Sleep, 18(6):478–500
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State of the Art Review

Magnocellular Nuclei of the Basal Forebrain: Substrates of Sleep and Arousal Regulation

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Summary: Magnocellular regions of the basal forebrain (BF) are recognized as important sites of sleep–wake regulation. Evidence is reviewed for the coexistence within the BF of mechanisms that regulate neocortical and limbic system arousal along with mechanisms that promote sleep. Arousal-related functions are mediated by a system of magnocellular cholinergic neurons. BF cholinergic neurons project monosynaptically to the entire neocortex and limbic telencephalon, exert excitatory effects on target cells and participate in the regulation of activated EEG patterns characteristic of waking and REM sleep. Evidence suggests that, within the waking state, the BF cholinergic system modulates processing of sensory information in the neocortex and is involved in cognitive processes. One or more noncholinergic cell types are responsible for the sleep-promoting functions of the BF. Neurons that display elevated discharge rates during transitions from waking to sleep and during nonREM sleep have been recorded in BF sites where electrical stimulation evokes sleep and experimental lesions cause insomnia. BF neurons function to promote sleep, in part, via descending inhibition of caudal hypothalamic and brainstem activating systems. GABAergic neurons located within magnocellular regions of the BF are hypothesized to mediate sleep-promoting actions. Afferents to the BF from hypothalamic and brainstem regions are functionally important for sleep–wake regulation. Thermosensitive inputs from the anterior hypothalamus modulate the activity of BF sleep- and arousal-related cell types. Excitatory effects of brainstem inputs to BF arousal-related cells have been documented. Additional evidence supports a critical role for GABAergic–cholinergic interactions, both within the magnocellular BF and at cortical and diencephalic sites, in the regulation of behavioral state. **Key Words:** Basal forebrain—Nucleus basalis—Preoptic area—Anterior hypothalamus—Arousal—NonREM sleep—EEG—Sleep–wake regulation—Acetylcholine—GABA.

The heterogeneous region of the mammalian ventral telencephalon known as the basal forebrain (BF) has been critically implicated in the regulation of sleep and wakefulness. Early studies of neuropathology in man, and lesion and stimulation studies in experimental animals, provided evidence that portions of the BF adjacent to the rostral hypothalamus function as a sleep-promoting area, capable of modulating somato- and viscero-motor activity and the EEG.

More recently, a collection of acetylcholine (ACh)-containing neurons has been localized to the BF, and these neurons were shown to project monosynaptically to the entire limbic telencephalon and neocortex. The BF cholinergic system appears to regulate important aspects of limbic system and neocortical arousal, to modulate sensory processing in the neocortex, and to participate in attentional processes. Degeneration of BF cholinergic neurons in Alzheimer's disease, and lesions of cholinergic portions of the BF in experimental animals are associated with slowing of the waking cortical EEG and cognitive deficits.

A goal of this review will be to reconcile the seemingly conflicting postulated roles for the BF in behavioral state regulation; that is, that of a sleep-regulating system and of one that enhances cortical activation. Evidence will be reviewed that suggests that sleep-promoting and arousal-related mechanisms coexist within the BF, and that these are neurochemically and, at least partially, anatomically distinct. First, the anatomy of the BF as it relates to these putative behavioral state-regulating functions will be reviewed. Second, I will review what is known about the behavioral neurophysiology of the BF cholinergic system. Third, the

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Accepted for publication April 1995.

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experimental evidence for a hypnogenic mechanism within the BF will be considered. Finally, I will summarize what is and is not known about interactions among BF cholinergic and noncholinergic cell types in the regulation of arousal and sleep.

ANATOMICAL CONSIDERATIONS

The review of BF anatomy here will be brief, with a focus on features relevant to behavioral state control. The reader is referred to recent comprehensive reviews of BF anatomy (1–5).

The BF comprises a heterogeneous set of structures on the ventralmost aspects of the telencephalon, adjacent to preoptic, supraoptic and rostral infundibular levels of the hypothalamus. Since the discovery of a system of ACh-containing magnocellular neurons that are the primary source of cholinergic innervation to the limbic system and neocortex, the term "basal forebrain" has become nearly synonymous with the magnocellular cholinergic system. Although this is an oversimplification, the distribution of cholinergic neurons within the BF constitutes a suitable reference point for considering the functional anatomy of this region as it relates to behavioral state control (Fig. 1).

The medial preoptic area and anterior hypothalamic areas are also frequently considered to be part of the ventral forebrain hypnogenic system. The anatomical and functional relationships of these areas to the magnocellular BF will be considered in a subsequent section.

The reader should be aware that important regions within the BF contain few magnocellular neurons, and have anatomical and functional relationships that are at least partially independent of the cholinergic cell groups and of sleep–wake regulating mechanisms. For example, the nucleus accumbens and portions of the substantial innominata are closely related to both the basal ganglia and the limbic system including the amygdala (5). These structures participate in motor control and limbic system–motor integration (6). In focusing on the role of the magnocellular systems in regulating EEG-defined sleep–waking states, these aspects of BF function will, for the most part, not be considered. However, a complete understanding of forebrain state-regulating functions will eventually have to incorporate the ways in which sleep–waking mechanisms interact with the striatopallidal and limbic system components of the BF.

Cholinergic neurons

The distribution of cholinergic neurons within the rat BF is shown in Fig. 1. Neurons that are immunohistochemically positive for the ACh-synthesizing enzyme choline-acetyltransferase (ChAT) occur as a continuous series of cell clusters that are contained within several structures that comprise the BF. From rostral to caudal, they are found in the medial septum (MS; Fig. 1A and B), the vertical (Fig. 1A) and horizontal (Fig. 1B–D) limbs of the diagonal bands of Broca (VDB and HDB), magnocellular preoptic area (MCP; Fig. 1C and D), subpallidal substantia innominata (SI; Fig. 1D and E) and the peripallidal nucleus basalis of Meynert (NB; Fig. 1E and F). ChAT-positive neurons are large and multipolar. Several fiber systems traverse these regions, including the medial forebrain bundle, anterior commissure, ansa lenticularis, ansa peduncularis and inferior thalamic peduncle. At many sites within the BF, magnocellular ACh neurons occur as clusters embedded among one or more of these fiber systems.

Cholinergic neurons of the BF are widely hypothesized to modulate the level of arousal or activation in a variety of limbic system and cortical sites (7–10). Consistent with this hypothesized function is the documented monosynaptic projection of BF cholinergic neurons to the entire limbic telencephalon and neocortex. Different subpopulations of BF cholinergic neurons have different projection targets. Neurons in the MS and VDB innervate the hippocampus, those within the HDB and MCP target primarily the olfactory bulb, entorhinal cortex and piriform cortex, and SI and NB cholinergic neurons project to the neocortex (11–17). There is a topographical organization to the neocortical projection with a rostral to caudal progression of SI/NB neurons reaching a medial to lateral sequence of cortical sites (14,17–19). This topography is not strictly somatotopic. For example, in rat sensorimotor cortex, adjacent subregions receive projections from distributed portions of the SI/NB (20). The projection should not be considered to be diffuse, however, as few individual cholinergic neurons ($<5\%$) project to multiple cortical sites (11,14,20).

These basic features of the BF–neocortical cholinergic projection are consistent across species, although some specific differences are noteworthy. In primates, the NB forms a fairly compact nucleus of cholinergic neurons closely associated with the globus pallidus (19). Nearly all of the cortically projecting neurons ($>95\%$) in the primate NB are cholinergic (19). In cats and rats, the cholinergic neurons of the NB are more diffusely organized, found within and adjacent to the globus pallidus, internal capsule and nucleus of the ansa lenticularis. The precise borders of SI and NB cholinergic neurons are not as distinct in these species as in primates. Significant numbers of noncholinergic projection neurons have been described in the NB of cats (16,21). In rat, 80–90% of NB projection neurons are cholinergic, but less than 50% of SI projection neurons are immunoreactive for ChAT (7,22).

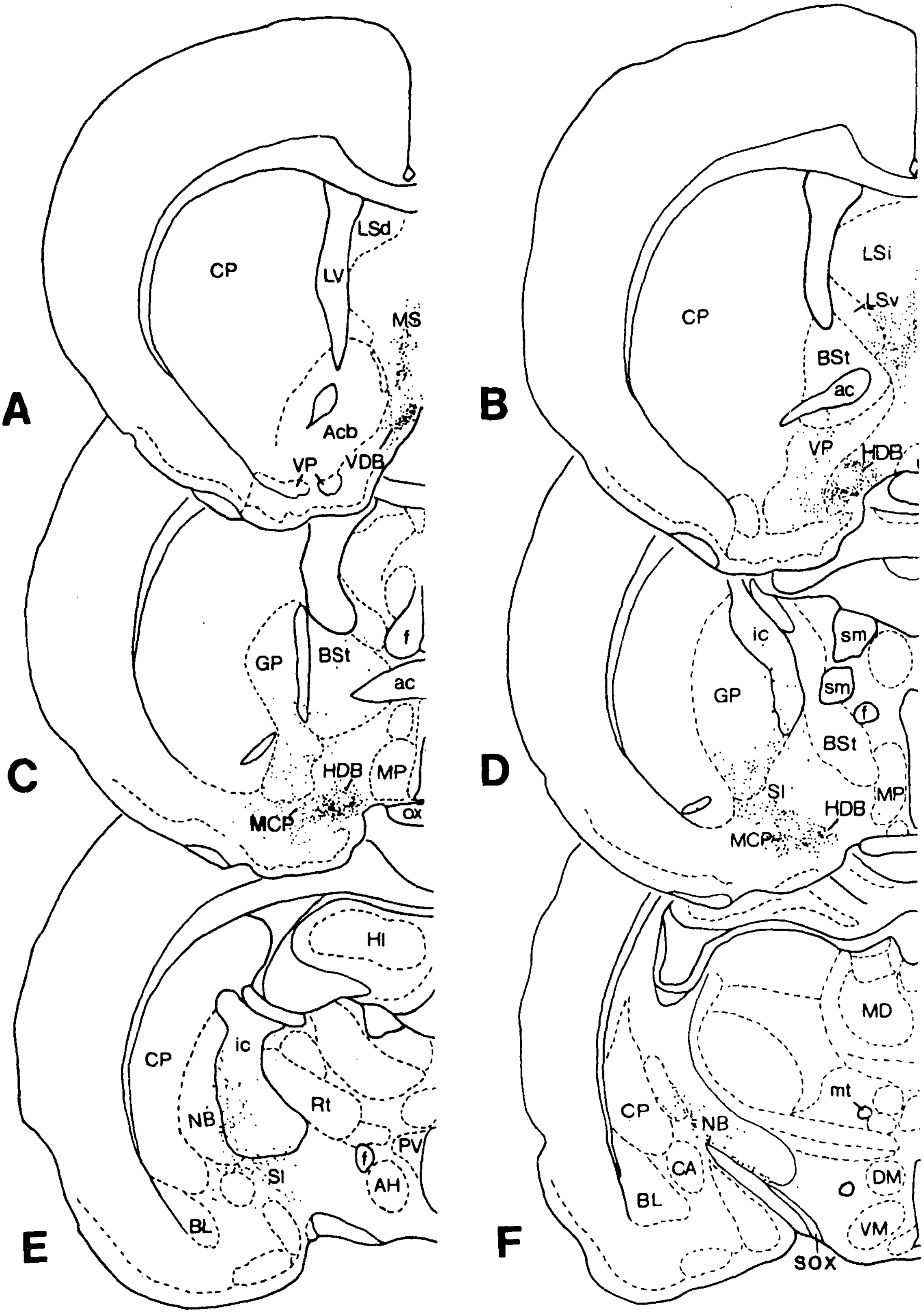
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FIG. 1. Distribution of ChAT-immunoreactive neurons (shown as small black dots) in the rat basal forebrain. Abbreviations: ac, anterior commissure; Acb, accumbens nucleus; AH, anterior hypothalamus; BL, basolateral amygdaloid nucleus; BSt, bed nucleus of the stria terminalis; CA, central amygdaloid nucleus; CP, caudate putamen; DM, dorsomedial hypothalamic nucleus; f, fornix; GP, globus pallidus; HDB, horizontal limb diagonal band nucleus; Hi, hippocampus; ic, internal capsule; LSd, LSi and LSv, lateral septal nucleus, dorsal, intermediate and ventral; LV, lateral ventricle; MCP, magnocellular preoptic nucleus; MD, mediodorsal thalamic nucleus; MP, medial

