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Modulation of normal and pathologic motoneuron activity during sleep: insights from the neurology clinic, Parkinson's disease, and comments on parkinsonian-related sleepiness

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1. Introduction

A description of electromyographic (EMG) activity during sleep demands familiarity with the organizational principles—anatomical, neurochemical, and physiological—that govern somatic motor system function. The final common pathway to initiate or suppress movements is the lower motor neuron, whose axons innervate striated muscle fibers. The neural circuits governing motoneuron activity are numerous, complex, and for the most part incompletely understood. It is important to speak conceptually of elements that have a significant impact upon motor behavior as 'pre-motor'. Pre-motor neurons include those whose axons directly contact motoneurons and others that, despite being several synapses removed from the neuromuscular junction, elicit movement when stimulated. The precise multisynaptic circuits through which these physiologically defined pre-motor influences reach motoneurons remain ill-defined. Pre-motor elements thus describe links of a chain that share in common an ability to modulate motoneuron excitability and thereby movement. This being said, it should become obvious from the discussion that follows that there are many pathways that converge in parallel upon motoneurons, rather than a strictly hierarchical chain built upon serial circuits.

In addition to pre-motor neurons and interneurons intrinsic to the spinal cord, the elements most relevant to this discussion are extrinsic: i.e. they originate from groups of neurons within the brain and are thus described as 'supraspinal' [1]. Current heuristic models of motor system structure and function recognize two divisions: medial and lateral somatic motor systems [2]. The medial system is devoted to modulation of eye, neck, axial, and proximal body movements and includes tectospinal (originating from deep layers of the superior colliculus), vestibulospinal, and reticulospinal (originating from the dorsal two-thirds of the medial tegmentum of the caudal pons and medulla) components. Descending pathways of this system course medially in the spinal cord and terminate principally in the ipsilateral, medial part of the ventral horn containing interneurons and motoneurons of axial and proximal muscles. This system is principally concerned with orienting the head and body relative to the visual fields under control of extrinsic eye muscles. The lateral system is devoted to voluntary movements of the extremities and includes the rubro- and corticospinal tracts. The rubrospinal tract is a phylogenetically old supraspinal system. It is exclusively crossed, descends in the dorsolateral funiculus of the spinal cord, and innervates premotor interneurons, although direct projections to motoneurons also exist. Corticospinal pathways mimic the rubrospinal pathway [3–5], but in parallel with an expanding neocortex, they take on greater specialization and importance in primates [1]. In their descent from the neocortex, many individual corticospinal axons give off collaterals to rubro- and reticulospinal neurons. The majority continue their descent and act monosynaptically upon motoneurons of distal musculature. The primary and supplementary cortices from which the corticospinal tract arise, as well as the red nucleus (the origin of the rubrospinal tract), are both microexcitable; when stimulated, they elicit movements primarily in distal, flexor muscles.

A substantial additional set of pathways originating from the brainstem influence spinal motoneurons. These include monoamine pathways (e.g. dopaminergic, noradrenergic, and serotonergic) and reticulospinal projections originating from the ventromedial medulla [6]. The caudal pons and contiguous ventromedial medulla are remarkable in having neurons that innervate a wide variety of motoneurons, from those innervating distal extremities to diaphragmatic [7],

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rectus abdominis [8], and pudendal [9] motoneurons. These supraspinal systems have received particular attention because they receive inputs from many forebrain structures designated as 'limbic' in nature or demonstrate activity that is highly correlated with sleep-wake state. These features have justified their consideration as a distinct 'emotional motor system' to many investigators in the field [6,10,11]. The practical clinical significance of these systems lies in the fact that: (1) many commonly prescribed, centrally acting drugs act to enhance or dampen monoaminergic neurotransmission; (2) there are age- and disease-related declines in the densities of many monoaminergic pathways; and (3) the ventromedial medulla also appears to participate in a multisynaptic pathway linking movement-related structures of the basal ganglia with lower motoneurons.

