Chapter 13

CONTROL OF MUSCLE TONE ACROSS THE SLEEP-WAKE CYCLE

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During normal sleep, muscle tone in the skeletal muscles diminishes from prior waking levels. In non-rapid eye movement (REM) sleep residual muscle tone is normally present. In REM sleep muscle tone is generally abolished, with the exception of tone in the diaphragm and extraocular muscles. Abnormalities in the regulation of tone across the sleep-wake cycle lead to a number of pathologies that can have enormous effects on health and safety. I will first describe the major pathologies of muscle tone control over the sleep-wake cycle and then review what we know about the underlying physiology that is disrupted in these disorders.

Non-REM Sleep Pathologies

Sleep walking consists of recurrent episodes in which the subject arouses from non-REM sleep, typically during the first third of the night, and shows complex behavioral automatisms that include leaving the bed and walking for some distance. Although it was originally thought to represent the acting out of a dream, Gastaut and Broughton (1965) and Jacobson *et al* (1965) independently confirmed that sleep walking occurs in non-REM sleep and is not normally associated with any dream-like mentation

or mentation regarding the executed movements. The link to deep non-REM sleep (stages 3-4) fits with the greater incidence in children, who have more deep slow-wave sleep than do adults. However, the disorder persists in adults with an incidence of 1% compared to the 15-30% incidence in children. Injuries are common and can be severe (Broughton, 2000).

Night terrors, arousals marked by screams, and associated motor activity can be linked to sleep walking or can occur independently and are always initiated in non-REM sleep. A number of drug treatments, including tri-cyclic benzodiazepines and carbamazepine, have been used to treat sleep walking and night terrors, but this treatment is not successful in many patients (Broughton, 2000).

The restless legs syndrome (RLS) is characterized by an irresistible desire to move the legs, usually associated with paresthesias/dysesthesias and motor restlessness. It is present in 5-10% of the adult population (Odin *et al.,* 2002). Most patients with RLS have periodic movements during non-REM sleep, a contraction of limb muscles especially prevalent in the tibialis anterior and that occurs every 10-30 s. Periodic limb movements (PLMs) are most numerous in the first half of the night. Although the vast majority of patients with RLS experience PLMs (PLMs in sleep), PLMs frequently occur independently of RLS. The RLS/PLMs syndrome produces profound insomnia (Hening, 2002; Parker and Rye, 2002; Trenkwalder, 2003). The etiology of the condition remains uncertain, but recent discoveries implicate dysfunction in areas of the nervous system from the spinal cord to the basal ganglia. Some current work has supported the hypothesis that the condition results from a deficiency of dopafninergic function based on abnormalities of iron transport and storage. Dopamine agonists are the most reliable treatment for severe cases, although other recent studies have used a number of other medications, including opioids and anticonvulsants (Hening, 2002). Dopamine agonists appear to act at the motoneuronal or adjacent spinal levels rather than in forebrain regions, since the phenomenon can be demonstrated in and reversed by dopamine agonists applied to the isolated spinal cord (Hening, 2002; Odin *et al.,* 2002). However, treatments are still unsatisfactory for most cases. A recent report found that RLS was associated with increased levels of hypocretin, making it the only neurological syndrome known to be associated with increased hypocretin and one of only a few syndromes associated with hypocretin abnormalities; narcolepsy, Guillain-Barre syndrome, and myotonic dystrophy being among the others (Ripley *et al,* 2001; Alien *et al.,* 2002; Martinez-Rodriguez *et al.,* 2003). Our finding that hypocretin release is linked to motor activity (Wu *et al,* 2002) suggests that this release and the release of other transmitters controlled by

interactions with hypocretin (John *et al,* 2003) may contribute to motor restlessness in waking as well as PLMs.