Also of potential importance for regulation of cortical activation is the ascending projection from the BF to a restricted number of thalamic nuclei. Projections have been demonstrated to the mediodorsal nucleus, anteroventral/anteromedial nucleus and rostral pole of the reticular nucleus in the cat (23,24). BF projections to these nuclei originate in the MS/VDB, HDB, MCP and SI, as well as in medial hypothalamic sites. Only 7–20% of this projection is cholinergic. A BF projection to the thalamic reticular nucleus in the rat has been described. This projection also contains cholinergic and noncholinergic components (25,26). The BF–reticular nucleus projection is of particular potential importance for EEG regulation, as the thalamic reticular nucleus is critically involved in controlling thalamocortical oscillations during sleep and wakefulness (see ref. 27 for review).

Another prominent limbic system target of BF cholinergic neurons is the basolateral nucleus of the amygdala. The cholinergic projection to the basolateral nucleus in the monkey arises primarily from the NB (28). The projection is more diffuse in rats, with the bulk of the projection arising in the SI and NB, but with contributions from the more rostral BF subdivisions (29–31). In rats this projection is about 25% noncholinergic; noncholinergic amygdalofugal neurons are intermixed with cholinergic neurons (29). Although cholinergic neurons projecting to the amygdala are located in BF regions that contain cortically projecting cholinergic neurons, very few individual neurons project to both sites (29).

Although projections from the BF to the caudal midbrain, pons and medulla have been demonstrated (see below), the bulk of these are not cholinergic (32). One established cholinergic projection is to the interpeduncular nucleus (IPN) at the midbrain–diencephalic junction. Consistent with the limbic system associations of the IPN, the bulk of the BF-IPN projection arises in BF areas that are associated with the limbic system, that is, the MS, VDB, HDB and MCP (33–36). The majority of IPN-projecting neurons in these areas are cholinergic (33). Few SI or NB cholinergic neurons project to the IPN (34).

Noncholinergic neurons

In addition to ChAT immunoreactive neurons, cells containing markers for alpha-melanocyte stimulating hormone, gallanin, somatostatin, neurotensin and other peptides have been located in magnocellular regions of the BF (37–40). The functional roles of these putative transmitter substances in the context of behavioral state regulation are not known. One important class of noncholinergic BF neurons that has been implicated in sleep–wake state control utilize gamma-aminobutyric acid (GABA) as a neurotransmitter. Codistributed with cholinergic neurons throughout much of the BF are neurons that are immunoreactive for glutamic acid decarboxylase (GAD), the synthetic enzyme for the neurotransmitter GABA (Fig. 2) (16,26,41–43). In the rat, GABAergic neurons outnumber cholinergic neurons by 2:1 (41). The majority of GABAergic neurons are small in size (< 15 μm) and may be interneurons (41). Others are medium to large multipolar neurons similar in size to cholinergic neurons, a morphology consistent with their being projection neurons (see below). A similar distribution of GABA-containing cell sizes has been described in the primate BF (44). In rats, overlap of large GABAergic neurons with cholinergic neurons is most extensive within the VDB, HDB, MCP, and rostral SI, and less extensive in the caudal SI and NB (Fig. 2) (41).

The existence of BF noncholinergic projection neurons distributed with cholinergic projection neurons is well established (3,17,22,23,32,33). A GABAergic component has been identified for the noncholinergic projection to the hippocampus (13), olfactory bulb (15), thalamus (26) and neocortex (16,45,46). Noncholinergic descending projections from the BF to the midbrain pons, and medulla are well documented (32,47,48). These projections may contain a GABAergic component. Recently, a descending GABAergic projection from the MS, VDB, HDB, MCP and SI to the posterior lateral hypothalamic area was documented in the rat (49).

Afferents to magnocellular regions of the basal forebrain

As in previous sections, the focus here will be on afferents to the BF that are most directly related to processes of behavioral state regulation. Ascending projection of brainstem monoaminergic and cholinergic neurons play critical roles in forebrain arousal (50,51), and are an important potential source of afferents to both arousal and sleep-regulating mechanisms within the BF. A substantial projection from the locus ceruleus to all of the major subdivisions of the

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preoptic nucleus; MS, medial septal nucleus; mt, mammilothalamic tract; NB, nucleus basalis; ox, optic chiasm; PV, paraventricular nucleus of the hypothalamus; Rt, reticular thalamic nucleus; IS, substantia innominata; SM, stria medullaris; SOX, supraoptic decussation; VDB, vertical limb diagonal band nucleus; VM, ventromedial hypothalamic nucleus; VP, ventral pallidum. Modified from ref. 61.

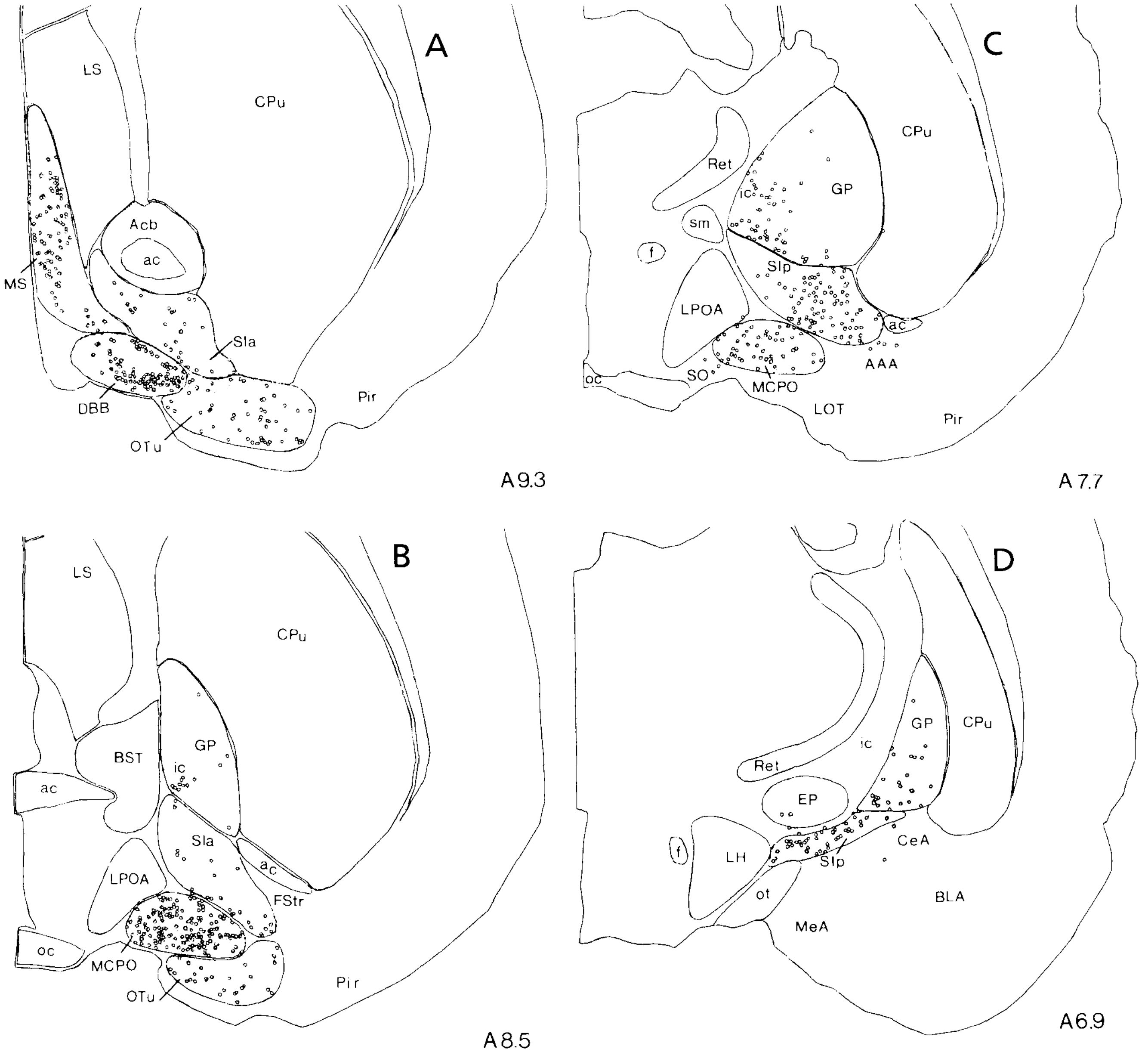

FIG. 2. Codistribution of ChAT-immunoreactive (open black circles) and GAD-immunoreactive (magenta dots) neurons in the magnocellular basal forebrain. The anterior–posterior levels shown in the lower right portion of each panel correspond to those in the atlas of Paxinos and Watson (181). Abbreviations not defined in the legend for Fig. 1: AAA, anterior amygdaloid area; BLA, basolateral amygdaloid nucleus; CeA, central amygdaloid nucleus; CPu, caudate putamen; EP, entopeduncular nucleus; Fstr, fundus of the striatum, LH, lateral hypothalamus; LPOA, lateral preoptic area; LOT, lateral olfactory tract nucleus; MeA, medial amygdaloid nucleus; ot, optic tract; OTu, olfactory tubercle; Pir, piriform cortex; RET, thalamic reticular nucleus; SIa and SIp, substantia innominata, pars anterior and par posterior. Modified from ref. 41.

magnocellular BF has been described (52,53). Noradrenergic fibers appear to make contact with cholinergic neurons at all levels, with the exception of the NB (1). Afferents originating within serotonergic cell groups of the raphe nuclei are distributed throughout the magnocellular BF (52–54). Afferents to the MS and VDB originate primarily in the median raphe nucleus and the majority of those to the remaining BF subdivisions originate within the dorsal raphe nucleus. Serotonergic-positive fibers from the dorsal raphe nucleus occur in close apposition to ChAT-reactive soma within the BF (1). Neurons within cholinergic nuclei of the pontomesencephalic tegmentum project heavily upon portions of the magnocellular BF, but appear to contact primarily noncholinergic cell types (52,53,55).