The distributions of the spinal monoamines are very similar to innervation of sensory (dorsal horn), autonomic (intermediolateral cell column), and motor (ventral horn) areas of the spinal cord. Dopaminergic fibers originate predominantly from the diencephalic A11 cell group, and to a lesser extent from the A13 group [12–15]. Spinal noradrenergic innervation originates from the locus coeruleus and subcoeruleal area [16–19]. The serotonergic raphe magnus projects to the dorsal horn, whereas the more caudally situated raphe pallidus and obscurus project principally to the intermediate zone, including direct innervation of Renshaw cells [20] and motoneuron cell groups [21,22]. Glutamate also appears to exist as a cotransmitter in many individual monoaminergic cells [2,23–26]. Two important inhibitory reticulospinal projection systems originating from the ventromedial medulla include pathways containing gamma-aminobutyric acid (GABA) or glycine. Nearly 40% of these appear to be GABAergic, 15% glycinergic, and the remainder a collage of glutamatergic and monoaminergic [11]. That 50% of the terminals descending from the ventromedial medulla and adjacent raphe cell groups make synaptic contact with motoneurons, primarily upon their proximal dendrites [11], emphasizes their relative importance in determining the state of motoneuron excitability. Neural collections in the caudal medulla, dorsal to the inferior olive, seem to exert an inhibitory influence upon motoneurons (e.g. the 'bulbospinal inhibitory zone' of Magoun and Rhines [27]), while rostrally situated neurons at the pontomedullary junction in proximity of the raphe magnus tend to enhance motoneuron excitability [28].

The physiological effects of the spinal monoamine systems are best categorized as 'neuromodulatory'. That is, rather than eliciting excitatory postsynaptic potentials (EPSPs) in motoneurons as does glutamate, or inhibitory postsynaptic potentials in motoneurons as do GABA and glycine, monoamines generally enhance motoneuron responses to excitatory and inhibitory influences [29,30]. By changing the strength of specific synapses and by altering neural membrane properties and specific ion conductances, monoamines rapidly reconfigure motor networks commensurate with environmental and homeostatic demands. By modulating the responsiveness of motoneurons and pre-motor elements to other excitatory or inhibitory inputs, neuromodulators affect the intensity, duration, and timing of motor output [31–33]. Moreover, because individual axons frequently traverse several spinal cord segments, coordination of movement sequences by muscles whose motoneurons are spatially separated (e.g. arm versus leg, proximal versus distal, agonists versus antagonists) is possible.

Long descending monoaminergic fiber systems also appear to have a significant role in modulating ascending sensory transmission either by acting postsynaptically on 'secondary' sensory spinal neurons, or by acting presynaptically upon the terminal axons of dorsal root afferents. Serotonin, noradrenaline, and dopamine, for example, all depress transmission from group II muscle spindle afferents [34–36] and depress motoneuron EPSPs via effects on metabotropic glutamate receptors at both pre- and postsynaptic sites [37]. Thus, prevailing views of monoamine modulation of spinal cord function include shared roles in promoting motor output and inhibiting sensory input.

2. Pathological motoneuron activity in sleep

2.1. Periodic leg movements in sleep (PLMS)

The final common pathway mediating PLMS are neural elements intrinsic to the spinal cord, given their unveiling below the level of pontine infarction [38] or spinal cord transection or pathology [39–42]. A strict derivation from a spinal locomotor network, common to many vertebrates, is unlikely because leg movements detected by standard surface electrodes placed over both anterior tibialis muscles most often occur simultaneously (versus alternately), can exhibit contraction with antagonists (namely, the gastrocnemius [41], personal observations), and may coincide with changes in the activity of upper limb or bulbar musculature (personal observations).

Identification of a single neurophysiological mechanism underlying PLMS remains enigmatic, although the principal deficit manifests as brainstem [43,44] and spinal reflex 'hyperexcitability' [45]. The origin of this enhancement of motoneuron output may reside in any one of several neural substrates outlined above. The recent delineation of *state-dependent* changes in spinal cord excitability demonstrated in restless legs syndrome (RLS)/PLM are of fundamental importance [45]. These changes manifest as: (1) decreased threshold of the flexor reflex (FR); and (2) segmental spread of the FR (from distal to proximal muscles). The FR is a widely studied phenomenon that can be modified by muscle and cutaneous afferents, Renshaw cells, presynaptic inhibition of afferents by intraspinal interneurons, and multiple supraspinal pathways. The pathophysiology of RLS/PLM does not reside in the principal sensory and motor elements themselves based upon observations that waking EMG

activity, resting motoneuron excitability, simple reflexes, and sensory-evoked potentials are generally normal [43,46]. The most powerful and consistent influences impacting upon RLS/PLM originate from outside the spinal cord in supraspinal, pre-motor circuits. This is best exemplified in the setting of spinal cord injury, where pharmacologic agents effective in treating RLS/PLM and dampening FR responses via local spinal circuits (e.g. dopaminomimetics and opioids), are generally, but not universally, *in*effective [41,42]. This argues that the primary benefit is mediated predominantly by alternate dopaminergic or dopamine-sensitive pathways located supraspinally.

