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State of the Art Review

Contributions of the Pedunculopontine Region to Normal and Altered REM Sleep

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Summary: The pedunculopontine (PPN) region of the upper brainstem is recognized as a critical modulator of activated behavioral states such as wakefulness and rapid eye movement (REM) sleep. The expression of REM sleep-related physiology (e.g. thalamocortical arousal, ponto-geniculate-occipital (PGO) waves, and atonia) depends upon a subpopulation of PPN neurons that release acetylcholine (ACh) to act upon muscarinic receptors (mAChRs). Serotonin's potent hyperpolarization of cholinergic PPN neurons is central to present working models of REM sleep control. A growing body of experimental evidence and clinical experience suggests that the responsiveness of the PPN region, and thereby modulation of REM sleep, involves closely adjacent glutamatergic neurons and alternate afferent neurotransmitters. Although many of these afferents are yet to be defined, dopamine-sensitive GABAergic pathways exiting the main output nuclei of the basal ganglia and adjacent forebrain nuclei appear to be the most conspicuous and the most likely to be clinically relevant. These GABAergic pathways are ideally suited to modulate the physiologic hallmarks of REM sleep differentially (e.g. atonia versus cortical activation), because each originates from a functionally unique forebrain circuit and terminates in a unique pattern upon brain stem neurons with unique membrane characteristics. Evidence is reviewed that changes in the quality, timing, and quantity of REM sleep that characterize narcolepsy, REM sleep behavior disorder, and neurodegenerative and affective disorders (depression and schizophrenia) reflect 1) changes in responsiveness of cells in the PPN region governed by these afferents; 2) increase or decrease in PPN cell number; or 3) mAChRs mediating increased responsiveness to ACh derived from the PPN. Auditory evoked potentials and acoustic startle responses provide means independent from recording sleep to assess pathophysiologies affecting the PPN and its connections and thereby complement investigations of their role in affecting daytime functions (e.g. arousal and attention). **Key Words:** Acetylcholine—Muscarinic receptors—Midbrain extrapyramidal area—Basal ganglia—Retrorubral field—Narcolepsy—REM sleep behavior disorder—Neurodegenerative disease—Schizophrenia—Auditory evoked potentials—Acoustic startle.

1.0 HISTORICAL BACKGROUND

Clinicians have long been aware that the neurobiological substrates that govern basic aspects of sleep–wake rhythms are located within subcortical brain structures. The curious "sleepy sickness" attending the encephalitis epidemic of 1917–1926 was the seminal event that precipitated searches within the brainstem for the organic bases of a panoply of neuropsychiatric illnesses, including many in which pathological sleep was a principal symptom. It was quickly recognized in the decades following that cortical excitability and behavioral "arousal" (viz, wakefulness) are modulated by an ascending reticular activating system (ARAS) that originates, at least in part, from the upper brainstem (1). The clinicopathophysiological significance of the ARAS was not immediately realized because its neural and pharmacological substrates could not be precisely defined. Anatomical information on the brainstem "reticular core" at the time, for example, emphasized its homogeneity and relative lack of discernible boundaries (2,3). Moreover, postulates that sleep reflected passive cessation of activity within the ARAS could not be easily reconciled with the realization in the late 1950s and early 1960s that sleep was an active process characterized by several stages with unique physiological characteristics. The discovery of a behavioral state in which cortical excitability did not coincide with generalized behav-

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ioral arousal, i.e. rapid eye movement (REM) sleep, in particular, challenged concepts of a monolithic ARAS as exemplified in REM sleep's alternate descriptor, "paradoxical" sleep. The nearly simultaneous discovery that the clinical condition of narcolepsy is characterized by the pathological expression of REM sleep or its individual components (e.g. atonia in the form of cataplexy) (4–6) provided primary motivation for much of the research that followed. As such, the "aroused", yet atonic state of REM sleep has been the predominant window through which much of our present knowledge of brainstem substrates of behavioral state control derives. In this regard, the reciprocal interaction model of REM sleep generation originally proposed by Hobson et al. (7) has been, and still remains, of immense heuristic value (8).

The key elements of the reciprocal interaction model hypothesize that REM sleep is modulated by reciprocal and opposite actions between acetylcholine- and monoamine-containing brainstem nuclei. Expression of REM sleep was originally postulated to result from cholinergic medial pontine reticular formation (mPRF) neuronal activity and/or cessation of activity in the serotonergic dorsal raphe (DR) and noradrenergic locus coeruleus (LC). The past 10 years have witnessed anatomical and physiological verification of this model with some minor, yet significant, modifications. It is now well established that the pedunculopontine (PPN) and laterodorsal tegmental (LDT) nuclei within the dorsolateral aspect of the midbrain-pontine junction, rather than intrinsic mPRF neurons, are the primary source of acetylcholine in subcortical circuits. PPN/LDT pathways to the thalamus, the PRF, and the ventromedial medullary reticular formation govern the cortical arousal, pontine-geniculate-occipital (PGO) waves, and muscle atonia that together define REM sleep.

Ascending and descending cholinergic pathways originating from the PPN/LDT are therefore viewed as composing the final common pathway for the expression of REM sleep. Particular interest has been devoted to their potential role in the pathophysiology of diseases in which the quality and/or quantity of REM sleep is perturbed, including narcolepsy/cataplexy, REM sleep behavior disorder (RBD), depression, and schizophrenia. Nonetheless, a coherent synthesis of the governance of normal and pathological REM sleep by the PPN/LDT has not emerged. Pathological alterations intrinsic to the PPN/LDT (e.g. increased or decreased cell number), disorganization of its output (i.e. efferent) pathways, and altered postsynaptic responses at muscarinic receptors in brain regions targeted by these efferents have all been proferred as substrates for disease-specific alterations in REM sleep. Potential modulation of normal and pathological REM sleep by brain regions that determine the responsiveness of the PPN/LDT has been less well studied. Difficulties in simultaneously defining the precise targets of inputs to the PPN/LDT region and efferent trajectories taken by the neurons so targeted have significantly hampered progress in this regard. Moreover, because inputs (i.e. afferents) from many disparate forebrain nuclei have been suggested, and their functional roles in aspects of behaviors occupying wakefulness emphasized, it has been difficult to extrapolate these findings to sleep and, specifically, REM sleep. The major output nuclei of the basal ganglia [i.e. the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr)] are a principal example of a forebrain afferent system of the PPN/LDT region that upon continued investigation is likely to impact significantly upon our understanding of aspects of normal and pathological behavioral state control. This belief is founded on two considerations: 1) cortico-striatal and related circuits intrinsic to the basal ganglia appear to be critical elements in the pathophysiology of human conditions in which behavioral state alterations are an important symptom, including Parkinson's disease, schizophrenia, obsessive-compulsive disorder, attention deficit disorder, and Tourette's syndrome; and 2) a principal target of the main output nuclei of the basal ganglia is the PPN/LDT region.

The major goal of this review is to coalesce recent work from disparate neuroscience disciplines and construct a framework for elucidating the PPN/LDT's role in normal and pathological behaviors in which state control is a prominent feature. Evidence will be reviewed that suggests that, at present, at least two discernible functional/anatomical substrates exist within the PPN/LDT region: the PPN/LDT proper, which coordinates "global" aspects of behavior with a particular role in promoting states characterized by cortical activation (e.g. wakefulness or REM sleep); and the midbrain extrapyramidal area (MEA), which appears devoted to affecting movement in a manner commensurate with behavioral state. A third, less well-defined region dorsal to the MEA and PPN (e.g. the retrorubral field and nucleus subcuneiformis) appears best suited to modulating behaviors traditionally defined within the limbic sphere. These three regions are neurochemically and connectionally distinct, but it should be recognized that they coexist in a relatively small brainstem area where extensive convergence of inputs and local interconnections are likely to exist. First, the anatomy and physiology of the PPN/LDT region will be reviewed as it relates to the three putative "functional" regions outlined above. Second, I will review how these regions may participate in several clinical syndromes in which sleep, and particulary REM sleep, are primarily affected, including narcolepsy, RBD,

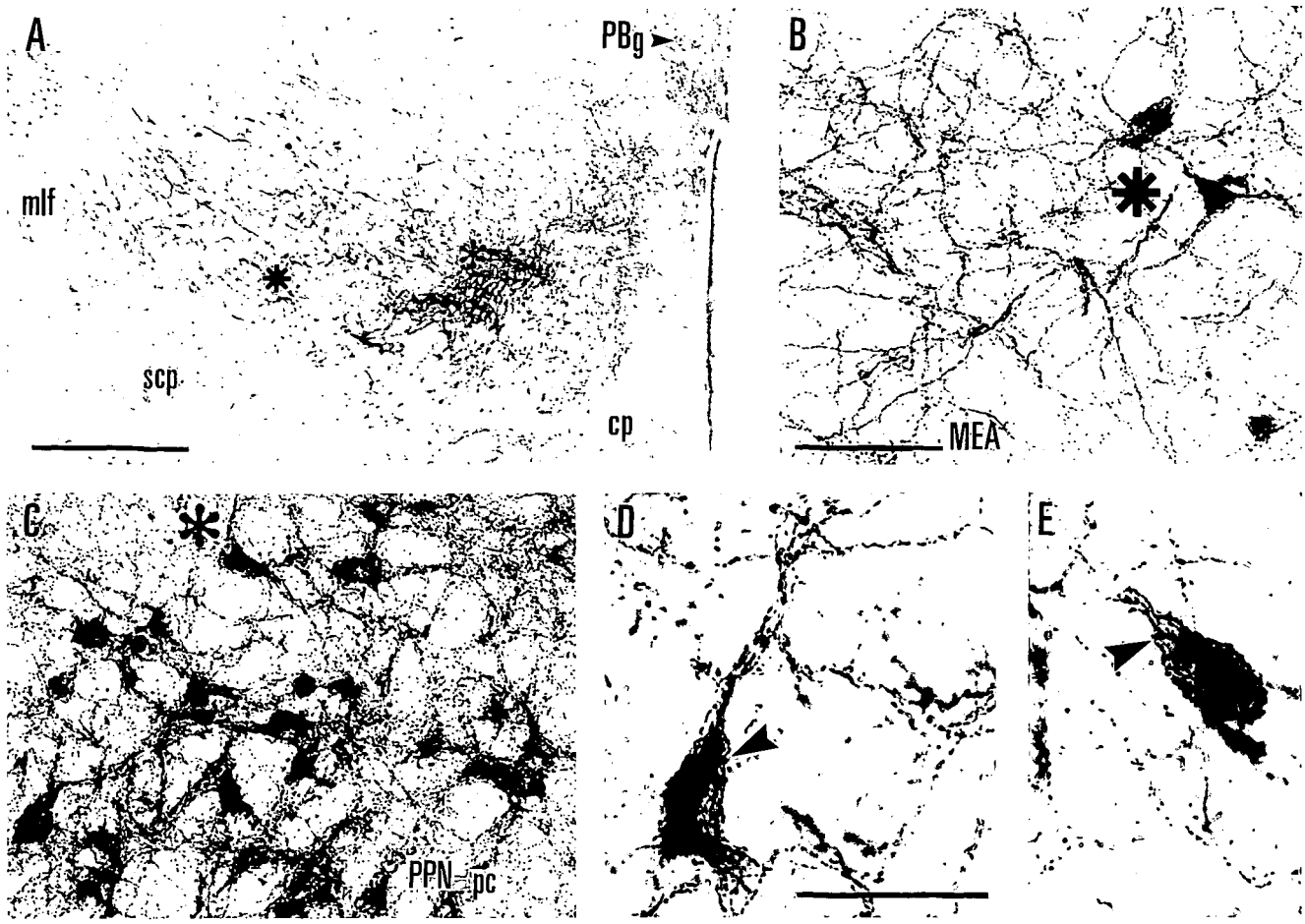
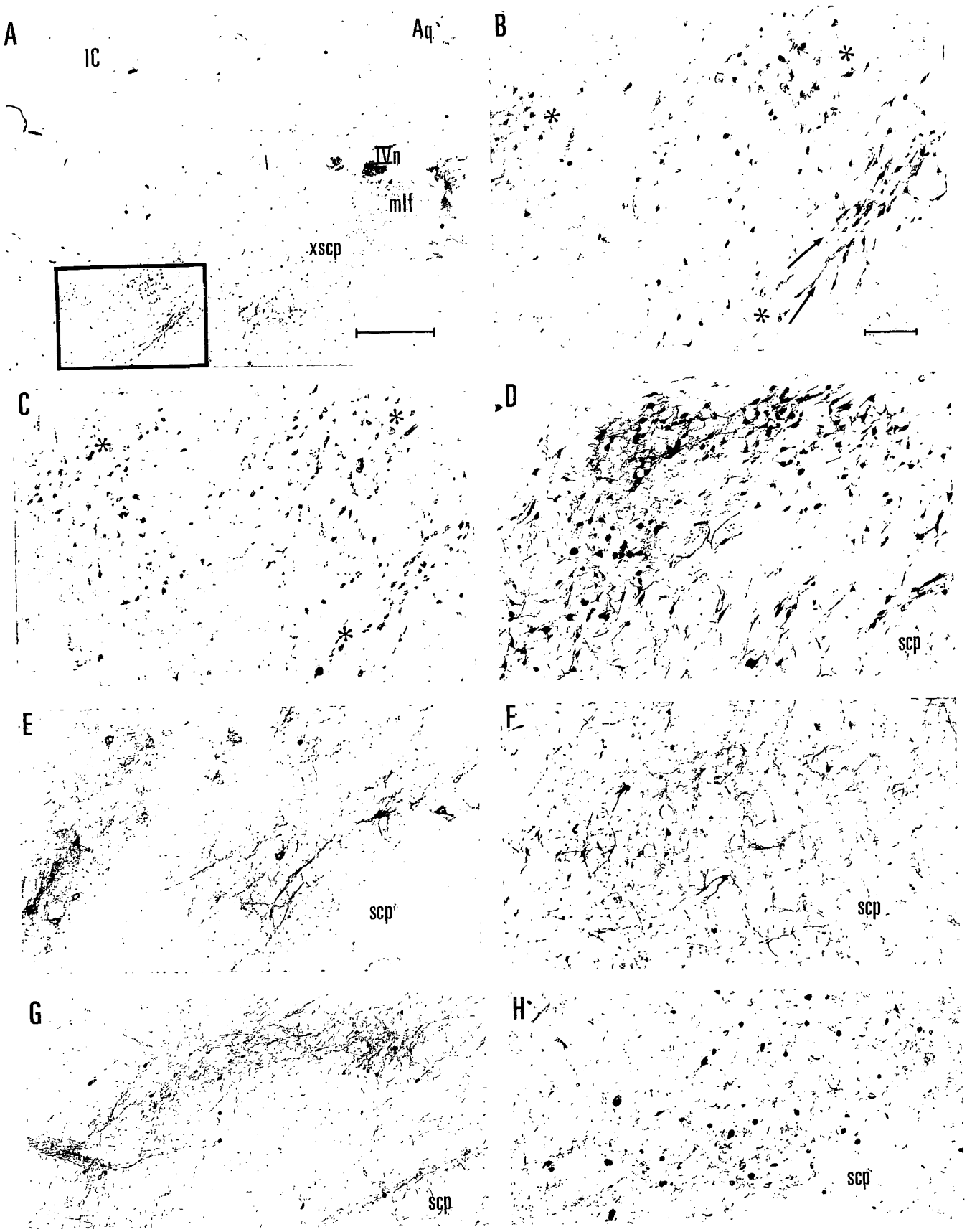


FIG. 1. Photomicrograph demonstration of the vesicular acetylcholine transporter (vAChT) in the nonhuman primate midbrain extrapyramidal area (MEA) (B) and adjacent pedunculopontine (PPN) region (C). Asterisks in B and C correlate to that in A. Cholinergic PPN somata and presumptive terminals are readily demonstrated, appearing more dense and perisomatic (arrowheads in D and E) in the PPN pars compacta (PPN-pc) (C) than in the adjacent MEA (B), where noncholinergic cells predominate. Calibration bars: A = 1 mm; B and C = 100 μm; D and E = 50 μm. Abbreviations: cp, cerebral peduncle; mlf, medial longitudinal fasciculus; PBg, parabigeminal nucleus; scp, superior cerebellar peduncle.

neurodegenerative conditions, and affective illness. Finally, I will briefly review a growing body of literature that describes several simple electrophysiological measures that aim to assess the integrity of the PPN/LDT region and its connections. Application of such technologies between the laboratory and clinic have the potential to complement and foster a growing appreciation of the clinical relevance of the PPN/LDT region.