Additional afferents to the BF that are of potential functional importance for sleep–wake regulation arise from throughout the brainstem reticular core (1,52–54). The projection from the midbrain preferentially targets the subpallidal SI and NB, whereas the MCP, HDB, VDB and MS are contacted predominantly by pontine reticular formation neurons. The EEG activating effects of the brainstem reticular formation are well known, and these BF afferents are of potential functional importance for both sleep- and waking-regulating mechanisms. Local BF injections of excitatory amino acid receptor antagonists block increased ACh release in cortex evoked by brainstem stimulation (56), indicating that a component of the brainstem projection that exerts excitatory effects on corticopetal BF cholinergic neurons is glutamatergic.

Portions of the posterior lateral hypothalamus, at levels extending from the mesencephalic–diencephalic junction to the perifornical area, participate in the regulation of arousal and EEG activation. These regions are the site of origin of a direct neocortical projection system (57). Lesions of these hypothalamic sites in experimental animals yield a syndrome of behavioral somnolence and enhanced cortical EEG synchrony (58–60). Cells within the posterior lateral hypothalamus also project to the magnocellular BF. Far lateral hypothalamic sites target the more dorsal peri- and subpallidal regions, and more medial portions project to the MCP and HDB (61). Fibers of this projection are found in close association with both cholinergic and noncholinergic BF neurons.

The medial preoptic area and anterior hypothalamus (MP/AH; Fig. 1) have important sleep-regulating functions, and projections from these midline structures to the adjacent magnocellular BF have been identified (61). Symmetric synaptic contacts from MP/AH neurons have been observed on BF cholinergic cells, suggesting an inhibitory influence. Neurophysiological evidence, reviewed later, indicates an inhibitory action on arousal-related, putative BF cholinergic neurons from temperature-sensitive neurons within the MP/AH (62).

Cholinergic regions of the magnocellular BF also receive afferents from the neocortex. These are also of potential interest in terms of the state-dependent neurophysiology of the BF. In the thalamo-cortical projection system, reciprocal cortical thalamic afferents are important in modulating synchronous discharge patterns of thalamic relay neurons during nonREM sleep (63,64). However, unlike the thalamo-cortical system where there is extensive reciprocity between the site of termination of thalamic afferents and the origin of the cortico-thalamic projection, the cholinergic BF receives projections from a comparatively restricted number of cortical sites. There are few projections from primary sensory or motor areas. The majority arise from allocortical regions, including orbital cortical areas, insular cortex and piriform cortex (1). The projection to the magnocellular BF from the prefrontal cortex is substantial, and innervates the HDB and portions of the MCP and SI most densely (65,66). Direct cortical projections to the NB are sparse. Cortical influences on cells in these areas may be mediated via multisynaptic pathways involving the striatum and nucleus accumbens (1).

FUNCTIONAL ASPECTS OF THE BASAL FOREBRAIN CHOLINERGIC SYSTEM

There has been intense interest in the behavioral neurobiology of the BF cholinergic system, in part because of its involvement in the neuropathology of Alzheimer's disease. Two significant neurological deficits in this disorder are slowing of the dominant cortical EEG frequencies and dementia. Accordingly, research efforts have focused on the role of BF cholinergic cell groups in regulating EEG activation and in cognitive functions.

Cholinergic regulation of neocortical arousal and activated EEG patterns

Substantial evidence points to an involvement of BF neurons, as the source of cortical ACh, in regulating neocortical activation. ACh-mediated activation of the cortex is important for expression of desynchronized EEG patterns (low voltage, mixed high frequencies) characteristic of waking and REM sleep. Spontaneous release of ACh measured at the cortical surface is elevated during waking and REM sleep, compared to nonREM sleep (67,68). Electrical stimulation of the SI/NB enhances cortical ACh release in the anesthetized rat (69,70). Stimulation at these sites also increases neocortical blood flow, an effect blocked by muscarinic antagonists, suggesting a vasodilatory role for the cholinergic innervation of cortical blood vessels (see ref. 71 for review). Regional cortical metabolic activation evoked by sensory stimulation is diminished following BF lesions in cats (72), a response that could reflect diminished regional blood flow as well as diminished neuronal activation. Within the waking state, rates of ACh release can vary with ongoing behavior, being elevated during locomotion compared to quiet waking (73,74). Ascending excitatory inputs to BF cholinergic neurons from the brainstem can influence cortical ACh release. Stimulation at the mesopontine tegmentum evokes EEG desynchrony and increased cortical ACh release (56). These effects are blocked by infusing glutamatergic agonists directly into the BF coincident with brainstem stimulation (56).

Reduced cortical ACh levels produced by excitotoxic

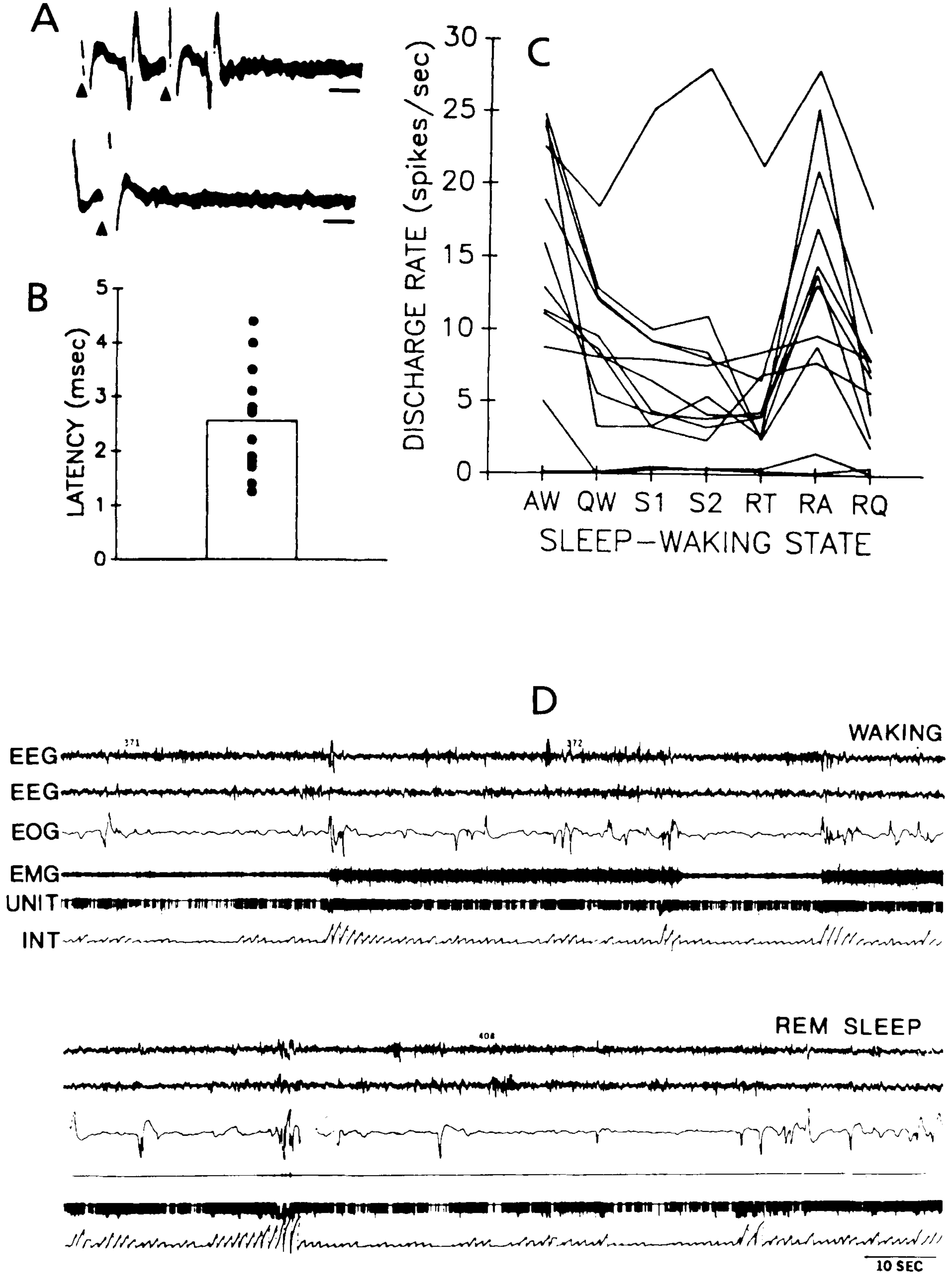

FIG. 3. State-dependent activity of identified BF projection neurons recorded in the unanesthetized, freely moving cat. A. Oscilloscope tracing of extracellularly recorded BF neuron that was antidromically driven in response to stimulation at the anterior cingulate bundle. Documentation of antidromic response showing fast frequency following (top trace) and collision of evoked spike with spontaneous action potential (bottom trace). Calibration = 1 millisecond. B. Mean (bar) and individual (circles) antidromic latencies for a group of putative

lesions of the caudal SI and NB in rats result in enhanced slow-wave activity (0–4 Hz) in the neocortical EEG during waking (8,75,76) and REM sleep (77). These effects are similar to those produced by systemic administration of muscarinic antagonists (see refs. 78,79 for review). Intracortical grafts of fetal BF tissue rich in cholinergic cells restore the behavioral modulation of cortical ACh release (80) and result in a return of normal waking EEG patterns (81). These findings suggest that a threshold level of background ACh release in the neocortex is necessary for the expression of the normal desynchronized EEG patterns of waking and REM sleep.