Imaging studies, clinical observations, and animal studies have focused principally upon the nigrostriatal component of the mesotelencephalic dopamine system as a potential key substrate in the pathogenesis of RLS/PLM. Reductions in dopamine uptake into presynaptic axons via the dopamine transporter [47] and in D_2 receptor binding seen in some imaging studies [47,48] suggest a relative excess of extracellular dopamine. However, these changes are of small magnitude and have not been confirmed in a more recent, larger, and better-controlled study [49]. Periodic limb movements also occur when the striatum is depleted of dopamine axons either experimentally [50], or in the face of neurodegeneration occurring with Parkinson's disease (PD) [51,52]. That RLS/PLM could be attributed to enhanced extracellular striatal dopamine but also occur in the setting of striatal dopamine loss is seemingly contradictory. This might be reconciled if one posits that primary/idiopathic RLS/PLM is rooted in a fundamental inefficiency of striatal dopaminergic signaling at post- rather than presynaptic sites. This would account for observations that the prevalence of RLS in PD patients lacking intact nigrostriatal dopaminergic axons mirrors that observed in the general population [53]. Alternatively, this could point to the principal pathophysiology residing outside dopaminergic nigrostriatal pathways, for example, in dopaminergic diencephalospinal pathways. As these pathways terminate largely in the dorsal horn where they likely inhibit superficial and deep tissue afferents, their dysfunction would provide the most parsimonious, unifying explanation for augmentation of the FR observed in RLS and the occurrence of abnormal sensations. Only one very preliminary experimental study has tested whether dopaminergic diencephalospinal pathway lesions can induce RLS/PLM [54]. While the findings are suggestive, they lack adequate behavioral analysis and a comprehensive accounting of the synaptic, cellular, and network mechanisms responsible.

The precise neural pathways that could convey the consequences of impaired striatal dopamine neurotransmission to spinal circuits that ultimately generate RLS/PLM begin with the striato-pallidal or striato-nigral pathways, as first suggested by Askenasy [55]. Pathways exiting the striatum ultimately engage the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNr), which in turn concentrate their outputs upon thalamocortical networks, the deep layers of the superior colliculus, and the brainstem pedunculopontine region [56]. Underactivity of D_2 receptor-responsive sensorimotor striatal circuits would be expected to enhance GPi and SNr inhibitory influences to each of these targets [57]. Amelioration of RLS symptoms following pallidotomy in a patient with coexistent, idiopathic PD provides direct evidence, albeit anecdotal, that activity in basal ganglia sensorimotor circuits modulates RLS expression [58]. Our ongoing experience remains consistent in observing near elimination of PLM by pallidotomy in some PD patients [56]. Removal of pathologic pallidal output to the upper brainstem and, in turn, of descending influences upon ponto-medullary inhibition of spinal motor circuits, is the most parsimonious explanation for these benefits (namely, reversal of spinal disinhibition). Further confirmation and delineation of this multisynaptic pathway linking the basal ganglia and spinal cord is needed, but it is a plausible construct which accounts for several findings in RLS/PLM including: (1) enhancement in excitability and impaired habituation of brainstem-mediated aspects of the blink reflex [43,44]; (2) activation of synaptic or cellular elements in the mesopontine reticular formation visualized by functional magnetic resonance imaging [59]; and (3) lesion load below the tentorium (e.g. in the brainstem) correlating best with PLM in multiple sclerosis [60].