2.0 ANATOMICAL CONSIDERATIONS

In accordance with the original definition of the PPN recognized in the human by Jacobsohn (9), the subprimate and nonhuman primate equivalents correspond to a conspicuous collection of magnocellular, cholinergic neurons (10–12) (Fig. 1). Neurons extend from the caudal pole of the substantia nigra to a rostral pontine level, and caudal to the trochlear nucleus are densely clustered lateral to the ascending limb of the superior cerebellar peduncle [e.g. the pars compacta of the nucleus (PPN-pc)]. Neurons in the most caudal aspect of the PPN occupy a "subceruleal" position and merge imperceptibly with the laterodorsal tegmental nucleus (LDT) located dorsally, within the central grey. Following the convention of Olzsewski and Baxter (13,14) in the human, other investigators include both cholinergic and noncholinergic neurons within the PPN and recognize two divisions: a more diffuse pars dissipata (PPN-d) located rostrally and medially, and a more cell-dense PPN-pc situated dorsolaterally in the caudal half of the nucleus. Defined in this manner, cholinergic neurons account for only 50% of all neurons contained within the PPN (10–12). Approximately 40% of all PPN neurons are located in the PPN-pc, with cholinergic neurons making up approximately 90% of the neuronal population present in the surrounding neuropil. Cholinergic neurons compose



25–50% of the neuronal population within the PPN-d (11,12). Combined, the total number of cholinergic cells in the PPN/LDT of each hemisphere approximates 2,200 in the rat (12) and 18,000 in the cat (15) and therefore is somewhat larger than the adjacent locus coeruleus. The PPN/LDT is estimated to constitute 16,000 neurons in the dog (personal observations) and ~20,0000 neurons in humans (16,17). The cytoplasm of these neurons is remarkably rich in free ribosomes, rough and smooth endoplasmic reticulum, golgi apparatus, and mitochondria, thus accounting for their dark appearance in Nissl stained material (12). These neurons are distinguishable on the basis of their expressing proteins associated with their employing acetylcholine (ACh) as a neurotransmitter such as choline acetyltransferase (ChAT, the synthetic enzyme for acetylcholine) and the vesicular acetylcholine transporter (vAChT) (Figs. 1 and 2A and B), and all also contain atriopeptin (i.e. atrial natriuretic peptide) (18). A multitude of additional enzymes, peptides, and neurotransmitters are expressed in varying subpopulations of these same neurons, including NADPH-diaphorase [i.e. nitric oxide synthase (NOS) (Fig. 2D) (19,20)], corticotropin-releasing factor (CRF) (Fig. 2C) (19,21), substance P (18,19), and glutamate (22–24). Histochemical visualization of NADPH-diaphorase is widely employed as a surrogate marker for the PPN/LDT beacuse it is simple to perform, yet its sensitivity and specificity in revealing cholinergic neurons have not been rigorously established. Cholinergic neurons within the PPN/LDT exhibit extensive dendritic domains, few dendritic spines, and divergent projections to widespread telencephalic, diencephalic, and rhombencephalic structures [reviewed in (25)]. Axons of individual cholinergic neurons branch extensively and therefore can simultaneously engage two functionally distinct brain regions such as the reticular thalamus and cortex (26), the reticular thalamus and "specific" thalamic relay nuclei (27), the centrolateral thalamic nucleus and lateral geniculate (28), and the "nonspecific" midline thalamic nuclei and pontine reticular formation (PRF) (29). Elegant morphologic studies of physiologically identified and intracellularly labeled LDT neurons have more recently confirmed the existence of local terminal plexus that may underly potent recurrent inhibition (30). These morphological features bring to mind the prototypical neuron of the brainstem's isodendritic reticular core originally envisioned as the essential neural substrate of the ARAS (2,3,31). Cholinergic PPN neurons and processes also exhibit intimate relationships with penetrating blood vessels that are most obvious in human brain (see arrows, Fig. 2B), suggesting potential important regulation of cerebral blood flow through the release of nitric oxide and acetylcholine. Perivascular termination of cholinergic axons has recently been demonstrated (32), and acetylcholine is well known to promote endothelium-dependent relaxation of cerebral blood vessels via a receptor with M2-like binding properties (33–35). Together with the physiological data to be presented below, these anatomical features are compatible with the view that the cholinergic PPN/LDT, like the brainstem dorsal raphe and locus coeruleus, is uniquely suited to coordinate thalamocortical processing and global aspects of behavioral state control (8,36).

Cholinergic PPN/LDT cells are commingled with smaller noncholinergic cells and are closely apposed to several other functionally distinct noncholinergic nuclei and fiber tracts. These features have made precise anatomical boundaries difficult to define, thereby hampering development of concensus terminologies for different cell groups in the region. This issue is of considerable practical importance when interpreting connectional, physiological, and activation/inactivation studies of the PPN/LDT region, because anatomical tracers, extracellular electrodes, and pharmacologics cannot be confined solely to the cholinergic subpopulation. Cytoarchitectural, cytochemical, and connectional analyses together are beginning to attribute heretofore unrecognized organizational features to

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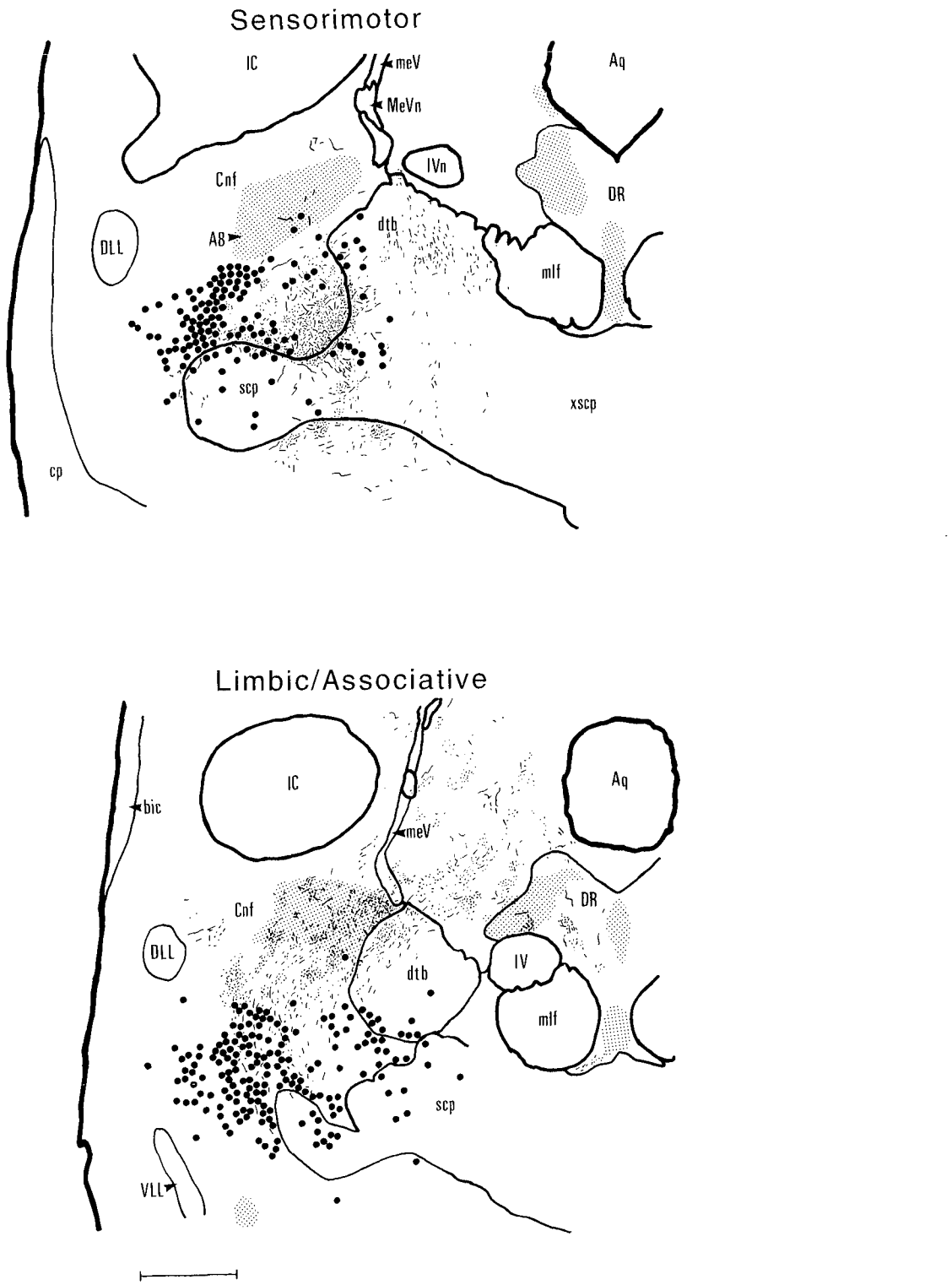
FIG. 2. Photomicrographs illustrating various neurochemical markers within the pedunculopontine (PPN) region in postmortem human brain from neurologically unaffected individuals (A–E) and those suffering from Parkinson's disease (F), Alzheimer's disease (G), and progressive supranuclear palsy (H). (A) Low-power magnification illustrating the relative position of cholinergic PPN cell bodies within the dorsolateral midbrain pontine tegmentum. The box delimits a field that is shown at higher magnification in B. (B) Higher magnification of cholinergic PPN cell bodies. The close apposition of clusters of cholinergic neurons to a penetrating blood vessel (arrows) suggests potential modulation of regional blood flow but has not been systematically studied. (C) Tissue section nearly adjacent to that in B, demonstrating the close correspondence between neurons positive for CRF-like immunoreactivity and cholinergic PPN neurons (asterisks correlate with same in B). (D) NADPH-diaphorase-positive neurons in a section ~1 mm caudal to those in B and C, demonstrating their close correspondence to cholinergic PPN perikarya. (E) A smaller contingent of cholinergic neurons in the human brain exhibit immunoreactivity for the m2 molecular receptor subtype, as demonstrated here (compare with B–D). (F) Marked loss of staining of NADPH-diaphorase-positive, presumptively cholinergic, neurons in the PPN region occurs in some cases of Parkinson's disease, as illustrated here (compare with D). (G) Selective involvement of cholinergic PPN neurons by the neurofibrillary tangle pathology of Alzheimer's disease occurs in many cases, as demonstrated here. (H) Involvement of neurons and astrocytes within the PPN region by the neurofibrillary tangle pathology of progressive supranuclear palsy is nearly universally observed and relatively nonselective, as illustrated here. Calibration bar in A = 1 mm; B–H = 250 μm. Abbreviations: Aq, cerebral aqueduct; IC, inferior colliculus; IVn, trochlear nerve; mlf, medial longitudinal fasciculus; scp, superior cerebellar peduncle; xscp, decussation of the superior cerebellar peduncle.



unique neuron subpopulations within the PPN/LDT region. Noncholinergic neurons juxtaposed to and admixed with cholinergic tegmental neurons are morphologically and connectionally heterogeneous. These subpopulations have not been the focus of rigorous analyses; yet, when compared with cholinergic neurons several general morphological differences are apparent: 1) these neurons are generally smaller (12,37); 2) remarkably fewer individual neurons innervate widely divergent targets (26–29); and 3) noncholinergic neurons have more somatic inputs (37). The most readily distinguishable population of noncholinergic neurons is contained largely within the traditional boundaries of the PPN-d. A majority (~70%) of these neurons are glutamatergic (22–24,38) and exhibit a restricted pattern of reciprocal connectivity with the basal ganglia and, as such, have been designated the midbrain extrapyramidal area (MEA) (see Figs. 1 and 3) (12,39,40). Because this cell population is to a great degree spatially, connectionally, morphologically, and neurochemically distinct from tegmental cholinergic neurons, we and others (41,42) prefer the MEA/PPN terminology [the Paxinos and Watson rat atlas (43) delineates a "subpeduncular tegmental nucleus" that conforms in all respects to the MEA]. The MEA/PPN convention emphasizes that the cholinergic cell population is not the focus of extrapyramidal connectivity in subprimates. Our recent findings in monkeys (44,45) and humans (45,46) further demonstrate this dichotomy and have been independently confirmed (47) (see below). Additional neuronal types contained within the traditional boundaries of the PPN include a small group of GABAergic interneurons (48,49) and noncholinergic neurons exhibiting projections to the thalamic midline, intralaminar and reticular nuclei (50,51), and pontine and medullary reticular fields (52). The dorsal border of the MEA/PPN is defined by the retrorubral field (RRF) and nucleus subcuneiformis, which are morphologically and neurochemically heterogeneous and relatively cell sparse. One small subpopulation of neurons in the RRF is dopaminergic and conforms to a cell group originally designated A8 by Dahlstrom and Fuxe (53). In the human, a portion of this dopaminergic population had been included within the borders of the PPN (13,14); however, its afferent and efferent connections are intimately focused upon limbic/associative brain regions, and therefore it is appropriately considered separately from the MEA and PPN. In their caudal subceruleal position, noradrenergic neurons extending ventrally from the locus ceruleus interdigitate with the MEA/PPN, most prominently in the feline (49,54). The heterogeneity of neurons contained within or surrounding the traditional boundaries of the PPN is also manifest in the diversity of their physiological responses as determined by stimulation of nigral afferents (55), behavioral state changes (36), and REM sleep-specific events such as ponto-geniculate-occipital (i.e. PGO) waves (56) (see below).