Discharge patterns of putative cholinergic neurons are consistent with observed patterns of cortical and limbic ACh release and with the postulated role of regulating EEG-desynchronized states. Neurons that exhibit elevated discharge rates during waking and REM sleep compared to nonREM sleep have been recorded in cholinergic cell-rich regions of the BF in unanesthetized cats (82–85) and rats (86,87). In cats, subpopulation of neurons with waking-related discharge were identified as cortically projecting using antidromic techniques (Fig. 3) (85). These neurons displayed increased firing rates during waking with movement compared to quiet waking, with further reductions in rate during nonREM sleep (85,88). Neurons in the NB region of rats, some identified as cortically projecting, exhibited peak rates while animals were awake and moving; discharge during polygraphically defined sleep was not examined (75). These latter findings are consistent with observed increases in cortical and limbic system ACh release within the state of wakefulness during locomotion (73,74).

As described in the previous section, cholinergic regions of the BF receive multiple brainstem afferents, and brainstem stimulation can increase cortical and limbic system ACh release. Midbrain or rostral pontine stimulation evokes excitatory responses or excitatory–inhibitory sequences in waking-related neurons recorded in the BF of cats (Fig. 5B) (85,89) and rats (87). In rats, stimulation-evoked responses could be blocked by iontophoretic application of beta and alpha-1 adrenoreceptor antagonists (87). In anesthetized rats, a subpopulation of identified cortically projecting neurons recorded in the VDB and MCP respond to pedunculopontine and dorsal raphe stimulation with evoked excitation or inhibitory–excitatory sequences (53).

Cholinergic neurons in the pedunculopontine region of the brainstem do not appear to exert significant functional influences on BF cholinergic neurons. As reviewed previously, brainstem cholinergic neurons appear to contact only noncholinergic BF cell types. Local administration of cholinergic agonists directly into the magnocellular BF has potent behavioral and EEG activating effects (90,91). However, local infusions of cholinergic receptor antagonists into the BF do not diminish the increase in cortical ACh release evoked by pedunculopontine stimulation (56). In contrast, administration of tetrodotoxin, procaine or glutamate antagonists into identical BF sites significantly attenuates brainstem stimulation-evoked cortical ACh release (56). These findings suggest that brainstem cholinergic afferents to the magnocellular BF exert effects on behavioral state primarily via actions on noncholinergic BF cell types, for example, either via activation of noncholinergic arousal-related neurons, or by inhibition of sleep-related cell types.

BF cholinergic mechanisms and cognition

Although the above evidence indicates the importance of BF cholinergic neurons in regulating activated EEG patterns during waking, the system does not function simply as a tonic arousal system. This is evident from the finding that putative BF cholinergic neurons display phasic, not tonic, discharge patterns during waking and REM sleep (75,85). Within the waking state, the BF cholinergic system appears to participate in the regulation of sensory, attentional and cognitive functions of the neocortex and limbic system.

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BF cholinergic neurons, identified as projection neurons. These cells displayed homogeneous estimated axonal conduction velocities (5.21 ± .71 m/second) that were faster than those for groups of sleep-related and state-indifferent BF projection neurons (85). Stimulation sites were primarily in the anterior cingulate bundle or the external capsule. C. State-dependent discharge of the group of BF neurons with antidromic latencies shown in B. The majority of cells had peak discharge rates in active waking (AW) and active REM sleep (RA). In most waking-related cells, discharge rate progressively declined from AW to quiet waking (QW) to nonREM, or slow-wave sleep (S1 and S2). Other abbreviations: RT, nonREM–REM sleep transition period; RQ, quiet REM sleep. Figure 3A–C from ref. 85. D. Polygraph recording of discharge of an identified cortically projecting basal forebrain neuron during episodes of waking and REM sleep. In both states, maximal discharge rates occurred in association with periods of active waking (waking with movement indicated by phasic EMG activation and high density of eye movements), and active REM sleep (indicated by bursts of rapid eye movements). During episodes of quiet waking and quiet REM sleep (indicated by comparative absence of eye movements in both states), discharge rate declined dramatically from maximum levels, even as the EEG remained fully desynchronized. Abbreviations: EEG, right and left sensorimotor cortical electroencephalogram; EOG, electrooculogram; EMG, dorsal neck electromyogram; UNIT, output of window discriminator, each downward pen deflection indicates a discriminated action potential; INT, integrated window discriminator output, reset to zero level at 1-second intervals. Figure 3D from ref. 88.

Loss of BF cholinergic neurons is a critical feature of the neuropathology of Alzheimer's disease, and is believed to contribute to cognitive deficits in this disorder (see ref. 92 for review). The cognitive effects of excitotoxin-induced lesions of cholinergic regions of the BF in experimental animals (primarily rodents) have been intensely investigated. Such lesions impair performance in a variety of learning tasks including t-maze, radial-arm maze, Morris water maze, delayed matching to sample and passive and active avoidance (see ref. 93 for review). A global impairment in cognitive function following such lesions implicates the BF cholinergic system as critical for normal acquisition and retention of newly learned responses.

Although BF lesions can produce profound memory disturbances in experimental animals, the extent to which selective loss of cholinergic neurons is responsible for these deficits is controversial (see refs. 94,95 for review). As reviewed in a previous section, there is extensive intermingling of cholinergic and noncholinergic neurons throughout much of the BF. Excitotoxins, such as ibotenic acid, can be expected to damage noncholinergic BF neurons as well as cholinergic ones. BF lesions produced by quisqualic acid are more effective in reducing cortical ACh levels than are ibotenic acid-induced lesions, but the former treatment can result in less severe learning and memory deficits than the latter one (95). Thus, global memory impairment may require destruction of both BF cholinergic and noncholinergic cell types.

Behavioral and neurophysiological studies suggest that rather than mediating memory processes directly, BF cholinergic neurons regulate attentional processes. Recent studies in the rat (96) and monkey (97) find evidence for impaired attentional focusing and not primary impairment of memory following excitotoxic BF lesions.

Neurophysiological evidence indicates that activation of the BF cholinergic neurons may produce regional enhancement of sensory processing within the cortex. Evidence from in vitro cortical slice preparations demonstrates that the effects of acetylcholine on cortical pyramidal neurons include a suppression of two rectifying potassium currents, I_m (muscarinic sensitive) and the calcium-activated I_{AHP} (after hyperpolarization) (98). Suppression of these currents reduces postexcitatory after hyperpolarizations (AHPs) and decreases spike frequency adaptation, thereby increasing pyramidal cell excitability. These actions have a net depolarizing effect, promote tonic single-spike firing characteristic of pyramidal cell discharge during desynchronized EEG states and render cortical cells more responsive to excitatory synaptic input (98).

Local cortical application of muscarinic agonists in anesthetized animals enhances the sensory-evoked responses of neurons in somatosensory (99), auditory (100) and visual cortex (101) recorded in vivo. Electrical stimulation of the NB combined with somatosensory (102,103) or auditory (104,105) stimulation augments evoked excitatory responses in cortical neurons. These effects are blocked by prior treatment with muscarinic receptor antagonists. Repeated pairings of NB stimulation with somatosensory or auditory stimulation enhances sensory stimulation-evoked responses in somatosensory (103) and auditory cortex (106) for several minutes. These long-lasting effects are present only when NB and sensory stimulation are repeatedly paired; repetitive stimulation of the NB alone is not effective.

This type of modality- or contingency-specific coactivation of BF cholinergic neurons could contribute to attentional focusing by enhancing the representation of selected sensory information in the cortex. One way in which such coactivation could be achieved is via collateral inputs to the BF cholinergic system from the primary sensory pathway. Such a mechanism may function in the auditory system, where a projection from auditory thalamus to cholinergic regions of the BF has been described (107).

Another mechanism by which BF activation could become associated with particular sensory stimuli is through conditioning processes. Within the primate NB, single unit recordings demonstrate that few putative cholinergic neurons respond to specific sensory, motor or mnemonic aspects of learning and memory tasks. Rather, a subset of NB neurons displays elevated discharge in response to delivery of reinforcement or to sensory stimuli that are associated with reward (108,109). In rats (110) and rabbits (111) a significant proportion of neurons recorded throughout the BF respond to the CS+, but not the CS− stimuli in classical conditioning paradigms. These findings suggest a physiological substrate of attentional focusing, in which stimuli that have come to be associated with delivery or availability of reinforcement activate BF cholinergic neurons, which, in turn, enhance processing of those stimuli in the appropriate cortical region (99,104,108,109).

The concept of cholinergic BF neurons as a source of cortical activation can be easily reconciled with a more specific role in modulating cortical excitability in response to particular kinds of stimuli or contingencies. As indicated by the EEG effects of NB lesions, a minimal level of ACh release in the cortex may be necessary to maintain the activated EEG patterns normally associated with wakefulness. In addition, BF neurons could respond to particular stimuli occurring within a specific context leading to further increases in ACh release in restricted cortical regions.

To summarize, neurons can be recorded within cholinergic regions of the BF that display firing rate profiles consistent with a role in regulating desynchronized EEG patterns. Reinforcement-related neuronal discharge can also be recorded within these regions, particularly in the primate NB. Because the state-dependent and cognitive correlates of BF neuronal activity have been studied by separate laboratories, the extent to which the spontaneous discharge of reinforcement-related neurons is modulated by sleep–waking state is not known. Nevertheless, both cell types can be considered to be putatively cholinergic because of 1) location, 2) the known behavioral state correlates of cortical ACh release and 3) identified cortically projecting BF neurons have been shown to be waking-related (75,85) or reinforcement-related (108,109).