The considerations above do not preclude the fact that PLM can be modified by other central pathways. In fact, rather than exhibiting a unique pathology, it is reasonable to posit that PLM can arise from one of several central sources. From the perspective of spinal reflexes and local motor circuits, factors favoring PLM expression can be categorized into two groups: the first reflecting disinhibition due to interruption of descending inhibitory pathways, and a second including facilitation due to direct enhancement of neural activity. An example of the former includes modulation by the pyramidal motor system, given reports that patients with hemiplegia due to cerebrovascular disease exhibit PLM that predominate in the hemiplegic limbs [61]. Incidental damage to corticospinal fibers in non-human primates also unveils periodic movements that occur synchronously in the contralateral upper and lower limbs during non-REM sleep (personal observations). Enhancement of neural excitability by monoamines, on the other hand, likely accounts for the widely accepted clinical experience that RLS/PLM can be exacerbated by a wide array of antidepressants, including those designed to selectively increase synaptic availability of serotonin (namely, serotonin reuptake inhibitors) [62,63]. Even in a majority of *normal* volunteers lacking pre-existing RLS/PLM, the norepinephrine and serotonin reuptake blocker venlafaxine (Effexor®) induces PLM to greater than 25/hour of sleep [64]. It is unknown which specific neural substrates mediate these observed effects, given the ubiquitous nature of monoaminergic spinal innervation outlined above. Plausible loci are multifold and include direct enhancement of motoneuron responsiveness, 5-HT_2 receptor-mediated facilita-

tion of the FR [65], and medullary raphe-mediated enhancement of spinal nociceptive transmission [66]. Decrements in monoaminergic neural integrity with aging, particularly of dopaminergic nigrostriatal cells, may also figure prominently in the pathophysiology of PLM given their steadily increasing prevalence along the lifespan. Thus, redundancy intrinsic to sensorimotor networks and the general lack of 'command' neurons (i.e. neurons both necessary and sufficient to generate a normal or pathologic motor behavior such as PLM) could readily account for heterogeneity as it regards the etiology of RLS/PLM and also account for variability in treatment responses.

2.2. PLM in Parkinson's disease (PD) and animal models of PD

Disordered sleep in the form of excessive nocturnal movement in PD was first noted in Parkinson's nineteenth-century *Essay on the Shaking Palsy,* and these findings have subsequently been confirmed and extended [67]. Periodic limb movements both with and without RLS complaints are common [53], occurring at a greater prevalence than in conditions lacking severe nigrostriatal dopamine neuron loss such as aging, Alzheimer's disease [51] and multisystem atrophy [52]. The intrinsic pathology in PD itself is likely to be the major contributor to these findings because early and/or untreated PD patients clearly exhibit disturbed sleep that includes excessive nocturnal movement [68–71]. Moreover, rats [50] and non-human primates [72] depleted of striatal dopamine bilaterally exhibit excessive nocturnal movement, and sleep in the parkinsonian patient deteriorates with disease progression [73–75]. Clinical improvements of PD seen with surgical interventions that restore balance to the altered basal ganglia neurotransmission accompanying nigrostriatal dopamine loss also improve sleep architecture [56,76]. Relative preservation of the dopaminergic diencephalospinal system in PD [77–79] makes it an unlikely contributor to the worsening of nocturnal movement in PD. The precise substrates accounting for the detrimental effects of nigrostriatal dopamine loss upon nocturnal movement are ill-defined. It is tempting to speculate that dopamine modulates brainstem circuits affecting PLM and REM sleep atonia. This does not occur via direct dopaminergic innervation of the brainstem but rather by indirect, multisynaptic routes linking the basal ganglia output nuclei with pontomedullary reticulospinal pathways via the dorsolateral pons, including the subcoeruleal region [56].

2.3. Sleepiness in PD: causes and potential neural substrates

Sleepiness in PD is common and very real. By self-report, approximately 10–50% of PD patients experience sleepiness. Many patients (nearly one half of those complaining of sleepiness) satisfy physiological criteria for narcolepsy, which is the prototypical disorder of sudden-onset sleep [80,81]. Clinical and experimental experience concur that the disease itself, and not simply medication or sleep disruption, accounts for much of the attendant sleepiness. Dopamine loss within mesolimbic and mesocortical circuits, which is characteristic of patients with advanced disease, cognitive impairment, and drug-induced psychosis, appears most responsible [81]. Reports of sleepiness with dopaminomimetics are numerous and appear to be dose-related, but unrelated to specific class of agent (e.g. levodopa versus ergot and non-ergot-derived D_2-like agonists), consistent with findings seen in healthy controls. These reports are largely anecdotal and have not documented or investigated the nature of related sleep-architecture changes. An excessive 14 h of total sleep, including excessive REM sleep, with pergolide use versus a normal 8.2 h of sleep without pergolide was recently reported [82]. Improvement in *most* measures of sleep continuity and architecture with pergolide was also observed. These findings suggest that drug-induced sleepiness in PD reflects an increased sleep drive versus an inability to remain awake. While only briefly alluded to in this report, another potential adverse effect of dopamine agonist use is enhancement of REM sleep-expression – particularly the phasic components of REM sleep (including movement) – which are likely the physiological correlates of dream-like, hallucinatory behavior [83]. While some investigators suggest that obstructive sleep apnea (OSA) and PLM coexisting with PD may also contribute to sleepiness and intrusion of REM sleep into daytime naps (SOREMs), this is controversial since sleepiness in *non*-parkinsonian patients is not completely explained by the severity of OSA and PLM. Thus, premorbid sleepiness level, which is increasingly recognized to be a heritable trait in the general population, may also be a relevant factor in PD.

