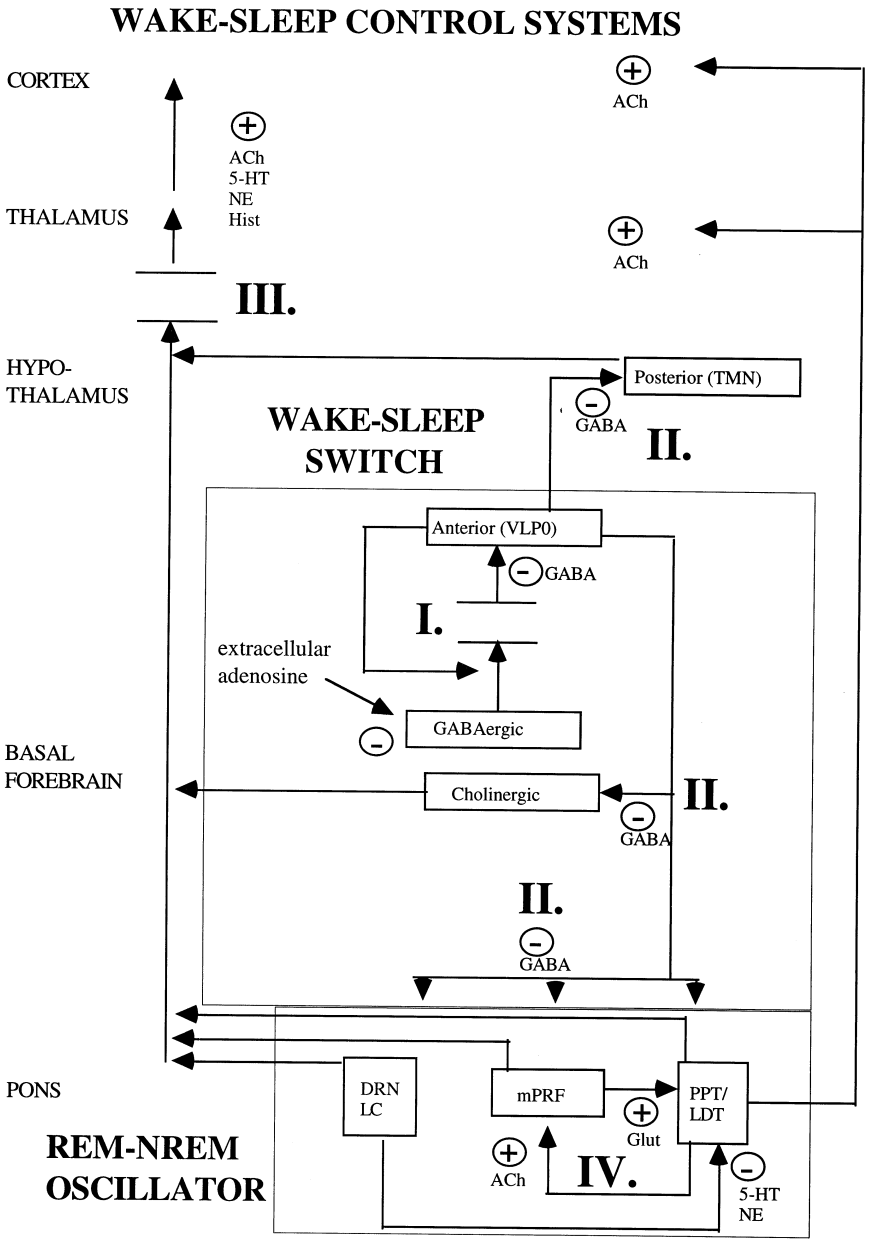


FIGURE 128.5. Integrated model of sleep onset and REM-NREM oscillation proposed by Shiromani et al. (83). *I,* During prolonged wakefulness, accumulating adenosine inhibits its specific GABAergic anterior hypothalamic and basal forebrain neurons that have been inhibiting the sleep-active ventrolateral preoptic area (VLPO) neurons during waking. *II,* Disinhibited sleep-active GABAergic neurons of the VLPO and adjacent structures then inhibit the wake-active histaminergic neurons of the tuberomamillary nucleus (TMN), as well as those of the pontine aminergic (DRN and LC) and cholinergic (LDT-PPT) ascending arousal systems thereby initiating NREM sleep. *III,* Forebrain activation by ascending aminergic and orexinergic arousal systems is dysfacilitated. *IV,* Once NREM sleep is thus established, the executive networks of the pons initiate and maintain the ultradian REM-NREM cycle. ACh, acetylcholine; DRN, dorsal raphe nucleus; 5-HT, serotonin; LC, locus ceruleus; LDT, laterodorsal tegmental nucleus; NE, norepinephrine; PRF, pontine reticular formation.