However, because of the anatomical configuration of the BF cholinergic system, cells recorded with extracellular techniques cannot be identified as cholinergic with any certainty, even when shown to be cortically projecting. Although the majority of cortically projecting neurons in the NB of the rat and cat are cholinergic, 10–20% are not. Within the MCP and SI, as many as 50% of cortically projecting cells are not cholinergic. This is reflected in the heterogeneity of axon conduction velocities and behavioral state correlates described for BF neurons in the rat and cat (85,112,113). Within the primate NB, the percentage of corticopetal cells that are also cholinergic approaches 100% (19). However, although some reinforcement-related neurons have been identified as cortically projecting, most recorded neurons cannot be identified as such. Due to the compact organization of the cholinergic cells within the primate NB, and with careful anatomical and physiological characterization of recorded cells (e.g. see ref. 109), cholinergic neurons can be most reliably and consistently recorded within the primate NB. In other species, and for neurons located within the BF but outside the NB in primates, confidently classifying recorded BF neurons as cholinergic remains problematic. To date, no easily implemented and reliable identifying feature of the extracellularly recorded activity of BF cholinergic neurons has been demonstrated.

Influence of intrinsic properties of BF neurons on state-dependent discharge patterns

Intracellular recordings of BF neurons using in vitro brain slice or dissociated cell preparations have revealed properties of cholinergic neurons that may assist identification in extracellular in vivo recordings, as well as provide potentially valuable information about their state-dependent physiology. An important advantage of intracellular recording in these preparations is the ability to determine the neurochemical phenotype of recorded cells. This is accomplished through intracellular injection of a dye combined with immunohistochemistry for specific neurotransmitter markers.

Using this approach, Khateb et al. (114) demonstrated that ChAT-positive neurons in brain slices containing the MCP/SI region of guinea pig BF possess T-type calcium channels. T-type calcium channels have also been identified in isolated putative cholinergic neurons obtained from the guinea pig MS (115). These channels are responsible for the voltage-dependent calcium current I_t. I_t is present in a variety of cell types including hippocampal neurons (116), thalamic relay neurons (117) and cholinergic neurons in the pontomesencephalic tegmentum (118). I_t has several interesting properties, but of direct relevance here is that its presence enables neurons to fire high-frequency bursts of action potentials in a voltage-dependent manner. I_t is inactivated when membrane voltage (V_m) is more depolarized than about -60 mV, but becomes deinactivated at more hyperpolarized levels of V_m (117). When cells that possess I_t are depolarized from this hyperpolarized state, they respond with a broad depolarizing spike that is calcium-mediated. This low-threshold spike can be crowned by a high-frequency burst (typically >200 Hz) of fast action potentials (117). The burst is usually followed by an AHP that is due, in part, to the voltage-dependent inactivation of I_t, although other currents can make important contributions to the AHP (117,119). When V_m is at levels >60 mV, depolarizing inputs evoke trains of single action potentials, as I_t is inactivated at these levels of V_m.

Thus, cells that possess T-type calcium channels have the ability to display two modes of firing, single-spike and high-frequency burst firing. A dramatic example of how this determines the state-dependent firing patterns of cells is observed in thalamic relay neurons. These cells preferentially display single-spike firing during wakefulness and REM sleep, and burst firing during nonREM sleep (see ref. 120 for review). Extracellular recordings of thalamic relay neurons during nonREM sleep are characterized by high-frequency bursts, followed by long periods during which no action potentials are recorded. These silent periods reflect AHPs that arise due to a combination of intrinsic properties and synaptic input (see refs. 27,120 for review). Burst firing in thalamic relay neurons during nonREM sleep is associated with impaired sensory transmission through the thalamus to the cortex. This occurs because relay neurons are unresponsive to afferent input during periods of AHP, and there is little correspondence between incoming volleys from primary sensory inputs and the output of the relay neurons to the cortex (27,120,121).

The demonstration of I_t in BF cholinergic neurons in vitro raises the question of the role of tonic versus burst firing in the normal in vivo physiology of these cells (114). For example, do the two firing modes display the same state correlates observed in thalamic relay neurons (i.e. single-spike firing in waking and REM sleep and burst firing in nonREM sleep)? Burst firing in BF cholinergic neurons during sleep could diminish the flow of activating influences from the brainstem and from ascending sensory pathways to the cortex (7). In the primate NB, putative cholinergic neurons are characterized by relatively tonic single-spike firing during wakefulness (109). Indeed, the absence of burst firing in waking is used to distinguish NB neurons from those in globus pallidus (109,122). In naturally sleeping cats, 43% of the neurons recorded in the ventral and peripallidal area displayed burst firing in nonREM sleep (83). In a population of waking-related neurons recorded in the MCP and rostral SI of unanesthetized cats, 16% displayed a pattern of burst firing exclusively during nonREM sleep that was identical to the pattern observed in the majority of neurons recorded in a thalamic relay nucleus (123). If more extensive mapping studies of identified cholinergic and noncholinergic neurons confirm initial findings from in vitro experiments that cholinergic neurons are the only cell type in the magnocellular BF to possess I_t, then the presence of extracellularly recorded burst firing could prove to be a simple marker for BF cholinergic neurons in vivo.

SLEEP-PROMOTING FUNCTIONS OF THE MAGNOCELLULAR BASAL FOREBRAIN AND MEDIAL PREOPTIC/ANTERIOR HYPOTHALAMUS

Prior to the current focus on the neurobiology of the BF cholinergic system and its relationship to cortical activation and cognition, this portion of the ventral telencephalon was implicated as the site of a sleep-promoting mechanism. Based on clinical correlations and the location of encephalitis-related neuropathology, von Economo noted a strong association of damage between the region of the rostral hypothalamus and preoptic area and symptoms of insomnia (124). Nauta examined the effects of transections at different levels of the hypothalamus on behavior and sleep–waking in the rat, and found that transections at supraoptic levels resulted in severe insomnia (125).

Subsequent experimental work has focused on the sleep-promoting functions of ventral telencephalic regions, including portions of the magnocellular BF that overlap with the locations of cholinergic neurons, as well as the nonmagnocellular medial preoptic/anterior hypothalamus (MP/AH; see Fig. 1). Published reports describing the effects of lesions, unit recording or chemical stimulation of the BF on sleep actually describe manipulations of the MP/AH, not the more laterally located magnocellular regions (e.g. 126,127). Although both areas are critically involved in sleep–wake regulation, they are anatomically and functionally very different. In addition, the term "basal forebrain" has evolved to refer principally to the magnocellular cholinergic system in much of the contemporary neuroscience literature. Including these regions and the MP/AH under a single "basal forebrain" rubric can be confusing to readers not familiar with the history of sleep research in this area. In the following section, the evidence for a hypnogenic mechanism within the magnocellular BF and the MP/AH will be considered separately.

Evidence for a sleep-promoting function in the magnocellular BF

Based on the work of von Economo (124) and Nauta (125), and the findings of Hess (128) and Kaada (129) demonstrating motor suppression and parasympathetic activation in response to electrical stimulation of the ventral telencephalon in experimental animals, Sterman and Clemente examined the effects of stimulation throughout the BF on EEG patterns and behavioral sleep in cats. They found that BF stimulation evoked cortical EEG synchronization in cats treated with Flaxedil (130) and EEG synchronization with behavioral sleep in unanesthetized, chronically prepared cats (131). The most effective sites were within the HDB, the MCP and the rostral SI. Stimulation in the region of the NB and caudal SI did not induce sleep. Although effective stimulation sites were in regions now known to contain cholinergic neurons, they are also the sites where overlap of cholinergic and GABAergic neurons is most extensive (41). At the more caudal BF sites where stimulation was not sleep-inducing, cholinergic neurons with cortical projection targets are the predominate magnocellular neuronal type. Subsequent studies demonstrated that discrete electrolytic lesions centered in the HDB of cats resulted in persistent insomnia (132,133). Neurotoxin lesions in the region of the HDB, MCP and rostral SI also caused chronic sleep loss in adult cats (134).

Single-unit recordings in unanesthetized, naturally sleeping animals have identified patterns of neuronal discharge within the magnocellular BF that are consistent with sleep-regulating functions. In work initially performed in freely moving adult cats using a chronic microwire technique, neurons recorded within the HDB, MCP and SI displayed peak discharge rates during nonREM sleep, and comparatively reduced rates during waking and REM sleep (Fig. 4A and B) (84). Sleep-related neurons constituted about 20% of the total cell sample. During transitions from periods of sustained wakefulness to sustained sleep, discharge of sleep-related cells initially increased several seconds prior to the first signs of EEG synchronization (Fig. 4C) (85,88). Sleep-related neurons were electrophysiologically identified as sources of projections to the neocortex and the brainstem (85). Estimated axonal conduction velocities of sleep-related projection neurons were significantly slower than those of waking-related, presumably cholinergic, projection neurons. Stimulation of brainstem arousal-related regions of the midbrain and pontomesencephalic tegmentum evoked orthodromic suppression of spontaneous activity in sleep-related cell types, in contrast with the orthodromic excitatory effects observed in waking-related BF neurons (Fig. 5A and B) (85).

The responses of neurons in the midbrain reticular formation (MRF) to BF stimulation were examined in a subsequent study to assess the functional significance of the descending projections of BF sleep-related neurons. In agreement with a previous study (135), stimulation at sites within the HDB and rostral SI in cats during wakefulness evoked prolonged periods of discharge suppression (average duration of 87 milliseconds), that was sometimes preceded by a brief period of excitation (Fig. 5C–F) (136). This finding suggests that BF sleep-related neurons participate in behavioral state control, in part, via a descending modulation of brainstem arousal systems. This is consistent with the ability of BF stimulation to antagonize behavioral activating effects of MRF stimulation in cats traversing a runway for a food reward (137). GABAergic neurons with descending projections are abundant in effective stimulation sites, and are candidates for mediating these inhibitory effects (49).

The presence of sleep-related neuronal discharge within the magnocellular BF, as originally described in cats, has been confirmed in rats. In urethane-anesthetized rats, a subgroup of BF neurons displayed elevated discharge rates during periods of EEG synchrony (138). These could not be identified as projection neurons and were hypothesized to be interneurons (138). Neurons displaying increased discharge rates during nonREM sleep compared to waking have recently been described within the HDB and SI of unanesthetized rats (86,87). Prostaglandin D_2 (PGD_2) has sleep-enhancing effects when administered centrally to rats (139), and about one-third of BF sleep-related neurons in rats were excited by iontophoretic application of PGD_2 (86). As in the cat, some BF sleep-related neurons could be confirmed to be a source of brainstem projections (87). Electrical stimulation of the pontine and medullary reticular formation caused suppression of discharge in about one-half of the sleep-related neurons examined (87).

Evidence for a sleep-promoting function of the medial anterior hypothalamus/preoptic area

As noted above, the stimulation sites of Sterman and Clemente (130,131), and the insomnia-producing lesions reviewed above (132,134), involved magnocellular portions of the BF, principally the HDB, MCP and rostral SI. The hypothalamic region located adjacent and medial to these rostral magnocellular BF sites, the MP/AH, is also important in sleep–wake regulation, and has primarily sleep-promoting actions. Although MP/AH behavioral state-regulating mechanisms appear to interact with both cholinergic and noncholinergic cell types within the magnocellular BF, there are substantial anatomical and functional differences between these two regions.