Nocturnal bruxism is a grinding or clenching of the teeth during sleep that differs from daytime parafunctional jaw muscle activity (Lavigne and Manzini, 2003). Not only does bruxism produce attrition of tooth, height by as much as 50% and loss of buccal tooth surface, it also frequently produces painful chronic temporal mandibular joint dysfunction (Lobbezoo and Lavigne, 1997). headaches, tooth sensitivity, and disturbed sleep. Incidence in adults ranges from 3 to 13%, with higher levels in children. Sixty to 80% of sleep bruxism episodes occur during non-REM sleep stages 1 and 2 (Lavigne arid Manzini, 2003). The incidence of sleep bruxism is higher in RLS patients (Lavigne and Montplaisir, 1994). Like RLS, sleep bruxism is sometimes improved by L-dopa treatment. The preponderance of evidence indicates that L-dopa acts by increasing dopamine availability at the motoncuronal level as it appears to do in RLS, i.e., the effect does not appear to be mediated by the basal ganglia or other forebrain regions (Lobbezoo *et al,* 1997).

Sleep apnea affects more than 18 million Americans. Sleep apnea more than doubles the risk of heart failure, and 37% of patients with heart failure have obstructive sleep apnea (Javaheri *et al.,* 1998; Sin *et al,* 1999; Shahar *et al,* 2001; Bradley and Floras, 2003). Untreated sleep apnea is also linked to memory problems, weight gain, impotence, headaches, and motor vehicle crashes (Bedard *et al,* 1993; Guilleminault, 1994; Naegele *et al.,* 1998; Salorio *et al,* 2002).

Evidence for brain damage in obstructive sleep apnea

Sleep apnea patients whose respiratory problems are satisfactorily treated with continuous positive airway pressure (CPAP) or by other means show persistent cognitive deficits, including impairment of short-term memory, sleepiness, and problems with language comprehension and expression (Bedard *et al,* 1993; Naegele *et al,* 1998; Beebe and Gozal, 2002). A recent MRI study by Harper's group demonstrated that obstructive sleep apnea patients have diminished regional gray matter volume in frontal, Parietal, cingulate and hippocampal cortex, and in the cerebellum (Macey *et al,* 2002). Two startling observations were a unilateral loss of gray mat-ter in cortical brain sites associated with control of the oral airway in the expression of speech (Broca's area), and that there are deficient functional responses in areas responsible for integration of sensory information for speech (Wernicke's area); those unexpected findings were coupled with the

observation that nearly 40% of the obstructive sleep apnea subjects studied had a history of stuttering or speech impediment since childhood (vs. 8% of controls). Adults with persistent developmental stuttering show damage to speech-related brain regions, including Wernicke's area (Foundas *et* al., 2001). The unilateral nature of the gray matter loss in well-perfused structures related to motor regulation of the upper airway suggests that this damage may be a cause rather than a consequence of obstructive sleep apnea. Harper's group found that obstructive sleep apnea is also associated with damage to CA1 regions of the hippocampus. Hippocampal structures are known to show significant changes in activity change prior to sigh-apnea sequences in animals (Poe *et* al., 1996) and, on stimulation, will elicit marked changes in respiration, including apnea in a variety of species (Anand and Dua, 1956; Duffn and Hockman, 1972; Ruit and Neafsey, 1988). Damage was also consistently seen in vermal regions of the cerebellum, especially the deep cerebellar nuclei, most prominently in the fastigial nucleus. These regions have an important role in muscle tone control (Asanome *et* al., 1998; Davis, 2000; Lazorthes *et* al., 2002), and are regulated by monoaminergic inputs (Guglielmino and Strata, 1971; Doba and Reis, 1972; Moises and Woodward, 1980). Bilateral damage in other regions unrelated to respiratory control suggests that the chronic intermittent hypoxia resulting from sleep apnea may over time cause further degenerative changes in the brain. These degenerative changes may well exacerbate any initial neurological deficits, thereby contributing to further airway collapse.

The hypothesis that obstructive sleep apnea might cause brain damage has been tested in rats. Gozal *et al* (2001) Subjected rats to chronic intermittent hypoxia for 12h/day for up to 14 days. The level of chronic intermittent hypoxia used was adjusted to produce a reduction in arterial oxygenation comparable to that seen in human obstructive sleep apnea. Intermittent hypoxia resulted in increased levels of apoptosis in the CA1 region of the hippocampus and in neocortex, but not in the CA3 hippocam-pal region, after 1-2 days. A marked reduction in the number of cortical and CA-1 cells bearing N-methyl-D-aspartate (NMDA) glutamate receptor binding sites was seen. In a prior study, rats exposed to hypobaric hypoxia showed a >35% reduction in NMDA binding sites in cortex and hippocampus (Pichiule *et* al., 1996). These results suggest that a glutamate-mediated excitotoxic process, killing cells with NMDA receptors, might be involved in mediating the effects of chronic intermittent hypoxia.