2.1 Output (i.e. efferent) pathways

2.1.1 PPN/LDT (acetylcholine ± glutamate)

The cholinergic PPN/LDT innervates widespread regions of the central nervous system. Ascending axons course to the caudal thalamus where they diverge into a dorsal division that innervates the entire thalamus and a ventral branch that ascends parallel to the medial forebrain bundle and diffusely innervates the ventral forebrain and adjacent nuclei (12,57). Outputs of the PPN/LDT generally course in parallel and terminate in the same regions; however, the LDT comprises a greater proportion of those directed toward "limbic"-related structures such as the anterior, laterodorsal and mediodorsal thalamic nuclei (50), the rostral "limbic"-related thalamic reticular nucleus (27), and the ventral tegmental area (58). Descending PPN/LDT axons innervate the pontine reticular formation and course through Probst's tract in the dorsolateral tegmentum. At the pontomedullary junction this pathway diverges and diffusely innervates the medullary

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FIG. 3. Camera lucida drawings depicting anterogradely labeled pallidotegmental axons (black stippling) and their relationship to several neurochemically defined cell populations at an anterior-posterior level of the mesopontine tegmentum, just caudal to the trochlear nucleus (IV) in the nonhuman primate brain. Pallidotegmental axons emanating from the sensorimotor pallidum remain largely medial to cholinergic neurons (black dots) that constitute the midpeduncular pontine (PPN) region and ventral to the dopaminergic A8 cell group (uniform shading). Additional axonal labeling, even more dorsally in the dorsal tegmental bundle (dtb), likely reflects labeling of axons of passage. The termination of pallidotegmental axons therefore corresponds to the "nucleus subcuneiformis" and PPN pars dissipatus, as described in the human brain stem by Olszewski and Baxter (14). In contrast, pallidotegmental axons emanating from the limbic and associative pallidum are located even more dorsally with respect to cholinergic PPN cell bodies within the "nucleus subcuneiformis" and the dopaminergic A8 cell group in the retrorubral field (uniform shading). The terminal pattern is also more widespread than for sensorimotor pallidotegmental axons in reaching the periaqueductal grey and dorsal raphe. Calibration bar = 1 mm. Abbreviations: Aq, cerebral aqueduct; bic, brachium of the inferior colliculus; Cnf, cuneiform nucleus; cp, cerebral peduncle; DLL, dorsal nucleus of the lateral lemnsicus; DR, dorsal raphe; dtb, dorsal tegmental bundle; IC, inferior colliculus; III, oculomotor nucleus; IV, trochlear nucleus; IVn, trochlear nerve; meV, mesencephalic tract of the trigeminal nerve; MeV, mesencephalic trigeminal nucleus; ml, medial lemniscus; mlf, medial longitudinal fasciculus; NBIC, nucleus of the brachium of the inferior colliculus; PBg, parabigeminal nucleus; SC, superior colliculus; scp, superior cerebellar peduncle; VLL, ventral nucleus of the lateral lemniscus; xscp, decussation of the superior cerebellar peduncle.

reticular formation (52). The primary target of brainstem cholinergic neurons is the thalamus with the highest terminal field densities in the anteroventral, reticular, lateral mediodorsal, and intralaminar thalamic nuclei (59). Greater than 50% of all cholinergic PPN/LDT neurons can be labeled by a single, large, thalamic retrograde tracer injection centered upon the intralaminar group (60). Similar quantitative analyses are limited but suggest that at least 20% of the entire cholinergic population innervates the medial medullary reticular formation (52), with smaller contingents (e.g. ~10% of the total population) innervating the lateral hypothalamus and ventral forebrain/substantia innominata (57,61–65), suprachiasmatic nucleus (66), lateral septum (57), superior colliculus (67), individual basal ganglia nuclei (38,58,68), the pontine tegmentum (69–71), and rostral ventrolateral medulla (RVL) (72). Within nuclei of termination, individual cholinergic axons derived from the PPN/LDT arborize extensively and describe many en passant synaptic contacts (38,73–75). Significant parallel pathways to the "nonspecific" intralaminar and reticular thalamic nuclei, the lateral hypothalamus, the ventral forebrain, the basal ganglia (see MEA, below), and the pontine and medullary reticular formation arise from noncholinergic neurons commingled with the PPN/LDT or from several adjacent noncholinergic nuclei (27,50–52,61,63–65,69–71,76,77). It is likely that detailed analyses might reveal that these "parallel" cholinergic and noncholinergic projections from the PPN/LDT region selectively target specific subpopulations contained within these heterogeneous regions (57,62–64). Cholinergic PPN/LDT neurons and their projections are nonetheless distinct from adajcent noncholinergic, presumptively glutamatergic neurons in several respects: 1) they provide a majority, if not all, of the PPN region's innervation of the "specific" thalamic relay nuclei (50), the lateral septum (57), and the superior colliculus (67); 2) individual axons can simultaneously innervate disparate and functionally unique brain regions (26–29); 3) they provide little (57) or no (39,40) innervation to amygdaloid nuclei and the striatum, respectively.

In summary, ascending cholinergic pathways from the cholinergic PPN/LDT innervate two distinct sets of targets, the "nonspecific" and "specific" thalamic nuclei and the substanita innominata and posterior lateral hypothalamus, both of which contain subpopulations of state-dependent neurons that project diffusely to cortex [reviewed in Saper (78) and Szymusiak (79)]. These features thereby provide the cholinergic PPN/LDT access to modulating cortical activity. There has been moderate success in precisely defining the organizational features, postsynaptic targets, and receptors underlying the neuromodulatory effects of these pathways in the thalamus and substantia nigra pars compacta. Similar details with respect to alternate targets of cholinergic pathways, particularly those descending from the PPN/LDT to REM sleep-related brainstem circuits, are presently lacking.

2.1.2 MEA (glutamate)

The noncholinergic cell population innervated by basal ganglia (i.e. the MEA) is believed to employ glutamate as its primary neurotransmitter. It is uniquely positioned to modulate motor-related basal ganglia output via outputs that reinnervate the basal ganglia and a separate set that descend to pontine and medullary reticulospinal centers. One subset of efferents from the MEA preferentially targets the dorsolateral striatum and supports our contention that its functional domain is principally devoted to basal ganglia sensorimotor circuits (40). Glutamate-like immunoreactivity has been localized in alternate MEA projections to the primate substantia nigra–pars compacta (SN-pc) (24,80) and rodent subthalamic nucleus (STN) (38). In the SN-pc and STN, MEA synapses are concentrated on somata and proximal dendrites (81,82), proximal to traditional basal ganglia inputs (83,84), and emphasize that the MEA is strategically positioned to markedly influence neural activity in the basal ganglia. Electrical or pharmacologic stimulation near the MEA evokes short latency excitatory responses in the SN-pc (85–88), STN (89), and GPi (90). Lesions that interrupt these excitatory influences reduce the GPi's high tonic discharge rate by 50% (91), a dramatic change that dwarfs that proposed to underly the pathophysiology of hyperkinesias (92). Another set of noncholinergic descending efferents to the pons, medulla, and spinal cord originates in the MEA (52) and has been independently noted to be spatially segregated from adjacent ascending cholinergic thalamic projection neurons (77; see their Fig. 1D–E). Difficulties in simultaneously defining the precise targets of inputs to the MEA/PPN and efferent trajectories taken by the neurons so targeted has nonetheless significantly hampered identification of multisynaptic pathways through this region and their functional roles. Although we have observed pallidotegmental axons contacting several neurons that projected back upon the GPi, the efferents of the majority of neurons contacted in a similar fashion by pallidotegmental axons are not known. Other investigators have identified pallidotegmental (93) and nigrotegmental (94) synapses on neurons in the vicinity of the MEA that in turn innervate pontomedullary reticulospinal centers. Whether movement-related basal ganglia output might be relayed to pontomedullary centers via the glutamatergic MEA, the cholinergic PPN, or both, and precisely which medullary centers

and neurons are innervated, are not known. Alternatively, through projections to the PPN, the basal ganglia may effect thalamocortical arousal, which in turn influences motor activity [see, for example, Steckler et al. (95)]. Accurate delineation of the mesopontine tegmental efferents targeted by primary basal ganglia output and their individual physiological roles will necessitate very careful anatomical and physiological investigations. It may be difficult to isolate the physiological effects due to glutamatergic influences originating in the MEA, because some efferents from cholinergic PPT neurons ascend (38,58,80) or descend (23,52) in parallel with MEA efferents and terminate in some of the same nuclei [see, for example, Futami et al. (96)]. The presence of GABA in some neurons in the PPT region (49) also raises the possibility that they also contribute to efferents from this region, as has been suggested by some recent findings (38). Fast synaptic transmission via glutamatergic synapses, rather than neuromodulation by acetylcholine and participation in circuits that are tightly linked with sensorimotor basal ganglia, nonetheless suggests a quite specific role for the MEA in modulating motor activity that awaits further definition.

2.1.3 RRF/nucleus subcuneiformis (glutamate and dopamine)

The anatomy and neurochemistry of the retrorubral field (RRF) and nucleus subcuneiformis have not been rigorously assessed. Because of their proximity to the subjacent MEA/PPN, they are frequently inadvertently involved in anatomical and electrophysiological investigations of the mesopontine tegmentum. The most conspicuous neurons are large, multipolar dopaminergic cells of the A8 cell group, although they comprise ~10% of the total neuronal population. The neurotransmitter content of the remaining neurons is unknown, although it is assumed a majority are glutamatergic. The majority of fibers from these regions ascend within the medial forebrain bundle and terminate predominantly in the shell of the nucleus accumbens, limbic, and associative territories of the striatum and forebrain comprising the "extended amygdala" (e.g. the bed nucleus of the stria terminalis, substantia innominata, and central nucleus of the amygdala) (57,97–99) (personal observations). The majority of descending fibers innervate the subceruleal region and parabrachial nucleus before descending in Probst's tract to the nucleus of the solitary tract (NTS) (52,98,100). Smaller contingents of ouptut fibers target the lateral preoptic area, dorsal hypothalamus, midline, intralaminar and reticular thalamic nuclei, the periaqueductal grey and dorsal raphe, as well as the pontine and medullary reticular formation (50,52,57,97,98). Prominent reciprocity of connections with limbic/associative basal ganglia circuits (see below) as well as the "extended amygdala", parabrachial nucleus, and NTS support considerations of these regions as limbic and visceral/autonomic related, respectively. These anatomical features are clearly unique from those of the adjacent MEA and PPN, although much less is known about their physiology and behavioral relevance.

2.2 Input (i.e. afferent) pathways

Anatomical and electrophysiological studies have identified many putative afferents of the cholinergic PPN/LDT, but because of their close proximity to the RRF/nucleus subcuneiformis, MEA, and caudally adjacent parabrachial nuclei, it has been difficult to determine precisely which of these afferents actually terminate in the region and, of these, which terminate on cholinergic neurons. Afferents to the mesopontine tegmentum region containing the PPN have been identified by orthodromic stimulation from the basal ganglia (87,89,90,101) and lateral preoptic area (LPO) (102). Morphologic and neurochemical characterization of midbrain tegmental neurons receiving basal ganglia inputs following intracellular recording (55,103,104) suggests that neurons inhibited by the SNr can be divided into three electrophysiologically distinct populations, but only a portion of one class appears to be cholinergic (approximately one-third of the total recorded population) (55). Interpretations of retrograde tracer studies are limited by an inability to restrict tracer injections to individual neurochemically defined subpopulations within and surrounding the PPN (105,106). A wide array of putative afferents are therefore demonstrable, and these are largely, but not universally, shared between the PPN and MEA (106). Anterograde tracing studies provide a much better delineation of the precise regional and somatic targets of labeled axons; however, this methodology has been applied in a limited fashion to only a handful of putative PPN/MEA afferents, including nucleus accumbens (107), the LPO area (102), medial prefrontal (108) and motor (109) cortices, and the cerebellar dentate nucleus (110). Immunolabeling of axons to reveal their neurotransmitter contact has also identified other potential afferents, including serotonergic (111), noradrenergic or dopaminergic (i.e. tyrosine hydroxylase immunoreactive) (12), and histaminergic (112) fibers. The neurochemical heterogeneity of the PPN region was not considered in most of these analyses, so whether the terminal fields of these afferents selectively target glutamatergic/dopaminergic RRF, glutamatergic MEA, or cholinergic PPN neurons is not known. We have employed combinations of anterograde labeling and immunocytochemical localization for ChAT with light

and electron microscopic analysis to avoid these methodological concerns and more precisely identify the brain regions that might differentially influence the excitability of the MEA/PPN. Serotonergic dorsal raphe (DR) projections to the PPN region were identified as particularly dense in the dorsal, compact portion of the PPN but also innervated the adajcent RRF and MEA. At the electron microscopic level, serotonergic axons contacted small caliber, noncholinergic and cholinergic dendrites in equal proportions (111). This afferent source of the mesopontine tegmentum containing the PPN/LDT is likely to play a key role in neuromodulation with respect to behavioral state given the DR's well-described state-related alterations in activity (see below). The nonselective targeting of cholinergic neurons by serotonergic fibers, however, suggests that the PPN/LDT is not preferentially modulated by the DR. The behavioral state-related significance of serotonin and the DR on adjacent neurons in the RRF and MEA is not known.