The MP/AH is an area of considerable functional complexity. Cells in this region play pivotal roles in the regulation of body temperature, body fluid balance, cardiovascular regulation, neuroendocrine control, reproductive physiology and behavior. Although some of these functional aspects interact with sleep–wake control mechanisms, behavioral state control is only one of many important regulatory functions that neurons of the MP/AH participate in.

Anatomically, the MP/AH and magnocellular BF are different. As with other periventricular portions of the hypothalamus, the cells in this area are medium to small in size and are densely packed. An extensive list of neuropeptides, hormone releasing factors and neurotransmitters have been localized to MP/AH neurons (se ref. 140 for review). No cholinergic neurons are found within these nuclei, but GABA-containing cells are numerous. GABAergic neurons with identified projections to the posterior lateral hypothalamic area form a lateral to medial continuum from magnocellular portions of the BF to the MP/AH (49). Similarly, a projection to the thalamic reticular nucleus and the anteromedial/dorsomedial thalamic nuclei has both magnocellular BF and MP/AH components (23,24). As reviewed previously, these pathways are of potential importance for sleep–wake regulation.

The evidence for a role of the MP/AH in the regulation of sleep and wakefulness is as extensive and as compelling as that for any region of the brain. It is likely that damage to the MP/AH was responsible for the insomnia observed by Nauta (125) after rostral hypothalamic transections in rats. Electrolytic or neurotoxin-induced damage to this area has been repeatedly shown to produce profound and long-lasting reductions in sleep (126,127,141,142). Microinjections of benzodiazepines (143), adenosine agonists (144),

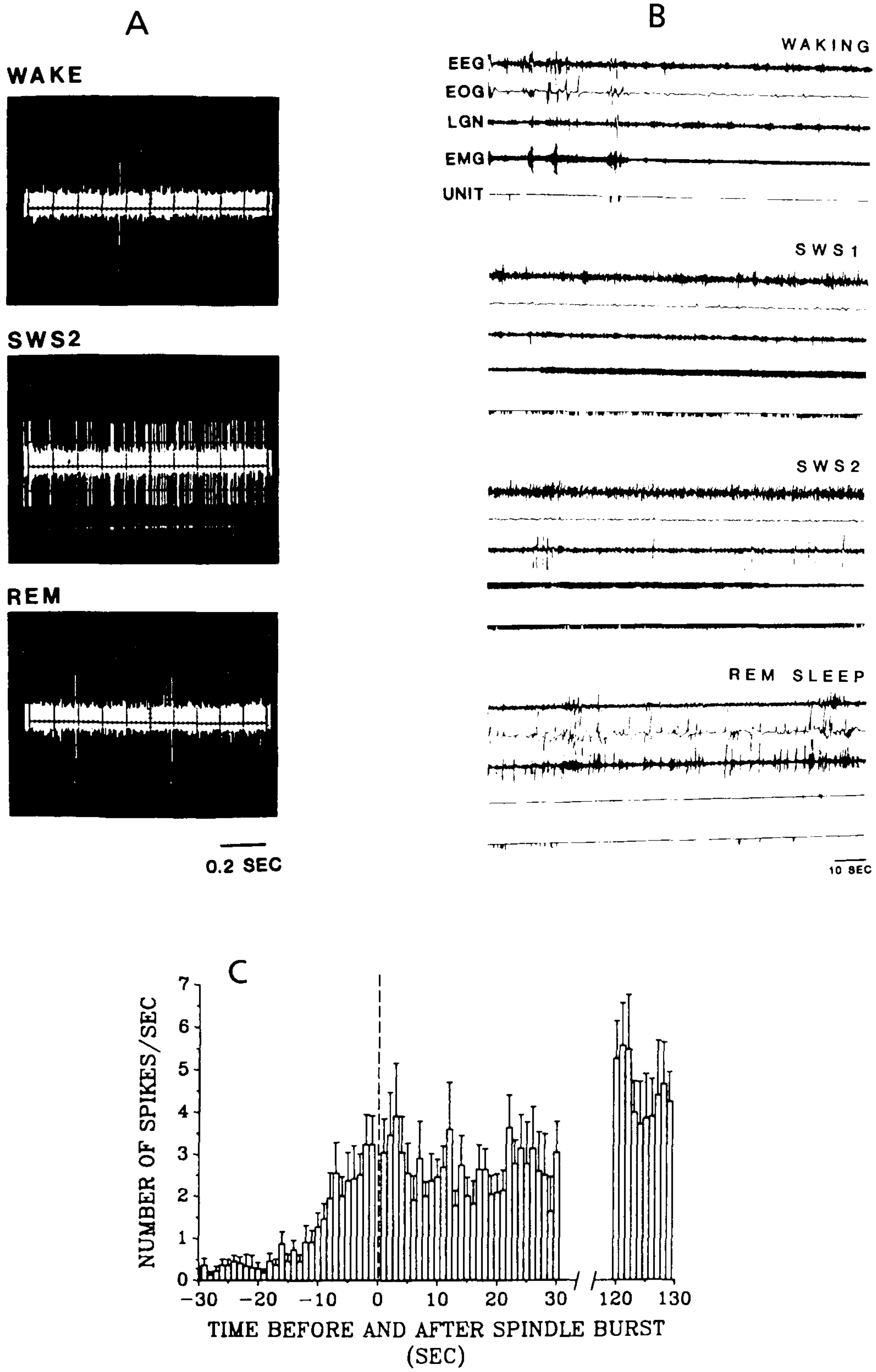

FIG. 4. Sleep-related neuronal activity in the magnocellular BF of unanesthetized, freely moving cats. A. Oscilloscope tracing of extracellularly recorded activity of a BF neuron during waking, stable nonREM sleep (SWS2) and REM sleep. Dots on the bottom trace reflect output of the window discriminator. B. Polygraph recording of state-dependent discharge in a BF sleep-related neuron. Shown are epochs of waking, light nonREM sleep occurring shortly after the transition from waking to sleep (SWS1), deep, stable nonREM sleep (SWS2) and REM sleep. The discharge rate increased from waking to SWS1, and attained maximal levels in SWS2. In this cell discharge rates during

PGD_2 (139) and 5-hydroxytryptamine (145) promote sleep. Microinjections of PGE_2 (139) and of the GABAergic agonist muscimol (146) into the MP/AH decrease sleep. Neurons that display increases in spontaneous discharge rate during nonREM sleep can be found within the MP/AH in comparative abundance (147–150).

The MP/AH is a critical thermosensing and thermointegrating region of the mammalian brain (151,152). Thermoregulatory and sleep-regulating functions of the MP/AH are closely related (153–155). Whole-body warming during a period of wakefulness is followed by a subsequent increase in Stage 3/4 sleep in man (156) and in deep nonREM sleep in rats (157). Local warming of the MP/AH via chronically implanted thermodes in experimental animals has acute sleep-promoting effects (158,159). Warming of the MP/AH during nonREM sleep in cats causes an increase in EEG delta (0–4 Hz) power in nonREM sleep as assessed by spectral analysis (160).

Following neurotoxin-induced damage to the MP/AH, cats display both sleep and thermoregulatory deficits (141). A major thermoregulatory deficit is an elevated core temperature threshold for elicitation of the evaporative cooling response of panting, that is, MP/AH-damaged cats will pant, but only when core body temperature is elevated 1.5–2.5°C above the baseline panting threshold. This suggests that the lesion-induced loss of MP/AH warm-sensing neurons has removed a component of the normal thermal stimulus to pant. Similarly, these cats have chronic insomnia when body temperatures are maintained at prelesion levels. However, when exposed to an elevated environmental temperature that causes an elevation in core temperature, normal amounts of nonREM sleep quickly return (141).

These findings support the hypothesis that warm-sensing neurons of the MP/AH exert a tonic modulatory control over sleep- and arousal-regulating mechanisms (153). If this hypothesis has merit, a subpopulation of MP/AH thermosensitive neurons should display spontaneous changes in discharge rate during transitions from wakefulness to sleep. This has been recently confirmed in a study of warm- and cold-sensing neurons recorded in the MP/AH of chronically prepared adult cats during sleep and wakefulness (150). A majority of warm-responsive cells displayed spontaneous increases in discharge rate during transitions from waking to sleep, whereas most cold-sensing neurons displayed reductions in discharge rate during sleep onset.

One possible site at which MP/AH thermoresponsive neurons could exert modulatory effects on sleep and arousal mechanisms is within the adjacent magnocellular BF. Projections from the MP/AH to magnocellular portions of the BF have been identified (61). MP/AH afferents are a possible source of inhibitory synaptic inputs to BF cholinergic neurons. Local warming of the MP/AH can influence the spontaneous and evoked activity of magnocellular BF neurons. In a sample of 174 BF neurons recorded in chronically prepared, naturally sleeping cats, 40% responded to local MP/AH warming with a change in spontaneous discharge rate (62). Of the neurons that displayed suppression of discharge during MP/AH warming, the majority (73%) were of the waking-related type. In contrast, sleep-related neurons comprised 62% of the BF neurons that responded to MP/AH warming with increased discharge rate.

MP/AH-thermosensitive neurons can modulate arousal/activating systems located outside the BF. MP/AH warming (161) or electrical stimulation (136) has been shown to suppress activity in midbrain reticular formation neurons. A majority of neurons within the posterior lateral hypothalamus display maximum discharge rates in waking and REM sleep with diminished activity during sleep with EEG slow waves (162). Lesions in this region promote EEG synchrony and somnolence (58,59). MP/AH warming results in suppression of spontaneous and brainstem stimulation-evoked discharge in waking-related neurons recorded in the posterior lateral hypothalamus of cats (163). MP/AH inhibition of posterior hypothalamic arousal mechanisms appears to be functionally important in sleep–wake state control, as the insomnia produced by MP/AH lesions is acutely reversed following microinjection of the GABAergic agonist muscimol into the posterior lateral hypothalamus (164). Identified GA-

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active REM sleep were similar to waking rates. Abbreviations same as in Fig. 3D. Figure 4A and B from ref. 84. C. Increased discharge of BF sleep-related neurons is an early correlate of transitions from waking to nonREM sleep. Shown is the relationship of neuronal discharge to sleep onset for 22 BF sleep-related cells. For each cell, transitions from alert wakefulness to deep nonREM sleep were analyzed. The first high-amplitude 10–15-Hz cortical EEG spindle burst in the transition sequence was identified and is indicated as time zero (dashed line). Bars indicate the mean (±SEM) number of spikes occurring during each of the 30 seconds preceding and immediately following the initial sleep spindle. The average number of spikes occurring during 10 consecutive seconds of deep nonREM sleep beginning 120 seconds after the spindle burst is also shown. In this population of cells, discharge rate began to increase between 10 and 15 seconds prior to spindle onset, and reached a plateau about 3–4 seconds prior to spindle occurrence. Rates during the 30 seconds after the spindle were not consistently higher than those in the few seconds preceding it. However, rates were elevated during deep nonREM sleep at 120 seconds after spindle onset. Figure 4C from ref. 88.