The implications of the findings of gray matter loss and altered neural processing of breathing and autonomic challenges in obstructive sleep apnea

are profound. The findings suggest that brain damage underlies the cognitive deficits found in obstructive sleep apnea of both children and adults, the altered sensory processing found in obstructive sleep apnea, and produces the abnormal atonia and sequencing of muscle activation found in the syndrome.

Overview of pathological conditions

Multiple modes of failure of the sleep motor control system in non-REM sleep are consistent with the complexity of the system. The disorders discussed above may involve different patterns of neurotransmitter disturbance at the motoneuronal level, possibly resulting from different patterns of change in the activity of higher neural structures.

REM Sleep Pathologies

Regulation of muscle tone in REM sleep

Most studies of muscle tone regulation across the sleep-wake cycle have emphasized the determinants of REM sleep atonia. Here, we briefly summarize the major findings. Figure 1 presents an outline of some of the major systems we have studied.

Evidence for glycinergic involvement in the atonia of REM sleep

Chase's group was the first to document hyperpolarization of motoneurons during REM sleep (Nakamura *et al.,* 1978). Their studies have indicated a major involvement of glycine in the suppression of tone in skeletal muscles during REM sleep. They found that REM was accompanied by a bombardment of trigeminal and lumbar motoneurons with inhibitory postsynap-tic potentials (IPSPs) (Chase and Morales, 1982). The glycine antagonist strychnine reversed these phasic potentials (Soja *et al.,* 1987), whereas the gamma aminobutyric acid (GABA) antagonists picrotoxin and bicuculine did not (Chandler *et al.,* 1980a,b; Chase *et al,* 1980, 1989). Membrane hyperpolarization, combined with the attenuation of IPSPs by strychnine, led to the hypothesis that glycine release was primarily responsible for the hyperpolarization of trigeminal and lumbar motoneurons during REM sleep (Chase and Morales, 1990). Glycine not only inhibits motoneurons directly, but also facilitates the response of NMDA glutamate receptors on motoneurons (Berger and Isaacson, 1999). Phasic reversible IPSPs were not

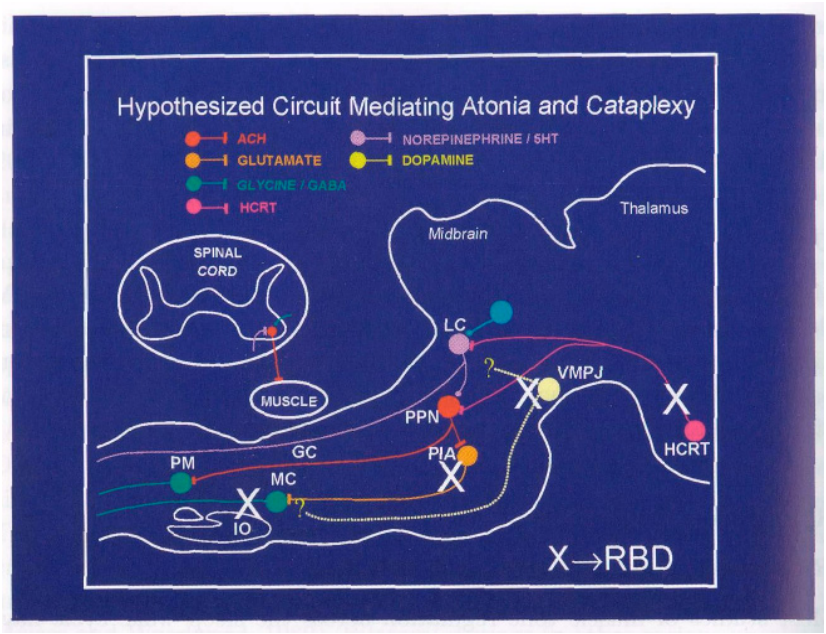

Figure 1. Some of the major pathways implicated in muscle tone control across the sleep-wake cycle. The systems are drawn on a sagittal section of the brainstem of the cat. See text for a description of the experimental evidence for the relationships illustrated. Xs illustrate points at which lesions are hypothesized to disrupt the mechanisms producing atonia, resulting in REM sleep without atonia. VMPJ, ventral mesopontine junction (Lai and Siegel, 2003); PPN, Pedunculopontine nucleus; 1c, locus coeruleus; GC, nucleus gigantocellularis; MC, nucleus magnocellularis; PM, nucleus magnocellularis.