Dopamine pathways help to maintain sleep/wake homeostasis and are responsible for the wake-promoting effects of psychostimulants [84,85]. Thus, the parkinsonian state itself is a major factor in the expression of sleepiness and SOREMs. The point is best made in animal models of disease that control for potentially confounding variables such as age, comorbid conditions, and medications. Rats spend less of their subjective day awake following destruction of nigrostriatal pathways with bilateral, intrastriatal infusions of the dopamine toxin 6-hydroxydopamine [50]. Similarly, daytime sleepiness and SOREMs have been precipitated in a single non-human primate following systemic delivery of the dopamine neurotoxin 1-methyl,4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [72]. The cellular and subcellular substrates underlying these disease-related effects remain ill-defined. These phenomena may reflect loss of dopamine's effects upon neural excitability in any one of a number of nuclei, which if unaffected by disease might otherwise serve to maintain normal states of thalamocortical excitability. One plausible substrate is novel dopamine pathways that *simultaneously* target movement-related subcortical circuits and the thalamus, which is

the final station for modulating cortical arousal [86]. Thalamocortical neuron firing rates and patterns are altered in non-human primates by focal applications of various dopaminomimetics [87].

Another plausible substrate, given the narcolepsy-like phenotype seen in many 'sleepy' PD patients, is hypocretin-containing neurons in the lateral hypothalamus known to degenerate in primary narcolepsy/cataplexy [88]. However, the findings of normal CSF hypocretin-1 levels in three PD patients with documented sleepiness argues against this hypothesis [89]. Other plausible neural substrates that deserve future investigation include targets of ventral tegmental area dopamine neurons including the prefrontal cortex, the cholinergic magnocellular basal forebrain, and midline thalamic nuclei. Alternatively, excessive daytime sleepiness (EDS) and SOREMs may reflect extranigral pathology in nuclei comprising the traditional ascending reticular activating system such as the dorsal raphe, locus coeruleus, and pedunculopontine tegmental nucleus (PPN). Dysregulation of the PPN region, an area known to promote thalamocortical arousal and REM sleep, may also be an important factor secondary to its position as a principal brainstem target of pathological basal ganglia outflow [56].

2.4. Summary

The preponderance of evidence argues that the pathophysiological basis of RLS/PLM resides in dopaminergic or dopamine-sensitive premotor circuits whose dysfunction results in disinhibition of spinal flexor reflex afferent pathways. Because many pathways converge upon this final common modulator of spinal sensorimotor function, the expression of RLS/PLM are likely influenced by numerous other supraspinal circuits, and are a common end point to numerous medical conditions/treatments. Two systems of primary interest in this regard include traditional nigrostriatal dopaminergic pathways and the less studied diencephalospinal dopaminergic pathways. The spectrum of sleep-wake alterations seen with the loss of nigrostriatal dopamine characteristic of PD includes PLM and EDS, yet their precise pathological bases remain elusive. Until more data are forthcoming, the most prudent clinical and experimental approaches should proceed from the assumption that the parkinsonian condition represents an underlying diathesis to sleepiness and SOREM expression that can be exaggerated by numerous coexistent factors including use of dopamine agonists and levodopa, sedative-hypnotics, and potentially other medications; primary sleep disorders; and potentially comorbid conditions such as depression. While sleepiness observed with levodopa and dopamine agonists in PD has been increasingly publicized, these agents also cause sleepiness in drug-naïve controls. Thus, how often drug use in PD contributes further to sleepiness remains unresolved.

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