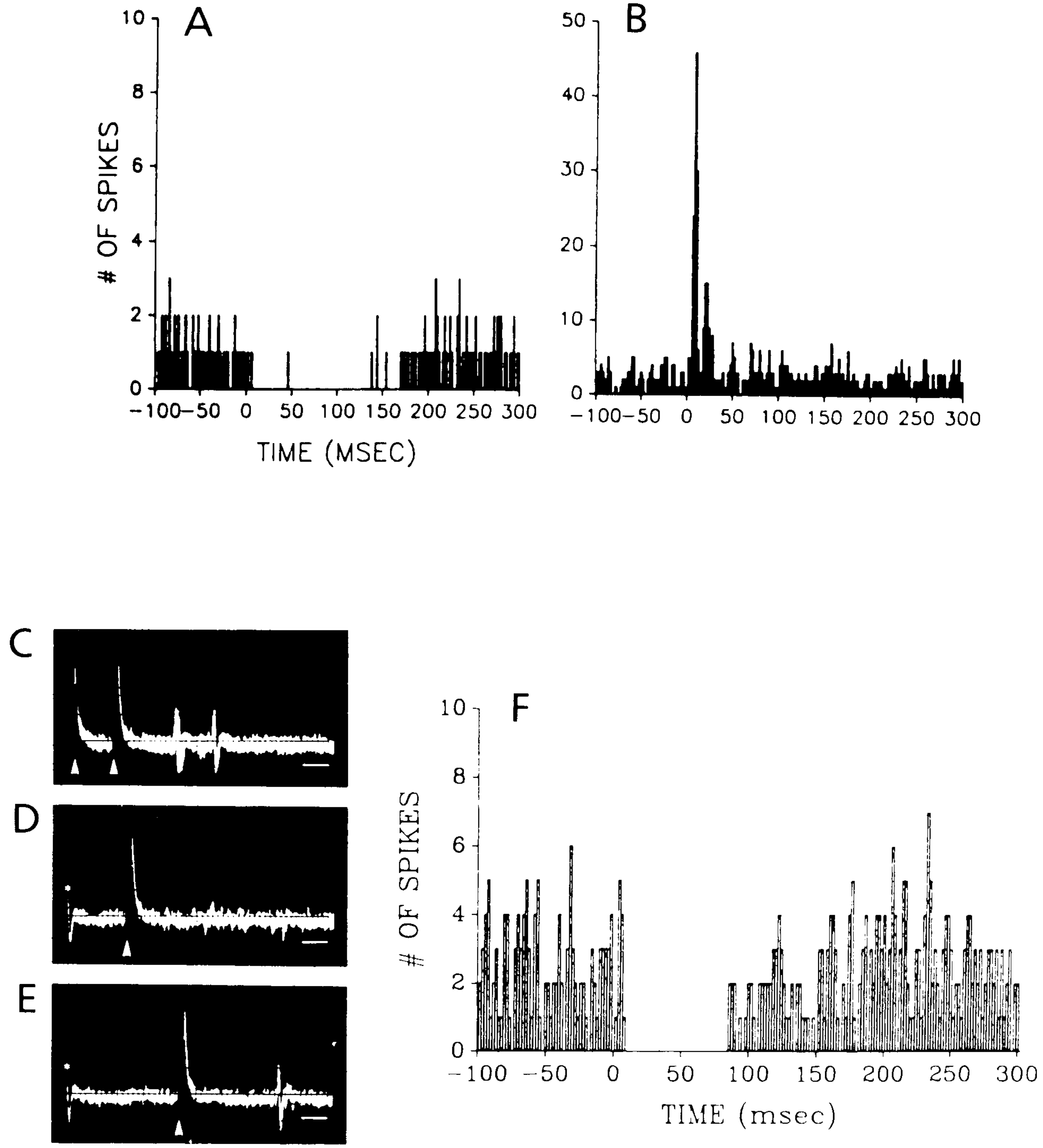

FIG. 5. A, B. BF sleep-related and waking-related cells exhibit qualitatively different responses following stimulation of the paramedian midbrain reticular formation (MRF). A. Low-intensity, single-pulse MRF stimulation (100 pulses of 0.2-millisecond duration delivered at a rate of 1 Hz) during nonREM sleep evoked suppression of discharge in a sleep-related neuron that lasted for > 150 milliseconds. Stimulation at the same site evoked short-latency excitation of the waking discharge in an identified cortically projecting, waking-related BF neuron. B. From ref. 85. C–F. Example of suppression of waking-related discharge in an MRF neuron in response to stimulation of the BF. C–E. This MRF cell was identified as projecting to the BF by antidromic activation. The evoked spike followed a high-frequency paired pulse (C) and collided with a spontaneous spike at short collision intervals (D), but not when the collision interval was longer than the antidromic latency (E). Calibration = 2 milliseconds. F. Peristimulus histogram of evoked orthodromic response in the same MRF cell, based on 100 BF stimulation pulses delivered during waking at a rate of 1 Hz. BF stimulation evoked suppression of waking discharge that lasted for approximately 70 seconds. The polarity of BF stimulation was reversed from that in C–E such that no antidromic response was elicited. Figure 5C–F from ref. 136.

BAergic monosynaptic projections from the MP/AH to the posterior lateral hypothalamus could mediate these inhibitory effects (49). The extent to which MP/AH GABAergic neurons are also thermosensitive is not known.

CHOLINERGIC-GABAERGIC INTERACTIONS IN THE BASAL FOREBRAIN AND THE REGULATION OF BEHAVIORAL STATE

This review of the behavioral state-regulating functions of the BF has summarized evidence for the coexistence of arousal- and sleep-regulating functions within magnocellular BF regions. The critically involved cell groups and what is known and/or hypothesized about the functional connections among them are summarized in Fig. 6.

The role of the magnocellular cholinergic system in arousal and activation is firmly established. One or more unidentified noncholinergic cell types are responsible for the sleep-promoting functions of the magnocellular BF, with GABAergic projection neurons being possible candidates for mediating descending inhibitory effects on hypothalamic and brainstem arousal systems. The functional roles of the ascending GABAergic projections to the thalamus and cortex have not been characterized, but sleep-promoting functions of the BF can be hypothesized to involve local circuit and projection GABAergic neurons. Magnocellular neurons subserving sleep and arousal functions overlap partially at rostral–ventral BF levels, particularly within portions of the HDB and MCP. Further caudally, in sub- and peripallidal areas, cortically projecting cholinergic neurons are more completely segregated from other magnocellular cell types. Thus, lesions centered in the HDB and MCP can cause insomnia (132,134), whereas lesions centered in the NB result in diminished EEG activation during wakefulness and REM sleep (8,75,77).

Cholinergic components of several mechanisms of cortical and limbic system activation have been identified, although noncholinergic cell types may participate in arousal-related processes as well. Activation of BF cholinergic neurons can be expected, via suppression of potassium channels, to diminish AHPs, promote tonic firing and render cortical neurons more responsive to afferent input (98). These features of pyramidal cell activation would function to generate the desynchronized EEG patterns characteristic of activated behavioral states. Indeed, results of neurotoxic lesions of the NB indicate that a tonic level of cortical ACh release appears to be necessary for maintenance of normal desynchronized EEG patterns of waking and REM sleep (8,75–77).

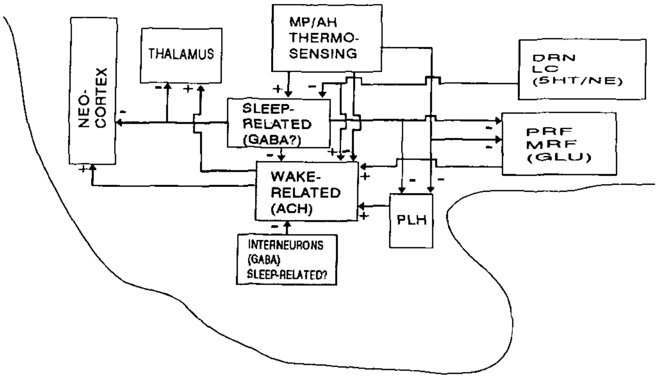

FIG. 6. Schematic representation of input–output relationships of BF state-regulating cell types. Schematic is shown within a horizontal hemisection of the rat brain to show approximate positions of cell types in the neuraxis. Rostral is to the left of the figure and medial is at the top. Cell groups located within the magnocellular BF are indicated by the shaded boxes. BF cholinergic neurons with waking-related discharge are shown as projecting to the thalamus and the neocortex, where they exert depolarizing effects on target neurons and promote arousal and activated EEG patterns. These BF cholinergic cells receive excitatory afferents from glutamatergic (GLU) neurons of the pontine and midbrain reticular formation (PRF and MRF), serotonergic (5HT) neurons of the dorsal raphe nucleus (DRN), noradrenergic (NE) cells of the locus ceruleus (LC) and posterior lateral hypothalamic (PLH) neurons. Inhibitory afferents to BF cholinergic, waking-related cells are hypothesized to arise from warm-sensing neurons of the MP/AH, BF sleep-related projection neurons and/or BF sleep-related interneurons. All three of these cell types are hypothesized to be GABAergic. Disfacilitation of BF cholinergic neurons could also arise from inhibitory effects of MP/AH and BF sleep-related neurons on the PRF, MRF and PLH. Not shown in this figure are excitatory afferents from brainstem cholinergic cell groups to noncholinergic, waking-related cells within the magnocellular BF. BF sleep-related cells are shown as sources of descending inhibitory influences on neurons in the PRF, MRF and PLH. They are also shown as hypothesized sources of inhibitory input to thalamus and neocortex that would act to promote synchronized EEG patterns in these structures during nonREM sleep. BF sleep-related cell types are further shown as receiving inhibitory inputs from brainstem arousal systems (those from the PRF and MRF are omitted in the figure for clarity of other connections), and excitatory inputs from MP/AH thermosensing neurons.