seen in these studies in non-REM sleep, suggesting that either glycine is not released in non-REM sleep or that it is released tonically, in contrast to the phasic glycine release of REM sleep.

After making these observations in the intact animal, Chase *et al,* developed an acute model of REM sleep atonia. Atonia was achieved by iontophoresing carbachol into the pons of the decerebrate cat (Morales *et al,* 1987). This acute preparation allows a more rapid analysis of the REM atonia mechanism. The studies of Morales *et al.* indicated that glycine has a role in the IPSPs seen in the decerebrate animal, as it does in REM sleep in the intact cat.

Chase's group has focused on the phasic inhibitory potentials occurring during REM sleep. However, the "main event" from a sleep apnea viewpoint may be the tonic muscle tone changes in non-REM and REM sleep, rather

than the phasic potentials during REM sleep that last only milliseconds. The work by Chase's group does not exclude the central participation of other transmitters in the overall regulation of muscle tone in REM sleep. It also says little about non-REM sleep muscle tone control.

Morrison *et al.* (2002) delivered transmitter agonists to the hypoglossal nucleus to determine whether muscle tone could be suppressed in urethane anesthetized animals. They found that glycine produced a suppression of muscle tone, supporting the idea that it could be responsible for the suppression of tone in REM sleep.

The role of GAB A in motoneuron inhibition during sleep

GABA is thought to be the most common inhibitory neurotransmitter in the brain, being active at 20-40% of brain synapses (Bloom and Iverson, 1971). However, its possible role in the reduction of tone in non-REM sleep and in REM sleep has received little attention. In their work on lumbar motoneurons in REM sleep models, Chase *et al.* (1989) found that iontophoresis of the GABA antagonists picrotoxin and bicuculine did not prevent motoneuron IPSPs in REM sleep. However, they did note that the GABA antagonists substantially reduced the IPSP durations. In other work, Okabe *et al.* (1994) found inhibitory effects of GABA on hypoglossal motoneurons recorded from anesthetized rats. In the urethane anesthetized rat, Liu *et al.* (2003) and Morrison *et al.* (2003) found that GABA suppressed muscle tone in the hypoglossal nucleus. They further found that GABA antagonism was ineffective in blocking atonia during REM sleep but did increase genioglossus muscle tone in non-REM sleep. They did not examine GABA release in either non-REM or REM sleep. GABA and glycine may be released by the same axon terminals but may also be released independently (O'Brien and Berger, 1999).

In our *in vivo* microdialysis studies of the locus coeruleus (Nitz and Siegel, 1997a), raphe (Nitz and Siegel, 1997b), and posterior hypothala-mus (Nitz and Siegel, 1996), we have shown that it is possible to measure GABA release across the sleep cycle. Moreover, we have found that there is a selective GABAergic inhibition of noradrenergic and serotonergic cell groups during REM sleep. This inhibition is likely to be responsible for the cessation of discharge in these cells during REM sleep. This cessation oi serotonin neuron discharge, likely caused by GABA action on the raphe magnus, pallidus, and obscurus, results in disfacilitation of at least one motoneuron group (the hypoglossal nucleus) during REM sleep, as outlinec

below. However, this indirect effect of GABA does not rule out a direct effect of collaterals of these same cells, or of other GABAergic interneurons or projection neurons, on motoneurons. It has been reported that both GABA and glutamate release in the thalamus are increased in non-REM sleep (Kekesi *et al.,* 1997). It remains to be determined if a similar pattern of release is seen in motoneuron pools.