Because previous definitions of the PPN-pc derived largely from Nauta and Mehler's description of this nucleus as a principal target of basal ganglia output (113), we (44,45) and others (47) have carefully reinvestigated the targets of pallidotegmental terminals from the sensorimotor division of the GPi and found them to preferentially innervate the primate equivalent of the MEA (Fig. 3). Electron microscopic and electrophysiological studies in rats also confirm that efferents from the primary output nuclei of the basal ganglia, i.e. the GPi and SNr, primarily target the MEA with a smaller contingent synapsing with the PPN. Nigrotegmental axons in the rat, for example, are most concentrated in the traditional PPN-d, where cholinergic cells constitute only 25% of all cell types (114), and within the PPN-pc, 85% of these axons make synaptic contact with noncholinergic neural elements (115). Morphological and neurochemical characterization following intracellular recordings also suggests that the primary output of the basal ganglia hyperpolarizes the MEA, with only 30% of the recorded population shown to be cholinergic PPN neurons (55,103,104). Restriction of immediate early gene c-fos expression to the MEA in monkeys following an amphetamine challenge provides "functional" evidence that the MEA represents the primary target of movement-related and dopamine-responsive basal ganglia output (Fig. 4D). Because the brainstem receives no direct dopaminergic innervation, and the response was abolished by destruction of nigrostriatal terminals in the contralateral hemisphere by intracarotid 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration, this finding suggests that the MEA is disinhibited (viz, activated) by dopamine's dampening of the GPi's GABAergic ouptut [see also, Wirtshafter (42)]. These findings have potential import to the pathophysiology and treatment of dopamine-responsive nocturnal movements because 1) there is a wealth of knowledge concerning dopamine's actions at unique receptor subtypes expressed upon individual basal ganglia subcircuits [e.g. D1 on the direct and D2 on the indirect striatal pathways (92,116–118) and D4 within the GPi (119,120)]; and 2) glutamatergic neurons in the vicinity of the MEA are necessary to maintain REM atonia (see below).

The growing recognition that the basal ganglia are organized into segregated pathways that subserve different functional roles (e.g. sensorimotor, oculomotor, limbic, and associative) lead us to further investigate whether output pathways to the brainstem are similarly organized. If recognizeable at the level of the brainstem, differential zones of termination for functionally defined basal ganglia subcircuits might yield important clues as to the behavioral domains of individual brainstem "nuclei". Indeed, termination of pallidotegmental fibers emanating from limbic and associative zones of the GPi define a relatively wide field that generally avoids the MEA and PPN, corresponding best with the RRF and immediately subjacent subcuneiform nucleus (Fig. 3). Similarly, in the rat, efferents of the ventral striatum (Fig. 4A) and ventral pallidum (Fig. 4B) (i.e. limbic-related basal ganglia nuclei) preferentially innervate the RRF and terminate as far caudally as the subceruleal region (Fig. 4C). In summary, a main descending output pathway of sensorimotor division of the basal ganglia (i.e. the pallidotegmental tract) takes origin from the same neurons contributing to innervation of motor thalamic nuclei (e.g. the VA/VL and centromedian (CM) thalamic nuclei) (121–123) and terminates in a convergent and perisomatic fashion primarily on MEA neurons that are likely to employ glutamate as a neurotransmitter (45). Parallel pathways from limbic and associative basal ganglia circuits terminate in a partially overlapping zone that is centered upon the RRF. Basal ganglia ouptut is also likely to contact cholinergic PPN neurons, albeit on their distal dendrites. Subdividing the PPN region into these functional/anatomical circuits finds further support in observations that the primary motor cortex preferentially innervates the MEA (personal observations), and that the RRF and MEA differentially innervate the limbic/associative and sensorimotor striatal territories (40), respectively. What proportion the basal ganglia contribute to the total synaptic input of RRF, MEA, and PPN neurons, and therefore, to what degree they compete with other synaptic influences in driving physiological responses in their efferent pathways, and which specific efferents are driven, are unknown. It is clear, however, that basal ganglia ouput to these three neuronal populations will manifest behaviorally in unique

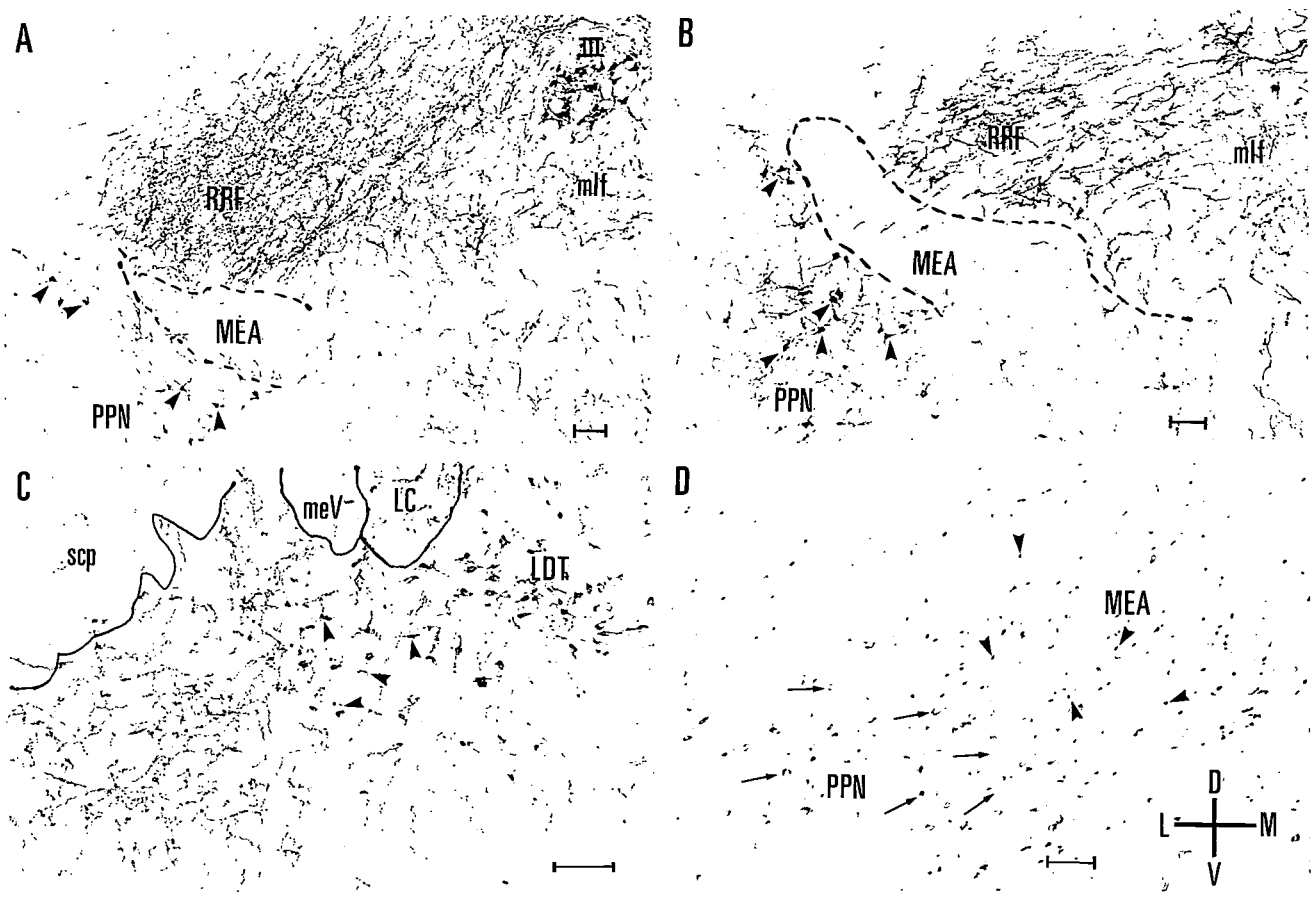

FIG. 4. Photomicrographs illustrating segregation of basal ganglia efferent pathways within the brain stem. (A) Output from the ventral striatum in the rat targets the retrorubral field (RRF), largely avoiding the subjacent midbrain extrapyramidal area (MEA) (cross-hatching) and pedunculopontine (PPN) region (arrowheads) as assessed by combinations of anterograde tracing and immunohistochemistry for choline acetyltransferase. Serpiginous black labeling represents labeled axons, whereas cholinergic PPN perikarya and dendrites are more lightly stained (arrowheads). (B) Brainstem innervation from the ventral pallidum coincides with that from the ventral striatum in the RRF, largely avoiding the subjacent MEA (cross-hatching) and PPN (arrowheads demarcate cholinergic cell bodies). (C) Output from the ventral striatum extends caudally to the subceruleal region where it interdigitates with cholinergic cell bodies (arrowheads), ventral to the locus coeruleus (LC) and laterdorsal tegmental nucleus (LDT). (D) Disinhibition of the PPN region via dopamine-mediated attenuation of basal ganglia GABAergic output upregulates nuclear expression of the immediate early gene c-fos in the MEA of the monkey (black nuclear staining; arrowheads) but not in adjacent cholinergic PPN perikarya (arrows). Calibration bars in each figure = 100 μm. Abbreviations: III, oculomotor nucleus; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; MEA, midbrain extrapyramidal area; meV, mesencephalic tract of the trigeminal nerve; mlf, medial longitudinal fasciculus; PPN, pedunculopontine nucleus; RRF, retrorubral field; scp, superior cerebellar peduncle.

ways on the basis of differences in their efferent connections and physiological and receptor characteristics, some of which are summarized in Table 1. Further elucidation of the detailed synaptic organization of basal ganglia ouptut confined to the PPN region would contribute to a better understanding of the structural and pharmacological substrates underlying many basal ganglia-mediated behaviors.

In summary, the application of modern neuroanatomical techniques in several species demonstrates at least two specific subpopulations in the mesopontine tegmentum, in addition to the cholinergic PPN, the RRF, and MEA, that are recognizeable based upon the specificity of their afferent (and efferent) connectivities with specific basal ganglia subcircuits. These findings challenge the conventional wisdom that the cholinergic "PPN" is the monolithic brainstem locus for convergence of a panoply of limbic, visceral, and sensorimotor information. Although this may yet be determined to be the case for individual cholinergic PPN neurons, our findings begin to paint a picture of functionally segregated circuits within the upper brainstem "reticular core". This concept of segregation is complemented by observations that motor behaviors resulting from stimuli applied near the "PPN" can be opposite in character depending upon the stimulus parameters (124) or the site of stimulus application (125,126).

TABLE 1. *Summary of the neurochemical, connectional, physiological, and receptor characteristics that differentiate the midbrain extrapyramidal area (MEA) from the cholinergic pedunculopontine (PPN) region*

	MEA	PPN	References
Neurotransmitter content/neurochemical characteristics	Noncholinergic, glutamate and GABA (?), parvalbumin containing	Acetylcholine, atriopeptin, NADPH-diaphorase, CRF, substance P, glutamate	(3, 12, 18, 19, 21, 22, 24, 28, 29, 31, 32, 34, 49)
Synaptic contacts from GPi	Numerous and perisomatic	Sparse and dendritic	(12, 45, 47)
Response to GPi/SNr stimulation	IPSPs	IPSPs	(63, 91, 94, 104, 107)
Response to systemic dopamine	IEG activation	Absence of IEG activation	(42) (See Figure 4D)
Efferents	Restricted; basal ganglia and ventral medulla	Widespread; thalamus, basal forebrain, pons, and medulla	(12, 25, 50, 52)
Physiological characteristics	Tonically active in EEG desynch. states and many displaying low-threshold Ca^{2+} spikes and bursting	Tonically active in EEG desynch. states with few displaying low-threshold Ca^{2+} spikes and bursting	(36, 56, 127, 161)
Response to ACh	None or depolarizing	Hyperpolarizing	(146, 147)
Muscarinic receptors	(?) m3	m2 predominates	(155, 156)
Response to 5-HT	None or slow hyperpolarizing	Hyperpolarizing	(146, 147, 161)
5-HT 2 receptors	Absent	Present	(331, 332)

ACh, acetylcholine; CRF, corticotropin-releasing factor; EEG, electroencephalograph; Gpi, globus pallidus; IEG, immediate early gene; IPSPs, inhibitory postsynaptic potentials; SNr, substantia negra pars recticulata.

3.0 ELECTROPHYSIOLOGICAL CONSIDERATIONS

It is now well accepted that acetylcholine (ACh) derived from the PPN/LDT plays a central role in the modulation of brain-active states such as waking and REM sleep (8,127). A majority of cholinergic cells exhibit increased excitability well in advance of other manifestations of brain activation during transitions from resting (electroencephalograph (EEG)-synchronized) sleep to either wakefulness or REM sleep (36). Prior to and during REM sleep, when PPN/LDT neurons increase their tonic discharge rates (36,56), ACh is released in the pontine tegmental field (128–130) and thalamus (131), two well-established terminal fields of PPN/LDT efferents. Chronic low-amplitude electrical stimulation of the LDT in freely moving cats increases REM sleep (132). Conversely, lesions of the PPN/LDT (133,134), or pharmacological blockade of their efferents (135,136), eliminate REM sleep and diminish wakefulness, or interfere with expression of REM sleep's individual, physiologically defined tonic and phasic components (e.g. atonia and PGO waves/extraocular movements, respectively).

Cholinergic innervation of thalamic-specific relay and "nonspecific" nuclei governs the prolonged states of EEG desynchronization accompanying wakefulness and REM sleep primarily by depolarization of thalamocortical cells. This excitation is mediated by a "leaky" K^+ conductance (I_{KL}) that is dependent on G-protein-coupled muscarinic ACh receptors (mAChRs) that are insensitive to pertussis toxin (36,127,137–139). Hyperpolarization of the thalamic reticular nucleus and increase in membrane conductance by ACh represent an alternate "indirect" pathway that also interferes with sleep spindle-related cyclic inhibitory postsynaptic potentials (IPSPs) in thalamocortical neurons (140). Complementing these tonic effects, cholinergic PPN/LDT neurons also transfer phasic ponto-geniculo-occipital (PGO) waves that appear in the thalamus prior to and during REM sleep (8,56,127,141,142). Because they are especially effective in blocking cyclic IPSPs in thalamocortical neurons (142,143), PGO waves represent a sine qua non for the occurrence of REM sleep. They have also been proposed as the neural correlate underlying dreamlike imagery (8,56,127), hallucinations (8,144), and orienting responses (145). Therefore, elucidation of the neural and pharmacological substrates influencing brainstem cholinergic neurons has garnered particular attention. Hyperpolarization of tonically active PPN/LDT neurons, and thereby inhibition of cortical "arousal", is mediated by serotonin, GABA, acetylcholine, opiates (8,49,127,146,147), adenosine (148), and norepinephrine (149), while hyperpolarization of a separate population of neurons displaying low-threshold calcium spikes (LTS) contributes to a burst firing mode and PGO waves. Histamine (146) and glutamate (150,151) are proposed excitatory transmitters in the PPT/LDT. Very little is known, however, concerning the nuclear source of these transmitters and the specific cell types of the PPN region with which they are in synaptic contact (e.g. cholinergic versus noncholinergic, tonically active versus bursters).