The activity of BF cholinergic neurons and the rate of cortical ACh release are modulated within the waking state (73–75,85,108,109), consistent with hypothesized roles in striatopallidal-related aspects of motor control and in cognitive functioning. The BF cholinergic input to the cortex appears to participate in attentional processes by selectively augmenting cortical processing of particular stimuli. Both direct cortical ACh administration and NB electrical stimulation enhance sensory stimulation-evoked responses in the corresponding cortical region (99–105). In addition to these neuronal responses, ACh-mediated vasodilation can augment regional cortical perfusion to meet enhanced metabolic demands (71). Sensory modality-specific or contingency-specific regional cortical activation can be achieved through excitation of subpopulations of BF cholinergic neurons via sensory collaterals (107), and/or conditioning-dependent activation of these neurons by stimuli or contingencies associated with reward (108,109).

The synaptic mechanisms that underlie the learned contingency-dependent aspects of BF cholinergic activation remain to be determined, but ascending inputs from brainstem-activating systems are likely to regulate tonic aspects of BF cholinergic excitability. These would include direct serotonergic, noradrenergic and glutamatergic afferents. Brainstem cholinergic afferents to the BF appear to influence primarily noncholinergic arousal-regulating mechanisms. Because these brainstem cell groups all undergo spontaneous decreases in neuronal discharge during transitions from wakefulness to sleep (165), withdrawal of brainstem-activating inputs could be an important determinant of state-dependent excitability changes in BF waking-related neurons. This would be analogous to the situation in thalamocortical relay neurons where these same brainstem systems exert tonic activating influences (51,166). The demonstration of I_t in identified BF cholinergic neurons studied in vitro (114,115), and the evidence for tonic firing in waking and nonREM sleep-related burst firing in putative BF cholinergic neurons in vivo (83,123), suggests further parallels with the thalamocortical system.

This review has emphasized cholinergic influences on the neocortex, but similar mechanisms could function in other targets of the BF cholinergic system. Cholinergic input to the hippocampus originates in the MS and VDB. The generation of activated EEG patterns within the hippocampus (hippocampal theta) is dependent upon this cholinergic input, and the hippocampal EEG is modulated by stimulation of brainstem afferents to the MS and VDB (54).

The cholinergic component of the BF projection to the thalamus is also of potential functional importance. Identified neurons in the pathway have not, to date, been studied across sleep–waking cycles. However, if discharge patterns of BF-thalamic projection neurons are similar to those of cortically projecting BF waking-related neurons, they could function to promote tonic firing and facilitate sensory transmission through the thalamus to the cortex during wakefulness.

Although the evidence for a sleep-promoting mechanism within the magnocellular BF is equally compelling, less is known about the cell types involved. The functional anatomy of ventral telencephalic sleep-promoting systems is further complicated by the important involvement of the MP/AH. Within the magnocellular BF, stimulation, lesion and unit-recording studies point to the HDB, MCP and rostro-ventral SI as sites where the sleep-promoting mechanisms can be most reliably manipulated. Among other cell types, these areas contain high concentrations of GABAergic neurons (41). Although many of these GABA-containing cells are interneurons, others have been identified as the source of ascending and descending projections (13,15,16,26,45,49). The descending GABAergic projection is of particular interest, as descending inhibitory effects appear to be a functionally important aspect of the BF hypnogenic system (135–137,163). A GABAergic projection to the posterior lateral hypothalamus has been identified (49). The extent to which noncholinergic projections from the magnocellular BF to mesencephalic and pontine arousal-related areas are GABAergic remains to be determined.

GABAergic neurons within the MP/AH can be hypothesized to mediate the sleep-promoting functions of this area as well. As previously indicated, identified GABAergic neurons that project to the posterior hypothalamus can be localized to the MP/AH (49). Local activation of MP/AH warm-responsive neurons results in short latency suppression of waking discharge in posterior lateral hypothalamic neurons (163). In cats with insomnia secondary to neurotoxin-induced MP/AH cell loss, microinjection of GABAergic agonists into the posterior hypothalamus restores sleep (164). Extracellular concentration of GABA within the posterior lateral hypothalamus of adult cats, sampled with in vivo microdialysis techniques, is significantly elevated during nonREM sleep compared to both waking and REM sleep (167). These findings suggest that descending GABAergic projections constitutes a mechanism via which the rostro-ventral magnocellular BF and MP/AH inhibit posterior hypothalamic arousal mechanisms and exert sleep-promoting actions (49,163).

The evidence for a descending action of the BF hypnogenic mechanism is most extensive, but ascending projections may also play a role. A restricted number of thalamic nuclei receive a projection from the magnocellular BF and MP/AH (23,24). This projection contains cholinergic and noncholinergic neurons, and has a GABAergic component (26). The proportion of this projection that is GABAergic is not known, nor has the state-dependent discharge pattern of cells in this projection been characterized. Nevertheless, such a projection could represent an additional source of sleep-related inhibition on thalamocortical neurons within the anteromedial/dorsomedial nuclei, and to the thalamic reticular nucleus. Depolarization of neurons in the thalamic reticular nucleus by microinjection of glutamate has been recently shown to suppress sleeplike rhythmic oscillatory discharge patterns in both the reticular nucleus and in the corresponding relay nucleus (168). Electrical stimulation of subpallidal portions of the BF evoked primarily inhibitory postsynaptic potentials in the thalamic reticular nucleus of anesthetized rats (169). GABA-mediated hyperpolarizations originating from BF and MP/AH neurons might then be expected to promote oscillatory burst firing in these nuclei during transitions from waking to sleep.

A subset of GABAergic neurons within the magnocellular BF project directly to the neocortex (16,45,46). A subset of sleep-related neurons recorded in the BF of cats has been identified as cortically projecting (85), although identification of such cells as GABAergic is not possible in the context of extracellular recording studies in intact animals. The functional role of the BF–cortical GABAergic projection is not well characterized. Anatomical studies indicate that terminals of BF GABAergic cells contact primarily GABAergic interneurons within the neocortex (46). This suggests that activation of this projection would produce cortical disinhibition, an effect that might be expected to yield cortical activation. However, in cortical slice preparations studied in vitro, drugs that moderately suppress GABA-mediated inhibition, presumably arising solely from interneurons in this preparation, produce enhanced synchronous burst firing in local cortical circuits (170). The extent to which such a mechanism could contribute to cortical synchronization during natural sleep in the intact brain remains to be determined.

In addition to interactions between BF cholinergic and noncholinergic projection neurons at brainstem, diencephalic, limbic system and neocortical targets, local GABAergic–cholinergic interactions within the BF are of potential functional importance for behavioral state control. As in thalamic relay neurons, diminished excitability and expression of high-frequency burst firing patterns during natural sleep in BF cholinergic neurons would depend on membrane hyperpolarization (27,120). This could be achieved via reductions in tonic brainstem depolarizing inputs, and through increased GABA-mediated inhibition. Both mechanisms are important in the thalamus.

Anatomical and physiological evidence supports hypothesized inhibitory GABAergic influences on BF cholinergic neurons. Cortically projecting BF cholinergic neurons are contacted by significant numbers of GABA-containing nerve terminals (171,172). Sources of GABAergic input to BF cholinergic neurons include local interneurons, axon collaterals of magnocellular GABAergic projection neurons, the MP/AH and the nucleus accumbens (1). Cortical ACh release in rats (173,174), cortical ACh turnover in guinea pigs (175) and high-affinity choline uptake in rat cortical tissue (176) are reduced following microinjections of GABA or GABA-A receptor agonists into SI/NB regions of the BF. In rats, unilateral infusion of GABA into the NB acutely reduced ipsilateral turning in a radial arm maze (177). Bilateral microinjections of the GABA-A receptor antagonist bicuculline into the SI of rats enhanced motor activity, and injections of the GABA-A receptor agonist muscimol into the same sites suppressed locomotion in rats (178). Muscimol microinjections into the SI attenuated increased locomotor activity evoked by local infusion of a quisqualic acid receptor agonist (179). In rats, SI microinjection of muscimol caused a dose-dependent impairment in performance of a visual discrimination task (180). Effects of muscimol on performance were partially antagonized by administration of physostigmine.

Due to the difficulty in determining the neurochemical identity of recorded cells during in vivo neurophysiological recordings, the state-dependent activity profiles of the GABAergic innervation of BF cholinergic cell groups are not known. As reviewed above, neurons with sleep-related discharge profiles are found in comparative abundance both within the magnocellular BF and the MP/AH. In addition, inhibitory effects on putative BF cholinergic neurons are seen in response to activation of MP/AH warm-sensing neurons by local warming (62). MP/AH thermoresponsive cell types display spontaneous changes in activity during normal wake-to-sleep transitions that are identical to those evoked by warming (150). Therefore, it seems reasonable to hypothesize that GABA-mediated inhibition from one or more of these ventral telencephalic sources participate in modulating the state-dependent excitability of the BF cholinergic projection system. This could constitute an additional mechanism through which GABAergic neurons in the magnocellular BF and MP/AH exert control over somatomotor and cortical activation, and function to promote sleep onset and nonREM sleep.

CONCLUDING REMARKS

The explosion of research on the neurobiology of the BF within the past decade has been fueled by the discovery of the cholinergic system and the recognition of its vulnerability in human neurodegenerative disorders such as Alzheimer's disease. As a result, considerable detail about the anatomy and cellular biology of this brain region is now known. This progress has been of substantial benefit to the field of sleep research. A critical forebrain arousal system has been identified and partially characterized. Possible cellular mechanisms responsible for the BF hypnogenic actions are better defined.

Future progress will depend, in part, on the ability to reliably identify BF cells recorded during natural sleep–waking states by transmitter phenotype, sources of afferent control and efferent targets. In this regard, in vitro studies of BF tissue are likely to be of critical importance. Only such studies can specify intrinsic properties and detail the neuropharmacology of identified cell types. This information can then be extrapolated to the characterization of cells recorded in the intact brain. A syncrgism among in vitro and in vivo approaches has been crucial to the recent advances in understanding the state-dependent neurobiology of thalamocortical systems (see 27 for review). This approach appears to hold equal promise for characterizing the ventral forebrain regulation of normal and disordered sleep.

Acknowledgements: The author thanks Drs. Dennis McGinty and Joel Benington for helpful comments on a previous version of this manuscript. This work was supported by the Medical Research Service of the Department of Veterans Affairs.

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