BF in sleep-wake control (6,69,73). The PPT-LDT provides a major source of excitatory input to the BF (6) (Fig. 128.4C-l). For example, Shiromani et al. (83) showed that PPT stimulation induces *c-fos* expression in a variety of BF nuclei. Similarly, PPT-LDT neurons were shown to release ACh into the BF of rats (99).

Glutamatergic activation is an important transmitter of reciprocal activation between the brainstem and the BF (Fig. 128.4C-m). For example, BF structures that activate the cortex can be activated by brainstem glutamatergic cells (100), the cortical EEG activation produced by cholinergic mesopontine stimulation of the BF is transmitted within the BF by glutamatergic (versus cholinergic) mechanisms (6) (Fig. 128.4C-n), and glutamatergic systems of the BF can, in turn, affect brainstem behavioral state modulation through projections to the mesopontine tegmentum (101).

In concert with closely related anterior hypothalamic cells such as those of the VLPO, specifically sleep-active BF cells (anatomically and neurochemically distinct from the wake-REM active cholinergic magnocellular neurons) function as NREM sleep-promoting elements (73,83). This may occur by GABAergic inhibition of posterior hypothalamic (Fig. 128.4B-b) and brainstem (Fig. 128.4B-a) arousal systems (73–75) as well as of more rostral structures (69) (Fig.

128.4B-f). In addition to their role in cortical activation and desynchronization (Fig. 128.4A-d and C-d), BF neurons have been associated with the specific physiologic features of NREM sleep. For example, although BF lesions can cause the emergence of slow waves (102), magnocellular cholinergic neurons may also participate in the generation of cortical slow waves (103).

As in the brainstem, neuromodulatory systems interact within the BF itself (e.g., the foregoing BF cholinergic-glutamatergic interactions). For example, BF cholinergic neurons may be under tonic inhibition by adenosine (18) (Fig. 128.4B-g). The BF nuclei therefore both directly participate in behavioral state-related functions and modify the activity of other areas involved in sleep such as the pontine REM generator.

Amygdala

Of particular interest in view of recent findings from human neuroimaging studies (see ref. 3 for review), the amygdala has reciprocal connections with pontine regions involved in the control of REM sleep (for reviews, see refs. 48 and 104).

Physiologic signs of REM have been shown to occur spontaneously in the amygdala and in other limbic structures (104). For example, in the cat, PGO-like EEG activity has been detected in the basolateral amygdala, and single-unit activity in the central nucleus (CN) of the amygdala increases during NREM sleep immediately preceding REM (variously termed the ''transitional stage,'' ''SP,'' or ''SPHOL'') and then increases further during actual REM (104). In addition, amygdalar lesions in the cat have been shown to decrease PGO frequency (104).

Physiologic signs of REM are also modifiable from the amygdala. For example, electrical stimulation of the cat amygdala significantly increased PGO number, spike density, and burst density (104). In addition, cholinergic stimulation of the cat CN enhanced REM sleep for several days by an increased number of REM episodes, an effect akin to the long-term REM enhancement by cholinergic stimulation of the peribrachial pons (104). Moreover, cholinergic stimulation of the CN concomitantly increased PGO density (104). Amygdalar stimulation also increased the amplitude and rate of acoustically elicited pontine PGO waves in the waking rat and burst firing of pontine cells in the rabbit (48).

Aminergic stimulation of the amygdala has also been shown to modify sleep in the direction predicted by reciprocal interaction for pontine sites. For example, serotonergic stimulation of the amygdala in the cat caused short latency changes of state from either NREM or REM (48). Similarly, noradrenergic stimulation of the amygdala suppressed sleep relative to wakefulness (48).