We have recently described that serotonergic/dorsal raphe projections to the PPN region are particularly dense in the dorsal PPN-pc, where they primarily contact small caliber, noncholinergic and cholinergic dendrites in equal proportions. Confirmation of cholinergic synapses upon cholinergic PPN/LDT neurons predicted by physiological studies has only been possible with more sensitive immunolabeling for the vesicular

acetylcholine transporter—vAChT (Fig. 1E–F). These terminals are presumed to arise from cholinergic PPN/LDT neurons themselves (30) and, as such, may provide a potent recurrent inhibition, although their potential origin from cholinergic magnocellular basal nucleus or other cholinergic nuclei has not been carefully considered. The muscarinic receptor mediating this putative autoinhibition is insensitive to blockade by pirenzepine (147), which rules out the m1 molecular receptor subtype, but this ligand does not discriminate among the m2, m3, and m4 receptor subtypes (152). Reports of the m2, m3, and m4 mRNAs in the "PPN region" with in situ hybridization techniques (153–155) do not carefully discriminate between cholinergic and noncholinergic neurons. Immunolabeling for the molecular mAChRs, however, reveals that the m2 subtype colocalizes with cholinergic PPN/LDT neurons in the nonhuman primate (156) and subprimates (personal observations). The expression of m2 in only a subpopulation of neurons in the human brain suggests that important species differences may exist (Fig. 2E) (156). A presynaptic location of the mAChRs upon afferents to the region is also likely (personal observations) and is complemented by recent findings that the nitric oxide signaling pathway in brainstem cholinergic neurons can modulate incoming afferent signals (157). Additional anatomical (158) and physiological (151,159) evidence suggests that excitatory transmission at non-N-methyl-D-aspartic acid (NMDA) and NMDA receptors in the PPN/LDT region may also modulate unique patterns of neural activity that affect REM sleep expression (160). A more detailed determination of mAChRs and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and NMDA receptors within synaptic circuits of the PPN/LDT region will advance understanding of one locus where cholinergic and glutamatergic modulatory actions on REM sleep are thought to reside. The role of serotonergic DR-PPN/LDT interactions within the context of the reciprocal interaction model of REM sleep modulation has, however, been the focus of most attention. It therefore provides a useful model around which to frame a discussion of the electrophysiological response properties of the PPN/LDT region and their potential functional signficance to the modulation of behavioral state.

The intrinsic electrophysiological properties of cholinergic PPN/LDT neurons recognized by different laboratories are in disagreement, possibly reflecting differences in the age or species of experimental animals. Most cholinergic LDT cells from neonatal rat, for example, display low-threshold bursting secondary to activation of a voltage-sensitive calcium current in vitro (161). It has therefore been hypothesized that during waking, when serotonergic dorsal raphe neuronal activity is maximal (162,163), bursting cholinergic neurons are relatively quiescent unless subject to sufficient depolarizing influences (56,139). Conversely, during REM sleep, when serotonergic dorsal raphe neurons cease firing (162,163), inhibition of cholinergic bursting neurons is removed. On the basis of this data, generation of a burst firing mode that favors PGO wave production during REM sleep would necessitate deinactivation of the low-threshold calcium current by transient hyperpolarizing synaptic events. Both local cholinergic (147,164) and GABAergic basal ganglia afferents (165,166) have been proposed as sources for these hyperpolarizing influences. Further evidence in support of a serotonergic dorsal raphe modulation of the discharge pattern of bursting cholinergic LDT/PPN neurons, and thereby PGO wave production, derives from several observations: 1) DR neurons cease firing immediately prior to the onset of each PGO spike (162); 2) PGO waves are "released" in wake and non-REM (NREM) sleep following chemical depletion of serotonin (167,168), reversible cooling or lesions of the raphe (168), or parasaggital cuts that isolate the raphe from the PPN (169); 3) PGO burst neurons are antidromically activated from the lateral geniculate nucleus (141,170–172), which derives its exclusive source of tegmental afferents from cholinergic neurons in the PPN, and to a lesser extent, the LDT (50,170,173,174) (personal observations); and 4) PGO waves can be completely suppressed by injections of cholinergic (nicotinic) antagonists into the lateral geniculate nucleus (143,175) and lesions (133,176) or reversible cooling (135) of the PPN region. Inconsistent with this hypothesis are independent in vitro analyses of PPN neurons in the adult rat (55) and guinea pig (147) and in vivo recordings in the adult cat (36,56) that suggest that the vast majority of low-threshold burst neurons are noncholinergic, whereas nonbursting neurons are cholinergic. The validity of this hypothesis is also questioned by observations that the release of PGO waves requires lesions of several serotonergic raphe nuclei rather than lesions restricted to the borders of the dorsal raphe (169). Serotonergic afferents to the PPN from the median raphe, supralemniscal nucleus (i.e. the B9 cell group), and/or raphe magnus (105,177) are potential sources for additional serotonergic innervation to the PPN/LDT. It remains to be determined if these putative afferents synapse in the PPN and what their role is, if any, in modulating REM sleep.

Models of serotonergic dorsal raphe–PPN/LDT interactions and REM sleep control that focus solely on PGO burst/cholinergic neurons largely ignore the status of the substantial populations of nonbursting and/or noncholinergic neurons in the PPN/LDT region. On the basis of in vivo studies, for example, PGO burst

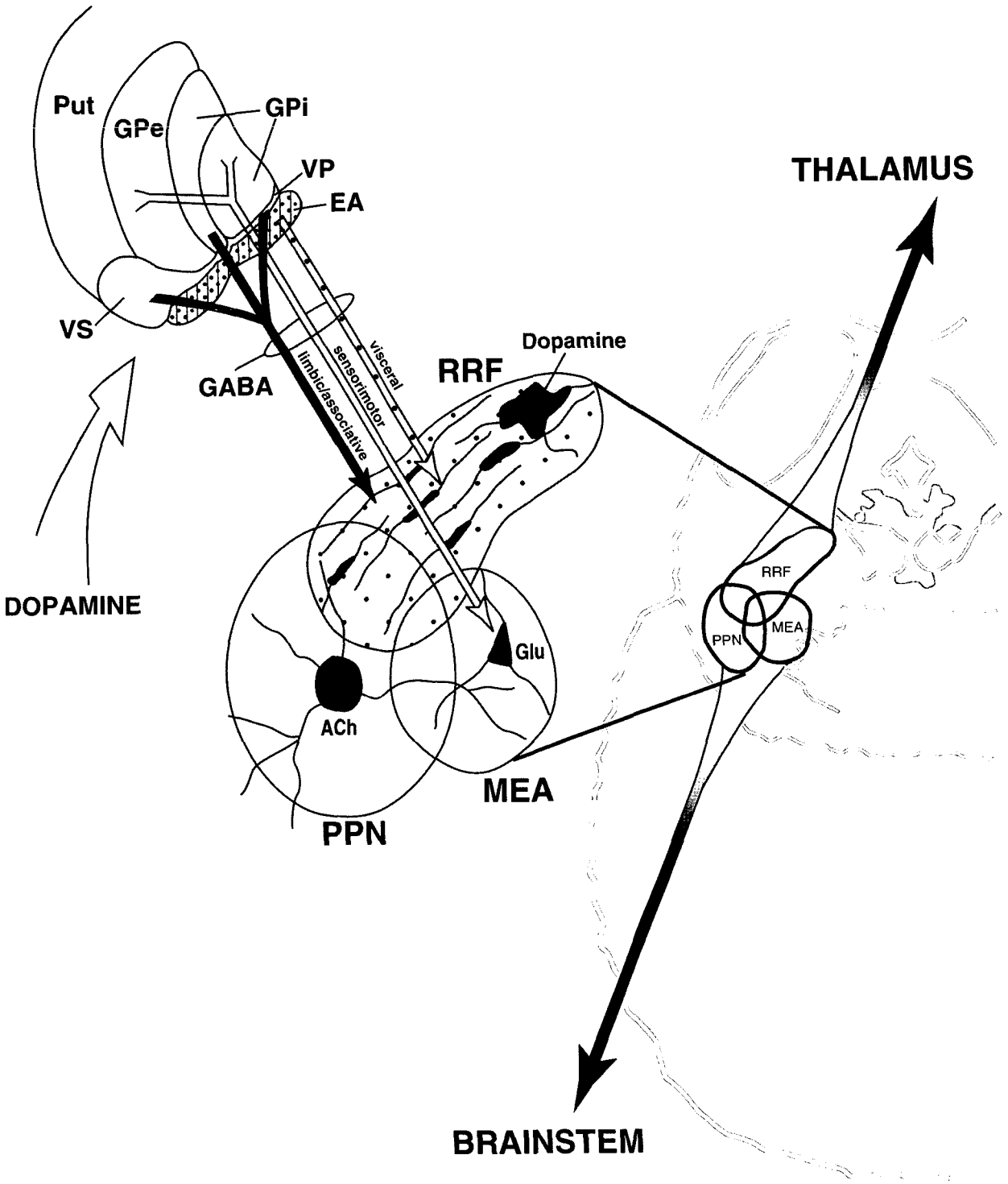

FIG. 5. Schematic diagram summarizing connectional/neurochemical features of basal ganglia output to the mesopontine tegmentum, including the retrorubral field (RRF), midbrain extrapyramidal area (MEA), and pedunculopontine (PPN) region, discussed in more detail in the text. Briefly, GABAergic hyperpolarizing outputs from dopamine-responsive basal ganglia circuits and the adjacent "extended amygdala" are segregated to specific sites within the PPN region. The majority of descending, sensorimotor-related pallidotegmental axons, which represent collaterals of fibers directed to the thalamus, establish predominantly perisomatic contacts on glutamatergic (Glu) MEA neurons. In contrast, limbic/associative pallidal output and parallel pathways from the "extended amygdala" converge upon the RRF and nucleus subcuneiformis. Small contingents of these segregated outputs are also likely to synapse with cholinergic (ACh) PPN neurons, probably on their distal dendrites. These modes of termination and unique intrinsic membrane properties of neurons in the PPN region dictate that the firing patterns of postsynaptic neurons are dramatically altered by these GABAergic afferents [e.g. enhanced GABAergic output promotes burst firing in neurons displaying low-threshold calcium spikes (LTS) and inhibits tonic activity in neurons lacking LTS]. Projections from these regions in turn innervate the thalamus and/or pontine and medullary reticular fields and thereby influence thala-

neurons represent only 9% of all neurons in the PPN/LDT region, with non-PGO-related neurons and PGO-related, but nonbursting neurons constituting 76 and 15% of the total recorded cell population, respectively (36,56). Tonically active, non-PGO-related neurons with efferent projections outside of the lateral geniculate nucleus may modulate tonic aspects of REM sleep, such as muscle atonia and/or EEG desynchronization. It is likely that these cells, particularly those that are cholinergic, are also hyperpolarized by serotonin (5-HT) (147,161). The effects of 5-HT on noncholinergic neurons in the PPN/LDT region are less well described, possibly because their small size precludes ready intracellular sampling and voltage clamping. In the neonatal rat LDT, 6/7 bursting noncholinergic neurons were hyperpolarized by 5-HT, whereas only 2/8 nonbursting, noncholinergic neurons were similarly hyperpolarized (161). In the adult guinea pig PPN, the hyperpolarizing effects of 5-HT on noncholinergic neurons are generally weak [(147); C. Leonard, personal communication]. One might have predicted a more widespread response given that dorsal raphe/serotonergic afferents to noncholinergic elements in the PPN region are as prevalent as those on cholinergic dendrites (111). Putative dorsal raphe/serotonergic projections to presumptive GABAergic interneurons (49,82) might indirectly affect the responsiveness of cholinergic neurons. Alternatively, dorsal raphe/serotonergic afferents of the PPN region may contact glutamatergic neurons that project to the basal ganglia, midline, intralaminar, and reticular thalamic nuclei, or pontomedullary reticular fields. It will be critical to determine if neurons classified by cholinergic/noncholinergic status and by bursting status display unique patterns of efferents and, if they do, whether they are differentially affected by 5-HT or alternate neurotransmitters. This will necessitate simultaneous identification of a neuron's projection pattern and its neurochemical identity in the in vitro slice preparation.

In summary, serotonergic innervation of the PPN/LDT region plays a key role in neuromodulation with respect to behavioral state given the DR's well-described state-related alterations in activity, i.e. serotonergic/dorsal raphe "tone" is a potent determinant of the ultimate discharge pattern of a majority of cholinergic and noncholinergic neurons in the PPN region. Specific REM sleep-related physiological activity is then dependent not only on the intrinsic electrophysiological properties of individual cholinergic and noncholinergic neurons but also their unique afferent connectivity (i.e. excitatory or inhibitory synaptic inputs). Putative sources of these afferent connections are numerous and originate from widespread brain regions but are, for the most part, inadequately described (see above). A more comprehensive picture of the determinants of PPN/LDT activity will emerge when detailed quantitative analyses of the synaptology of identified afferents is applied to some of these putative afferent sources. Determination of the uniqueness of the efferent connections of neurons contacted by these afferents may ultimately identify specific neuronal populations and neural circuits that subserve individual components of REM sleep [e.g. see discussion in Rye et al. (45)].

4.0 DISEASE SPECIFIC CONSIDERATIONS

The anatomical/physiological features of the PPN/LDT region highlight its unique position as reflector of a massive collection of descending forebrain influences either back upon forebrain circuits or to nuclei further down the neural axis (see Fig. 5). Parallel or divergent axonal trajectories of noncholinergic and cholinergic neurons within the PPN region afford them the ability to modulate forebrain and brainstem-mediated behaviors in a coordinated or independent manner, respectively. The segregation of forebrain afferents within the PPN region (e.g. the RRF, MEA, and PPN/LDT proper) provides additional potential for noncholinergic and adjacent cholinergic brainstem circuits to operate independently from one another in affecting behavior. These organizational features may come into play in several clinical disorders in which motor activity is discordant with behavioral state. The most parsimonious explanations for cataplexy and sleep paralysis in narcolepsy, for example, posit that a unique neural system modulating REM atonia can be differentially decoupled from generators of the thala-

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mocortical processing and the excitability of premotor and motor neurons, respectively. The degree to which the glutamatergic MEA, the cholinergic PPN, or both, relay forebrain influences to these sites, precisely which neurons are innervated, and how this innervation influences behavioral state are details that require further investigation. Ascending cholinergic and glutamatergic pathways innervate "specific" and "nonspecific" thalamic nuclei and promote cortical arousal, whereas descending pathways modulate rapid eye movement (REM) atonia and other REM sleep-related phenomena (e.g. eye movements and cardiac and respiratory functions). These divergent pathways are amenable to assessment with the middle latency auditory-evoked response (P1) and the acoustic startle reflex (ASR), respectively; however, the specific neural and pharmacological substrates contributing to their modulation by the PPN region require further investigation. Abbreviations: EA, extended amygdala; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; IC, inferior colliculus; IV, trochlear nucleus; MEA, midbrain extrapyramidal area; mlf, medial longitudinal fasciculus; PN, pontine nuclei; PPN, pedunculopontine tegmental nucleus; Put, putamen; RRF, retrorubral field; VP, ventral pallidum; VS, ventral striatum; xscp, decussation of the superior cerebellar peduncle.

mocortical "arousal" of REM sleep. Similary, RBD can be viewed as a glimpse of waking-patterned motor activity that becomes inappropriately coupled to generators of thalamocortical arousal of REM sleep (178). The following discussion, centered around specific diseases, emphasizes that a more critical analysis of how different brain regions modulate the responsiveness of the PPN/LDT region is likely to yield important clues as to the pathophysiology underlying aspects of REM dyscontrol in narcolepsy, RBD, and schizophrenia. In addition, pathological alterations intrinsic to the PPN/LDT region (e.g. increased or decreased cell number) may be particularly relevant to abnormalities of REM sleep observed in narcolepsy, neurodegenerative diseases, and schizophrenia. Finally, postsynaptic responses at muscarinic receptors in brain regions targeted by cholinergic efferents of the PPN/LDT have been proferred as substrates for disease-specific alterations in REM sleep that accompany narcolepsy and depression. Progress in deciphering the pathophysiology of these "protypical" examples of REM dyscontrol has been expedited by the availability of canine narcolepsy/cataplexy and pontine-lesioned cat models that emulate the human conditions of narcolepsy and RBD, respectively. It should be appreciated that cholinergically mediated state of REM sleep has important additional functions that remain less well defined. Pontine cholinergic mechanisms, for example, may contribute to the pathophysiology of central apnea and sudden infant death syndrome (SIDS) because REM sleep state-dependent release of ACh suppresses ventilatory responses to hypercarbia (129,179). Cholinergic modulation of REM sleep may also contribute to higher cognitive functions because selective suppression of REM sleep in healthy subjects interferes with perceptual learning (180). As additional functions of REM sleep are elucidated, possibly within the realm of the development and plasticity of neural connections, the role of cholinergic brainstem circuits in essential and pathological behaviors should become increasingly recognized.

4.1 Narcolepsy/cataplexy

Classic narcolepsy is a neurologic disorder characterized by excessive daytime sleepiness and symptoms reflective of REM sleep dyscontrol, including cataplexy, sleep paralysis, RBD, and hypnagogic and hypnopompic hallucinations (181,182). Polysomnography frequently reveals a decreased latency to REM sleep and two or more sleep-onset REM sleep periods during naps the following day. A growing body of evidence suggests that the pathological REM sleep accompanying narcolepsy reflects, at least in part, enhanced responsiveness of postsynaptic mAChRs to ACh released from PPN/LDT axon terminals in the mPRF. Levels of ACh in the mPRF increase by ~60% during REM sleep (128) at the same sites where microinjections of cholinomimetics evoke REM sleep, an action that can be blocked by muscarinic receptor antagonists (136,183–187). An increase in cholinergic synaptic activity in narcolepsy is presumed to reside in mAChRs, because: 1) the ACh release during normal REM sleep approximates that observed in the canine narcolepsy/cataplexy model during food elicited cataplexy (i.e. FECT) (188,189); 2) pontine ACh and ChAT levels are not elevated in canine narcolepsy (190,191); 3) brainstem muscarinic binding sites are increased in canine (192,193) and human (194) narcolepsy; and 4) muscarinic agonists aggravate narcolepsy and, particularly, cataplexy (195).

Significant interest has been directed at defining the pharmacological receptors and synaptic circuits in the mPRF that effect ACh's action on REM sleep. This is motivated by the belief that their identification will hasten the development of selective antagonists that might inhibit the pathological expression of REM sleep in narcolepsy. Previous anatomical and physiological investigations addressing some of these voids have been extensive. They have relied almost exclusively upon pharmacological ligands to discriminate among a variety of muscarinic binding sites (M1–M3) (196–198). The inability of these reagents to discriminate among five molecularly defined mAChRs (e.g. m1–m5) (199–201) has precluded precise identification of the pertinent mAChRs and circuits that exacerbate or alleviate narcolepsy and cataplexy (202). Within the mPRF, ACh is thought to initiate REM sleep by an mAChR-mediated inactivation of the outward potassium current (I_M), which is coupled to a pertussis toxin-sensitive G protein (203) and depolarizes a subset of mPRF neurons. Precise identification of this neuronal subpopulation has been hampered by the fact that the mPRF lacks demonstrable "nuclei" and exhibits a heterogeneous pool of receptors (196,197) that is reportedly expressed relatively homogeneously and at modest levels when compared with adjacent brain regions (198). In situ hybridization studies of the cellular distribution of mAChRs have provided little detail on the mPRF (154,155) and cannot discriminate between presynaptic versus postsynaptic location of mAChR proteins. The importance of an M2 and/or M3 receptor can be inferred from behavioral/pharmacological (202,204–206), radiolabeled ligand binding (196–198) and physiological (207,208) studies. Depolarizing and hyperpolarizing responses of separate subpopulations of mPRF neurons to ACh (207,208) suggest actions on at least two distinct mAChR subtypes. Because of their insensitivity to blockade by pirenzepine, these effects describe a non-

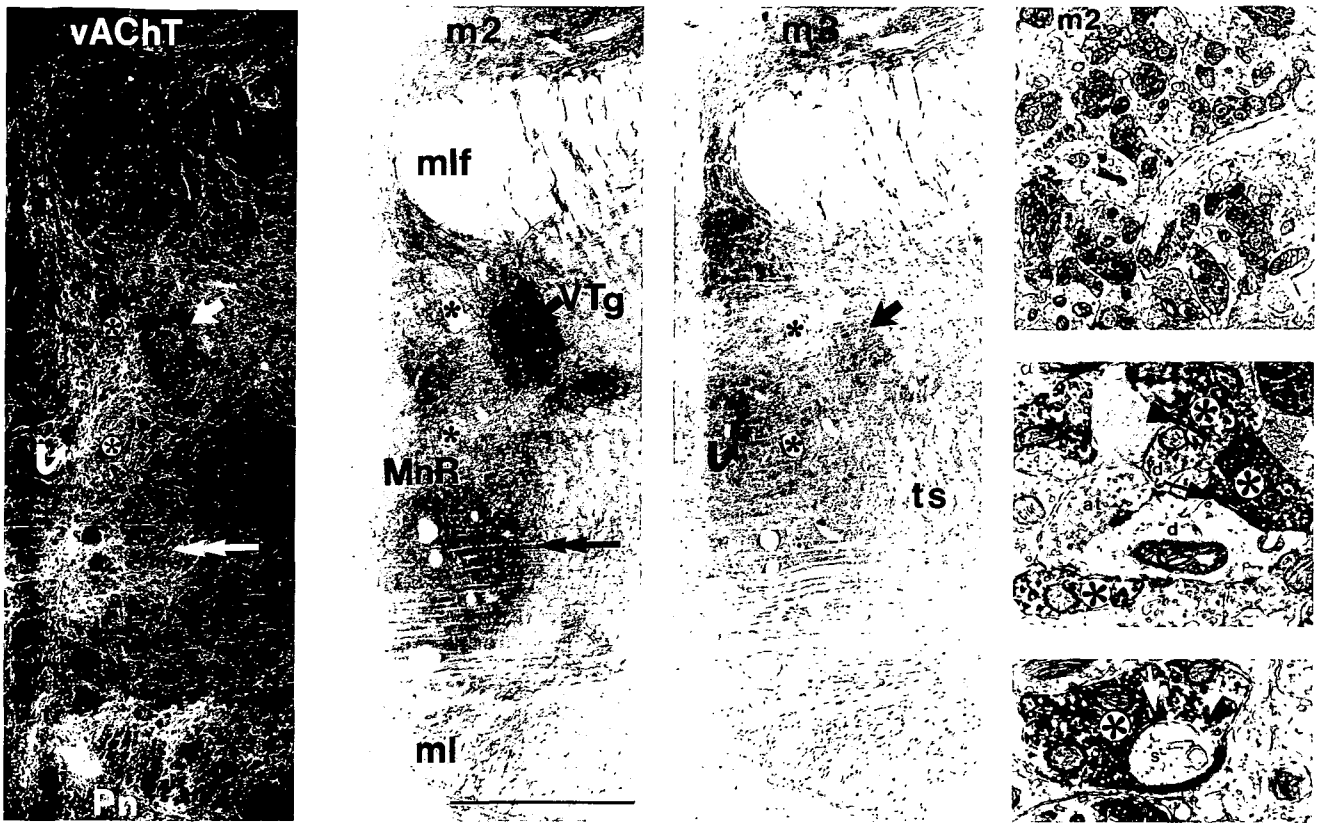

FIG. 6. Light microscopic visualization of cholinergic terminals (vAChT) and muscarinic subtype receptors m2 and m3 on immediately adjacent sections through the so-called carabachol-sensitive pontine rapid eye movement (REM) induction zone in the nonhuman primate (asterisks and arrows denote equivalent blood vessels and locals, respectively, on these adjacent tissue sections). Neurotransmitter/receptor mismatch is marked in the ventral tegmental nucleus (VTg): i.e. a relatively sparse field of cholinergic terminals is coincident with a dense m2 immunoreactive and moderate m3 receptor staining (note comparably broad arrows for vAChT, m2, and m3). Mismatch is also demonstrated between cholinergic terminals and m3 receptor staining in the dorsal median raphe (MnR) (compare curved arrows for vAChT and m3). Again, in the immediate paramedian area of the ventral MnR (i.e. under the curved arrow), a dense cholinergic terminal field does not correspond to equally dense m2 and m3 receptor fields. Rather, m2, but not m3, is concentrated a bit laterally (double-headed arrow). Neurotransmitter/receptor mismatch strongly suggests actions of synaptic acetylcholine via "volume transmission". Moreover, the m2 receptor is located predominantly presynaptically in the ventral VTg, as demonstrated by electron microscopy (three far-right electron micrographs), suggesting that ACh may affect REM sleep by augmenting or inhibiting release of alternate neurotransmitters. Electron micrographs demonstrate that the m2 molecular receptor is presynaptic to dendrites (d) and spines (s) (asterisks on electron dense reaction product indicative of m2-positive presynaptic terminals). One m2 positive dendrite (d*) presumptively postsynaptic to an m2-positive terminal is demonstrated (arrowhead). One non-m2-positive dendrite (d) receives synaptic input from both a labeled m2-positive terminal (arrow) and unlabeled terminal (at). White arrows indicate two dense-cored vesicles compatible with monoamines or peptides in one of the m2-positive terminals. Calibration bar = 2 mm. Abbreviations: ml, medial lemniscus; mlf, medial longitudinal fasciculus; MnR, median raphe; Pn, pontine nuclei; ts, tectospinal tract; VTg, ventral tegmental nucleus of von Gudden.

M1-like pharmacology that is consistent with the pharmacology of the m2, m3, and m4 molecularly defined subtypes (152). The location of the m3 receptor may be most relevant to considerations of cholinergic excitation implicated in mPRF-modulated REM sleep because this subtype suppresses a spontaneous I_M when expressed individually in cell lines (209) and mimics the response of 65% of mPRF neurons to ACh (207). Pure hyperpolarizing responses to ACh occur in another 20% of mPRF neurons (207) and are likely to reflect action at m2 because they approximate those of PPN/LDT neurons where inhibition is likely to reflect an m2 effect (see above). Presynaptic mAChRs expressed on cholinergic afferents of the mPRF (i.e. autoreceptors) provide a novel mechanism for inhibition of ACh release and thereby modulation of REM sleep in the cat (210). In summary, despite significant strides in deciphering the physiology of ACh within the mPRF, the synaptic circuits, both presynaptic and postsynaptic, and mAChRs critical to REM sleep modulation remain undefined.

We have applied antibodies to the vAChT (211) and mAChR subtype-specific antibodies (212,213) to assess more accurately the synaptic sites and molecular receptor subtypes at which ACh engages the established circuitry underlying REM sleep expression in the nonhuman primate mPRF. Our initial immunoelectron microscopic studies have revealed differential distributions of cholinergic terminals (i.e. vAChT) and the m1–m4 mAChR proteins, which suggests a greater

complexity in cholinergic modulation of REM sleep than previously postulated (see Fig. 6). Because each molecular mAChR subtype is differentially coupled to unique ion channels and second messenger systems (209,214–217), the expression of mAChRs on specific presynaptic and postsynaptic circuits provides a tremendous diversity for ACh's modulation of REM sleep. Within the mPRF, receptor protein expression does not coincide strictly with cholinergic synapses as revealed with vAChT; an example of transmitter-receptor mismatch that has previously been noted in studies of cholinergic innervation of the medulla (218). The dense and predominantly presynaptic localization of m2 in a zone relatively devoid of cholinergic synapses immediately ventral to the ventral tegmental nucleus (VTg) (Fig. 6) corresponds to a locus where microinfusion of cholinomimetics is most efficacious in enhancing REM sleep (136,187). This finding suggests that ACh's role in REM sleep may involve modulation of release of alternative transmitters at presynaptic mAChRs and transmission beyond traditional synaptic boundaries (e.g. volume transmission). Modulation of the release of GABA, glutamate, aspartate, and ACh by actions of ACh at presynaptic mAChRs has previously been established in an alternate brain locus, the hippocampus (219–223). In the vicinity of the mPRF, the m2 and m3 mAChRs are also expressed in unique circumscribed loci in a region where previous attempts at architectonic divisioning have met with limited success. These chemoarchitectonic features likely reflect the fact that segregated neuronal subsystems within the mPRF (e.g. the median raphe, VTg, pontine tegmental field, pontine oralis, and caudalis) mediate coma (224,225), eye and head movements (226), and atonia (23,124,227) and are modulated in unique ways by ACh. These findings challenge the conventional thinking that ACh's role in REM sleep modulation is purely a postsynaptic phenomenon and demonstrate the power of immuno-electron microscopic analysis with specific antibodies to proteins involved in cholinergic neurotransmission to advance our understanding of REM sleep mechanisms. Specifically, segregation of mAChRs to unique presynaptic and postsynaptic elements suggests that specific synaptic circuits are differentially modulated by ACh. Correlating specific patterns of mAChR expression in the mPRF with its efferent and afferent connections would substantially improve postulated models of REM sleep mechanisms by including local and distant, cholinergic and noncholinergic, neural circuits.