It has therefore been proposed, by Morrison et al. (48) and by Calvo and Simon-Arceo (104), that the amygdala (and, in particular, the CN) stimulates lateral pontine areas involved in REM sleep initiation (Fig. 128.4C-k) that, in turn, initiate REM sleep. However, the continuation of REM-NREM cycling in the pontine cat (2) obviates an obligatory role for amygdalar stimulation of the pons in the initiation of REM, at least in the cat.

Thalamic Structures and Intrinsic Thalamocortical Oscillatory Rhythms

Dysfacilitation of thalamocortical relay neurons after sleep onset allows the emergence of underlying thalamocortical oscillatory rhythms (for reviews, see refs. 127 and 128) (Fig. 128.4B-h). GABAergic neurons of the thalamic reticular nucleus hyperpolarize and dysfacilitate thalamic relay neurons as NREM deepens (127,128). In this hyperpolarized condition, thalamic neurons become constrained to burst-firing patterns first in spindle (12 to 14 Hz) and later in delta (1 to 4 Hz) frequencies as NREM deepens from stage 2 to delta sleep (127,128). The cortex may further constrain these spindle and delta wave–generating thalamocortical bursts within a newly described slow (less than 1 Hz) oscillation seen in cats (127,128) and humans (106).

Mesopontine cholinergic neurons provide a major excitatory input to the thalamus during the EEG activated states of wakefulness and NREM sleep and, during REM, cholinergic excitation alone may prevent the emergence of intrinsic thalamocortical oscillations (6). Findings that ascending cholinergic input from the mesopontine tegmentum influences thalamic blood flow (109) and thalamic NO release (81) (Fig. 128.4C-i) are of particular interest in light of positron emission tomography neuroimaging studies showing a REM-associated increased thalamic blood flow (reviewed in ref. 3). Other thalamic structures such as centralis lateralis nucleus possibly participate directly in the modulation of REM sleep (110).

Basal Ganglia

Although receiving less focus in past experimental studies of sleep in animals, the extensive activation of basal ganglia and related structures in positron emission tomography neuroimaging studies of human REM sleep suggests their involvement in the neural networks subserving this behavioral state (reviewed in ref. 3). There are extensive reciprocal projections between the basal ganglia and the PPT region (3,193). This connectivity has been postulated to subserve several specific roles. For example, Allan Braun and colleagues at the National Institutes of Health in Bethesda, Maryland suggested that the basal ganglia may play a role in the rostral transmission of PGO waves (reviewed in ref. 2), whereas Rye (3) suggested that striatal projections to the pedunculopontine region may serve to modulate movement to accord with behavioral state. Additional possibilities are suggested by the extensive activation of the ventral striatum and surrounding BF in REM (reviewed in ref. 2). For exam-

ple, Eric Nofzinger and colleagues at the University of Pittsburgh suggested that an important function of REM sleep is the integration of neocortical function with BF and hypothalamic motivational and reward mechanisms (reviewed in ref. 2).

CONCLUSIONS

Interactions of diverse neuromodulatory systems operate in widespread subcortical areas to amplify or suppress REM sleep generation as well as to facilitate onset and offset of the control of behavioral state by the pontine REM-NREM oscillator. An ascending medial brainstem and diencephalic system of multiple nuclei with extensive reciprocal interconnections and system-wide sensitivity to neuromodulation controls the regular alternation and integration of the sleep-wake and REM-NREM cycles. The existence an executive aminergic-cholinergic reciprocal interaction system controlling REM-NREM alternation in the pontine brainstem has been strongly confirmed by recent findings. The interaction of pontine structures with other brain structures can now begin to be studied in ways that will enrich our understanding of how the distinctive features of each conscious state are mediated and how their stereotyped sequencing is controlled.

ACKNOWLEDGMENTS

This project was funded by National Institute of Drug Abuse grant RO1-DA11744-01A1, the MacArthur Foundation Mind Body Network, and National Institutes of Health grants MH-48,832, MH13923, and MH01287. We wish to thank James Quattrochi, Bernat Kocsis, Robert Stickgold, Rosalia Silvestri-Hobson, Subimal Datta, Matthew Walker, Roar Fosse, and Dawn Opstad.

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Neuropsychopharmacology: The Fifth Generation of Progress. Edited by Kenneth L. Davis, Dennis Charney, Joseph T. Coyle, and Charles Nemeroff. American College of Neuropsychopharmacology © 2002.