Although the above considerations account for much that has been postulated concerning ACh's role in narcolepsy, some symptoms may reflect pathologies in alternate synaptic circuits and neurotransmitters that either directly or indirectly involve ACh and the PPN region. Cholinergic cell number in the PPN/LDT, for example, has been reported to be increased in the canine model of narcolepsy/cataplexy (228), possibly by as much as 100% (229). Whether this finding is recapitulated in the human condition, and whether it is specific to cholinergic brainstem neurons, needs to be investigated because it likely reflects an important anomaly in the developmental sequence of brainstem circuits. Deciphering alterations in the afferent and efferent connections of the PPN/LDT and mAChR expression that accompany any increase in cholinergic cell number should help resolve the critical neural substrates governing narcolepsy and other disorders characterized by the pathological expression of REM sleep.

The expression of narcoleptic symptoms either together or as individual components (e.g. cataplexy or hypnagogic hallucinations) may also reflect enhanced neural activity in the PPN/LDT region that is a direct consequence of alterations in afferent pathways that originate in subcortical forebrain nuclei. The forebrain circuits most likely to contribute to narcoleptic symptoms by interacting with the PPN/LDT are dopamine responsive because 1) systemic D2/D3 agonists aggravate canine and human narcolepsy/cataplexy [reviewed in Nishino et al. (188)]; 2) dopamine receptor densities are elevated in the basal ganglia and amygdala of canine and human narcolepsy (230–233); 3) local administration of D2/D3 agonists in the ventral tegmental area or external segment of the globus pallidus aggravate canine cataplexy (234); 4) these same nuclei engage the RRF/MEA/PPN either directly or via multisynaptic routes (see above); and 5) the MEA is disinhibited in a cell-specific manner following systemic administration of dopaminomimetics (Fig. 4D). On the basis of the anatomical and physiological considerations discussed earlier, disinhibition of the PPN's efferent pathways may promote PGO waves and REM sleep, whereas a similar action on descending glutamatergic pathways from the MEA may enhance REM atonia (viz. cataplexy). Pathologies independent of primary narcolepsy that "activate" the MEA and possibly the PPN by disturbing the integrity of their dopamine-responsive GABAergic afferents might therefore be expected to manifest narcoleptic symptoms; indeed, pathological involvement of the substantia nigra pars reticulata (SNr) has been associated with narcolepsy (235). Isolated bilateral infarctions of the SNr have also been associated with peduncular hallucinosis, a clinical syndrome that bears a remarkable semblance to hypnagogic hallucinations experienced by narcoleptics (236). Similarly, potential dampening of the GPi's GABAergic output to the MEA through D4 receptor blockade (119,120,237) may account for anecdotal reports of enhanced REM sleep and cataplexy in humans following administration of the D4 antagonist cloza-

pine (238,239). Although the postulate that the altered dopamine transmission in narcolepsy ultimately manifests itself through the PPN/LDT is an attractive one, it has not been tested directly. Investigations of the pharmacological receptors mediating dopamine's aggravation of cataplexy, and behavioral state in general, have been relatively few and limited primarily to assessments of systemically administered drugs that recognize only two classes of dopamine binding sites (D1 and D2/D3) (reviewed in Rye and Bliwise (166)]. The inability of these reagents to discriminate among the molecularly defined dopamine receptors (e.g. D1–D5) (240) has prevented a precise determination of the pertinent receptors and synaptic circuits underlying the well-described exacerbation of cataplexy by D2/D3 agonists and whether it might involve the PPN/LDT region.

There are several additional pathologies or neurotransmitter alterations described in canine narcolepsy/cataplexy, whose role in the expression of clinical symptoms may also directly or indirectly involve brainstem cholinergic synaptic circuits. Adrenergic mediated hyperpolarization of cholinergic PPN pathways that promote REM atonia may account for observations that cataplexy is aggravated by alpha$_1$-adrenergic antagonists (e.g. prazosin) (241,242) and can be blocked by atropine (188,195). Alterations in the magnocellular basal forebrain and amygdala of narcoleptic canines have also recently been implicated in mediating narcoleptic symptoms; however, the precise synaptic circuits involved and how they interact with cholinergic, REM–sleep-inducing brainstem circuits is ill defined. Cataplexy can be modulated by basal forebrain circuits that are sensitive to ACh (243,244), REM sleep periods are abbreviated by adrenergic (245) or prolactin (246) microinfusions into the central nucleus of the amygdala, and axonal degeneration has recently been described in the basal forebrain and amygdala of the narcoleptic canine (247).

In summary, alterations in cholinergic and monoaminergic circuits and receptors in narcolepsy are diverse and involve widespread regions of the central nervous system. From original investigations that emphasized brainstem circuits in modulating the pathophysiology of narcolepsy, interest has recently migrated to forebrain nuclei and their circuits. A cohesive picture of the pertinent receptors and pathways participating in the pathophysiology of narcolepsy and cataplexy, nonetheless, remains elusive. In part this reflects an incomplete understanding of the critical synaptic circuits and diversity of newly discovered molecular receptors that orchestrate normal REM sleep. The careful application of modern neuroanatomical techniques to brainstem regions long implicated in REM sleep generation, as reviewed here, reveals hitherto unappreciated organizational features at the pathway, cell, receptor, and synaptic levels. Together, these findings provide critical insights into the normal and pathological expression of REM sleep or its components that await physiological and behavioral verification.

4.2 REM sleep behavior disorder

Interference with the maintenance of REM sleep atonia manifests clinically as REM sleep behavior disorder (RBD). It can be the presenting symptom of Parkinson's disease (PD) (248,249), multiple system atrophy (250), and olivo-ponto-cerebellar degeneration (251) and is said to occur in 15% of all patients with PD (252) and an unknown proportion of narcoleptics (253). The MEA/PPN region and the subceruleal region with which it is contiguous have been implicated in the pathophysiology of RBD (166). Glutamatergic and cholinergic neurons in the MEA/PPN region play a critical role in maintaining atonia, particularly atonia that accompanies REM sleep (178). Neurons overlapping in distribution with the MEA display REM sleep-specific increases in neural discharge (176), project to medullary regions essential in maintaining REM atonia (23,52), and, when lesioned, release complex motor behaviors in REM sleep in animals (172,176,254) and humans (248,251,255). The pathophysiological basis of RBD may lie in injury to the PPN itself, because it is involved by the primary pathology of several neurodegenerative diseases (see below). Alternatively, abnormal afferent signals originating in the basal ganglia may alter neural responsiveness in the MEA/PPN region via the pallidotegmental tract discussed above. Efferents from the SNr (94) and GPi (93) make synaptic contact with tegmental neurons projecting to the ventromedial medulla, yet it remains unclear if RRF neurons, MEA neurons, PPN neurons, or all of these participate in this multisynaptic route linking the basal ganglia with the lower motor centers involved in modulating REM atonia. Given that many nocturnal movements, including those in REM sleep, are responsive to dopamine, it is tempting to hypothesize that a subpopulation of dopamine-responsive neurons in the PPN region innervate a ventral medullary region widely recognized to modulate atonia (256,257), particularly atonia that accompanies REM sleep (172,176, 178,258,259).

The functional role of basal ganglia ouput to the RRF/MEA/PPN with respect to physiological measures of nocturnal movement is unclear. Neurons in the GPi (166,260) and SNr (127,165) discharge phasically at rates exceeding those seen in wakefulness (200 vs. 50 Hz) in concert with phasic events of REM sleep (e.g. eye movements and phasic EMG bursts),

TABLE 2. *Quantitative assessments of REM sleep and detailed analysis of eye movement densities and phasic EMG events in REM sleep before and after pallidotomy*

Features of REM sleep	Pre-pallidotomy	Post-pallidotomy
REM sleep (% TST)	2	10
% REM sleep μepochs (2.5 seconds) occupied by eye movement	20	17
% REM sleep μepochs (2.5 seconds) occupied by any movement	30	114
Chin movement	18	6
Left arm movement	8	3
Right arm movement	9	6
Left leg movement	10	2
Right leg movement	5	<1

EMG, electromyograph; REM, rapid eye movement; TST, total sleep time.

Subject was a 53-year-old man with medically intractable Parkinson's disease (PD). Note the dramatic reduction in phasic electromyograph events in REM sleep in chin and all limbs following unilateral (right hemisphere) pallidotomy. This is a specific effect related to pallidotomy, because medication status is unchanged for polysomnographic testing and medically treated PD controls do not exhibit wide night-to-night variations in nocturnal movement. Striatal dopamine depletion in PD is accompanied by excessive inhibition of the midbrain extrapyramidal area (MEA), which may underly the expression of excessive nocturnal movement (166). The beneficial effects of pallidotomy on nocturnal movement are likely to reflect release of the MEA from excessive pallidal inhibition, because previous investigations have associated nocturnal movements with reticulospinal systems (333) but have failed to implicate alternative targets of basal ganglia output (e.g., thalamocortical circuits) (334).

although a direct causal relationship has not been established. Neural discharge in these main output nuclei of the basal ganglia is otherwise slightly below waking discharge rates during quiet periods of REM sleep in which atonia predominates. We hypothesize that much of the GABAergic basal ganglia output targets glutamatergic RRF and/or MEA neurons, which, in turn, activate the ventromedial medullary zone that promotes REM atonia. Heightened phasic discharge of the GPi that occurs transiently or that is persistent in pathological states such as PD (261) would be expected to excessively inhibit the MEA, thereby allowing for the expression of movement that overcomes REM atonia. This hypothesis is borne out by clinical experience that excessive nocturnal movement in PD (166) can be reversed by removing excessive inhibition of the MEA by pallidotomy in individual cases (see Table 2). It also consistent with the fact that pathological nocturnal movements observed in several clinical disorders (e.g. periodic leg movements of sleep and RBD) are 1) responsive to dopaminomimetic therapy (e.g. through dampening of GPi output; see above); 2) aggravated by dopamine antagonists; and 3) characterized by diminished dopaminergic "tone" in the basal ganglia (Table 3). Considerably more work is necessary to establish that these hypothesized multisynaptic circuits indeed modulate nocturnal movements, including RBD, and the precise cellular and pharmacological substrates involved.

4.3 Neurodegenerative diseases

A variable degree of cell loss in the PPN region has been reported in Alzheimer's disease (AD) (262–264), Parkinson's disease (PD) (262,264–268), and progressive supranuclear palsy (262,264) (PSP) (Fig. 2F–H). It is attractive to postulate that these pathologies may contribute to REM sleep-specific abnormalities observed in these conditions, including 1) marked reduction in REM sleep time (269,270); 2) loss of REM atonia and RBD (271,272) (see above); and 3) complete absence of REM sleep (273), respectively. Such simple clinicopathological correlations are notoriously difficult to establish. The majority of studies, for example, are not rigorously quantitative and do not carefully consider the viability of surrounding noncholinergic nuclei, such as the MEA, which likely have unique roles in modulating REM sleep phenomena. Considerations focused solely on the integrity of the cholinergic PPN also ignore how other brain regions that are primarily or secondarily involved by a disease process might contribute to disease-specific behavioral state alterations. For example, in AD, PD, and PSP,

TABLE 3. *Summary of clinical disorders characterized by nocturnal movements, and treatment and pathophysiological considerations that emphasize their potential origin in dopamine-responsive basal ganglia circuits*

Disorder	Nocturnal movements	Treatment	Aggravators	Pathophysiological basis in basal ganglia	References
PLMs	PLMs in stage 2 ≫ REM sleep	L-dopa, D2 agonists, opiates, benzodiazepines	pimozide (D2 antagonist), metaclopramide	Decreased affinity of striatal D2 receptors	(335–338)
RBD	Phasic EMG activity in REM sleep; PLMs	L-dopa, D2 agonists, benzodiazepines	Neuroleptics	(?) Pre-parkinsonian	(248, 249, 339–342)
Narcolepsy	PLMs and RBD	L-dopa, D2-like agonists	Neuroleptics	Increased D1 and D2 binding sites in GPi	(253, 343, 344)

EMG, electromyograph; GPi, internal segment of the globus pallidus; PLMs, periodic leg movements in sleep; REM, rapid eye movement; RBD, REM behavior disorder.

additional brainstem neurons with significant roles in behavioral state control, particularly brainstem monoaminergic nuclei, also degenerate (268). Furthermore, conventional neuropathological examination cannot divulge physiological changes that are believed to be the ultimate mediators of clinical symptomatology, such as the heightened discharge of GPi neurons in PD that occurs secondary to dopamine cell loss in the substantia nigra (see above). Prospective application of alternate measures more reflective of physiological activity in the PPN region and its connections (see below) to these patient populations, in combination with detailed postmortem neuropathological examination, should help reveal the contribution of PPN circuits to specific clinical syndromes. Alternatively, this goal will be realized by application of similar methodologies or detailed polysomnography to a select group of patients with incidental [e.g. McKee et al. (236)] or controlled (e.g. pallidotomy for PD) lesions that are restricted to brain regions with known effects on the responsiveness of specific PPN cell populations.

4.4 Affective illness

4.4.1 Depression

The nocturnal (274–277) and daytime (278) sleep of patients with primary depression exhibits many features that approximate those seen in narcolepsy [reviewed in Benca (279)]. In particular, nocturnal REM sleep latency is shortened, phasic events in the first nocturnal REM period are exaggerated, and REM sleep can intrude into daytime naps, albeit at latency well beyond the range observed in narcolepsy. Cholinergic PPN/LDT synaptic circuits discussed above figure prominently in two hypotheses that have been proposed to explain these observations: the reciprocal interaction model of Hobson and McCarley (7,280), and the increased cholinergic to catecholaminergic activity ratio model (281). Because cholinergic PPN/LDT circuits are common to both hypotheses, it is clear that they are not mutually exclusive. The reciprocal interaction model argues that deficient monoaminergic tone, particularly in the form of decreased serotonergic dorsal raphe firing, plays a permissive role in "disinhibiting" the PPN/LDT and thereby the cholinergic synaptic circuits that orchestrate REM sleep (8). Alternatively, the increased cholinergic activity hypothesis suggests that the pathological REM sleep characteristic of primary depression, as in narcolepsy, reflects a heightened sensitivity of mAChRs to ACh released from REM sleep-promoting PPN/LDT circuits. This concept is supported by observations that muscarinic agonists markedly decrease the latency to REM sleep in depressives (282) and in their relatives at risk for developing depression (283). Because our knowledge of cholinergic synaptic circuits and receptors in neural systems governing REM sleep is so rudimentary and has not been systematically investigated in animal models of depression [e.g. see Yavari et al. (284)] or in postmortem brain tissue of depressives, it is difficult to invalidate either hypothesis. Both emphasize the importance that continued delineation of brainstem cholinergic synaptic circuits has to understanding the pathophysiology underlying REM dyscontrol and coincident depressive symptoms in endogenous depression.

4.4.2 Schizophrenia

Since the early part of this century, it has been repeatedly speculated that the hallucinatory experiences of schizophrenics might represent intrusions of dreams (i.e. REM sleep phenomenon) into waking life [reviewed in Gillin and Wyatt (285)]. This theory has met with considerable skepticism because 1) many cases of "schizophrenia" constitute a subgroup of stimulant-responsive narcoleptics in whom hallucinatory experiences are an unusually prominent feature (286–291); and 2) a plausible biological substrate common to REM sleep dyscontrol and schizophrenia has been lacking. Although it remains controversial as to whether schizophrenia is characterized by REM sleep intrusions into daytime naps, REM dyscontrol in the form of markedly shortened nocturnal REM latencies has recently been established in untreated schizophrenia (292,293). Moreover, converging lines of evidence argue that the pathophysiology underlying REM dyscontrol and hallucinosis may reside within cholinergic brainstem circuits. It is well known, for example, that muscarinic agonists aggravate negative schizophrenic symptoms (294,295), and $NADPH^+$ neurons in the PPN, but not the adjacent LDT, are reported to be increased by as much as 100% in a subpopulation of chronic schizophrenics (16,17). These findings are difficult to reconcile with reports that the synthesizing enzyme for ACh, i.e. ChAT, is markedly decreased in the pontine tegmentum of schizophrenics (296). Moreover, independent confirmation of these findings employing immunolabeling for ChAT within PPN/LDT regions has not been forthcoming (297). An alternative model describing REM dyscontrol and hallucinosis in schizophrenia may reside within the dopamine-responsive basal ganglia circuits that directly target the PPN region via the pallidotegmental tract. Most biological models of schizophrenia have hypothesized dopaminergic augmentation of neural activity in thalamo-cortico-striatal limbic circuits to account for intrusive thoughts, motor restlessness, and frank hyperkinesis (298). The resultant dampening of GABAergic output

from the basal ganglia reinforces thalamocortical activity but ignores the fact that an equal component of this output descends and converges upon the PPN region, where it presumably disinhibits specific pools of neurons. A resultant heightened responsiveness in cholinergic and adjacent noncholinergic neurons in the PPN region might account for schizophrenic features of REM dyscontrol via efferents that in turn ascend to reinnervate the thalamus or descend to caudal brainstem centers. The details of these synaptic connections are yet to be fully worked out, and the effects of pallidal output on REM sleep-specific neuron populations in the PPN region are yet to be determined. The organization of basal ganglia output to the PPN region is equally relevant to attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder, and Tourette's, where biological models have also emphasized the importance of dopaminergic augmentation of thalamo-cortico-striatal activity in basal ganglia circuits parallel to those implicated in schizophrenia (299–301). Although these disorders are frequently accompanied by sleep pathology (302,303), in contrast to schizophrenia, abnormalities of REM sleep have not yet been widely appreciated.

5.0 BRAINSTEM REFLEXES MODULATED BY THE PPN: POTENTIAL APPLICATION TO CLINICAL DISORDERS

The recognition and characterization of disorders in which REM sleep is primarily affected (e.g. narcolepsy, RBD, and neurodegenerative diseases) are presently limited to polysomnography (PSG) and multiple sleep latency testing (MSLT). Investigating the neurobiological mechanisms common to REM dyscontrol and affective illness is similarly constrained. Such testing is time consuming, costly, and not practical for assessing clinical response to pharmacological interventions. Alternative procedures that might provide a window on the functional anatomy of the PPN region, such as functional magnetic resonance imaging and positron emission tomography, do not afford the resolution necessary to investigate a heterogeneous brain region that approximates 5 mm in diameter in humans. Many features of electrophysiologically recorded responses elicited by suprathreshold auditory stimuli delivered singly, in pairs, or at sustained higher frequencies [e.g. 0.5–10 Hz, or the middle latency auditory evoked response (P1 potential), acoustic startle reflex (ASR), and paired pulse stimulation (PPI)] are increasingly recognized to be modulated by the PPN region and provide an opportunity to assess its functional integrity in disorders of REM sleep [reviewed in Reese et al. (304) and Swerdlow (305)]. These measures are attractive tools because they are altered in specific ways by pathologies that involve the PPN or its afferent connections, they are easily obtained in an outpatient or inpatient setting, and their application in experimental animals continues to elucidate their underlying cellular and pharmacological substrates.

5.1 Assessment of the ascending cholinergic ARAS

The auditory-evoked response occurring at approximately 50 milliseconds [i.e. the middle latency auditory evoked response (MLR)], also called the P1 potential, is believed to reflect a component of arousal/alertness, given its presence during wakefulness, disappearance during slow-wave sleep, and reappearance in REM sleep (306). Because it is easily obtainable and quantifiable, the MLR has attracted some interest as a diagnostic tool for diseases exhibiting disorders of behavioral state control. Because the response is 1) abolished after lesions that include the cholinergic PPN/LDT (307); 2) abolished by anticholinergic medications and reestablished with medications that increase central ACh (307); and 3) markedly attenuated in a subpopulation of Alzheimer's disease in which PPN pathology is likely present (308–310), it has been proposed that the critical mediator of the MLR is the cholinergic wing of the ascending reticular activating system originating in the PPN/LDT. Narcolepsy has been associated with decreased latencies (311,312) and amplitude (313) of the P1 and a decreased habituation of the P1 at higher rates of auditory stimulation in a subpopulation of narcoleptics (312). A similar inability of the P1 to habituate in narcolepsy has been reported in a paired pulse stimulus paradigm (314). As might be expected given the similarities in clinical and pathological features between narcolepsy and schizophrenia discussed above, failure to habituate the second P1 response in a paired pulse paradigm has been described in schizophrenia (315). Although these findings suggest that the amplitude, latency, and habituation of the P1 response are potentially useful means to assess narcolepsy and schizophrenia, the specific neural and pharmacological substrates governing each of these individual features of the P1 remain obscure, and the clinical correlates vague. Pharmacologic agents that increase synaptic availability of serotonin and norepinephrine enhance the amplitude of the P1 in narcoleptic and hypersomnic patients, but it is unclear if this effect is dependent upon ascending cholinergic pathways (312). Investigation of the effects of cell-specific and pathway-specific physiological changes in the PPN region on the P1 potential will encourage its wider clinical application. As PD is frequently accompanied by REM dyscontrol that likely reflects pathologic alterations in the PPN region and/or its afferent connections (see above), MPTP animal models of parkin-

sonism provide a unique opportunity to elaborate upon the underlying behavioral and cellular correlates of the P1 response. Marked diminishment of P1 amplitudes and REM sleep follow the systemic administration of MPTP and display recovery characteristics that coincide with improvement of parkinsonian motor symptoms (316,317). Parkinsonian patients fail to habituate the second P1 response in a paired pulse paradigm (318). Although this finding might be operationally defined as a "disinhibition" of the substrate(s) generating the P1 potential in the PPN region, on the surface it seems paradoxical given that activity in the GABAergic pallidotegmental pathways is enhanced in the parkinsonian state (see above). Increases in tonic levels of firing in cholinergic neurons are unlikely to account for the P1 response characteristics in PD because hyperpolarizing influences would be expected to inhibit activity in ascending cholinergic pathways. Perhaps the P1 response characteristics of PD are more reflective of an enhanced burst firing mode in the subpopulations of noncholinergic and cholinergic neurons that display LTS susceptible to activation by hyperpolarizing influences (see above). Alternatively, the cellular correlates of P1 response characteristics in PD may reflect other aspects of cell responsiveness of the PPN region that are secondary to alternate pathologies in the human condition (e.g. dorsal raphe and/or PPN pathology; see above). Enhanced firing in tonically active ascending cholinergic pathways might be expected in individual patients with significant pathology in the dorsal raphe, given the known hyperpolarizing effects of serotonin upon cholinergic PPN neurons. Deciphering between these possibilities demands further evaluation of the P1 in experimental animals where the cellular pathology is more predictable, or in a within-subject's paradigm in which P1 is evaluated prior to, and after, controlled lesions of the internal pallidum for relief of parkinsonian symptoms (e.g. pallidotomy).

5.2 Assessment of descending pathways from the PPN region

The acoustic startle response (ASR) to a suprathreshold auditory stimulus manifests as an increase in electromyograph activity at approximately 5–70 milliseconds (dependent upon the muscle and species investigated) (304,319,320). The amplitude and latency of the ASR and particularly its inhibition by a weak preceding auditory stimulus [i.e. prepulse inhibition (PPI)] are robust phenomena with obligatory neural substrates that lie in the pontomedullary reticular formation (321). These responses have received some attention with respect to assessing the cellular responsiveness of the PPN region and activity along its descending connections because 1) auditory stimuli evoke short latency responses in the form of PGO waves and appear coupled to phasic events of REM sleep (56,142,322,323); 2) the PPN region innervates pontine regions critical for the ASR (324); 3) the amplitude of the ASR and PPI are markedly attenuated following electrolytic or cytolytic lesions of the PPN region (324,325); and 4) PPI is also dampened by dopamine-sensitive basal ganglia circuits that likely enhance the responsiveness of the PPN region (see above; Fig. 4D) (325–328). Although attenuation of the PPI in schizophrenia correlates with sensorimotor gating abnormalities as assessed by vigilance and distractability tasks (329), it is unclear how it might reflect abnormalities in the PPN region and in REM sleep, as discussed above. The PPI is also reported to be normal in PD patients acutely withdrawn from medications, with subsequent attentuation seen with apomorphine but not L-Dopa (330). It would be interesting to evaluate PPI in primary disorders of REM sleep such as RBD, in which clinical manifestations are thought to reside in the integrity of the PPN region or abnormalities in descending glutamatergic MEA and cholinergic PPN pathways. Application of the PPI to disorders of REM sleep thought to reside in brainstem cholinergic synaptic circuits awaits further, more precise identification of its cellular and pharmacological substrates in well-defined clinical disorders and animal models.

6.0 CONCLUDING REMARKS

The increased interest in the neurobiology of the PPN/LDT within the past decade has been fueled by the discovery of a contingent of cholinergic neurons within these regions that had been predicted by experimental and clinically derived models of behavioral state control. The prototypical disorders of depression and narcolepsy have spawned much of our knowledge concerning the critical role of cholinergic brainstem circuits in promoting REM sleep. The clinical diversity of REM sleep alterations, however, demanded a more careful consideration of the input-output relationships, synaptic organization, and pharmacology of the PPN region, as reviewed here. Such an analysis reveals previously unsuspected organizational features of brainstem circuits that in part reconcile the seemingly conflicting postulated roles of the PPN in behavioral state regulation and motor control that had been based upon a separate literature that emphasized its relationships with the basal ganglia. Considerable details of the anatomy, ontogeny, and cell biology of this heterogeneous brain region remain to be determined.

The present review emphasizes that REM sleep control by brainstem synaptic circuits is far more complicated than previously suspected and should not be lim-

ited solely to considerations of cholinergic PPN/LDT neurons. Neuronal populations in rat, nonhuman primate, and human PPN region display unique connectional and neurochemical characteristics and are therefore likely to subserve distinct functional roles with respect to REM sleep control that demand further investigation (see Fig. 5). The output of parallel, segregated basal ganglia circuits to the PPN region is a conspicuous feature across species that affords recognition of two noncholinergic "nuclei", the RRF and MEA. Terminal fields are dense, convergent, and perisomatic. In contrast, basal ganglia output to cholinergic PPN neurons likely occurs on distal dendritic domains and therefore competes with more abundant proximal synaptic inputs in determining the responsiveness of neurons with a more widely appreciated role in effecting REM sleep. Although functional anatomical models of the basal ganglia have chosen to emphasize relationships with thalamocortical circuits, the size and functional import of pallidotegmental projections to the PPN region should not be underestimated. This projection is extensive and arises via collaterals from basal ganglia output to the thalamus and, as reviewed here, clearly brings forebrain circuits into focus as potential determinants of many aspects of normal and pathological REM sleep. Novel substrates involved in modulating normal and pathological REM sleep reviewed here also include potential actions of ACh on release of alternate neurotransmitters via presynaptic muscarinic receptors in pontine synaptic circuits known to modulate REM sleep. Discordance between cholinergic terminals and receptors in this same pontine locus suggests that cholinergic volume transmission may also play a role in modulating REM sleep. Treatments directed at specific disorders of REM sleep will only be realized when specific voids in our knowledge regarding all these circuits are critically addressed. With respect to disorders characterized by excessive or inappropriate REM sleep expression, for example, further elucidation of the pathways and receptors mediating the responsiveness of the PPN/LDT are critical to establish. A systematic analysis of the postsynaptic neural elements and molecular receptors mediating ACh's actions within the medial pontine reticular formation would also be critical in this regard. With respect to disorders characterized by an inability to maintain REM atonia, it will be important to establish the synaptic relations, receptors, and descending connections of glutamatergic RRF and MEA neurons. Realization of the clinical relevance attending the pathway-, cell-, receptor-, and synapse-specific features of the PPN region will require electrophysiological and behavioral paradigms that respect the anatomical limitations placed upon them. Hopefully, anatomical, electrophysiological, and behavioral studies can move forward in step so that the PPN region's modulatory actions on REM sleep and the development of more specific treatment strategies for disorders of REM sleep are realized.

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