Evidence for serotonin involvement in the atonia of REM sleep

Kubin *et al.* (1993) used a version of the decerebrate carbachol model to study hypoglossal motor activity. They focused on the hypoglossal nucleus because of studies that showed that tongue hypotonia was one of the major causes of obstructive sleep apnea (Sauerland and Harper, 1976). Kubin *et al.* (1994) found that serotonin release in the hypoglossal nucleus was decreased during carbachol-triggered REM sleep. During carbachol atonia, injection of serotonergic agonists into the hypoglossal nucleus reduced the carbachol-induced suppression of tone (Kubin *et al.,* 1996). While serotonin manipulations had a potent effect on hypoglossal tone, injection of glycine antagonists during periods of carbachol triggered REM sleep did not block atonia (Kubin *et al.,* 1993). Kubin *et al.* concluded that the atonia mechanism in hypoglossal motoneurons was fundamentally different from that which had been seen by Chase and Morales in trigeminal and lumbar motoneurons. They concluded that serotonergic disfacilitation was the major factor responsible for REM sleep atonia in the hypoglossal nucleus, whereas glycinergic hyperpolarization was responsible for atonia in trigeminal and lumbar motoneurons.

Does the neurochemistry of REM sleep atonia in hypoglossal, trigeminal, and lumbar motor systems differ? The evidence listed above suggests that two distinct atonia mechanisms are operating in lumbar and trigeminal vs. hypoglossal motoneurons in REM sleep: amino acid-mediated active inhibition in lumbar motoneurons and serotonin-mediated disfacilitation in hypoglossal motoneurons. However, closer examination of the results suggests that atonia generation in these regions need not differ. Chase and Morales used iontophoresis to come to the conclusion that glycinergic mechanisms were involved. They reported that iontophoresis of strychnine reduced, but did not eliminate, the hyperpolarization seen in skeletal motoneurons (Soja *et al.,* 1987, 1991). Kubin *et al.* (1992) used microin-jection of agonists and antagonists to substantiate the involvement of

serotonin. Kubin *et al.* reported that, whereas much of the reduction in hypoglossal discharge could be countered by serotonin microinjection. some of the carbachol-induced reduction in tone remained. They concluded that the study "demonstrates that other, non-serotonergic mechanisms also contribute to the carbachol-induced suppression" (Kubin *et al.,* 1996). It may well be that hypoglossal motoneurons are subjected to phasic glycinergic IPSPs as are trigeminal motoneurons. Indeed, Yamuy *et al.* (1999) subsequently showed that hypoglossal motoneurons. like masscter and ventral horn motoneurons, receive glycinergic IPSPs during REM sleep. Conversely. the trigeminal and lumbar motoneurons receive an extensive scrotonergic innervation (White *et al.,* 1996). Hyperpolarization in the trigeminal as well as hypoglossal motoneurons during REM sleep could be partially due to dis-facilitation by serotonin (or norepinephrine or glutamate — see below), as well as glycinergic inhibition.

The serotonergic disfacilitation and glycinergic inhibition hypotheses are not mutually exclusive. *In vitro* studies by Umemiya and Berger (1995) indicate that glycinergic inhibition is enhanced in the absence of serotonin. Therefore, *in vivo,* serotonergic withdrawal and increased glycinc release in REM sleep may act synergistically to hyperpolarize the motoneuron. Application of serotonin may eliminate most of the hyperpolarization of REM sleep, and blockade of glycinc may also eliminate most of the hyper-polarization. It is also quite possible that a blockade of norepinephrine or other transmitters would also prevent most of the hyperpolarization; i.e., one should not expect these effects to sum up to 100%.

Supporting a role for serotonergic mechanisms in the atonia of the limb muscles is the preservation of the activity of serotonergic neurons during REM sleep without atonia. This is in contrast to their reduction of activity in non-REM sleep and cessation of activity during normal REM sleep (Trulson *et al,* 1981). This suggests that some of the "inhibition" of skeletal motor activity occurring during normal REM sleep may in fact be disfacilitation. Lesions that produce REM sleep without atonia return serotonergic activity and perhaps motor facilitation to REM sleep. These mechanisms and interactions may also have a role in non-REM sleep motor dysfunction.

Role of norepinephrine in motoneuron facilitation

In acute studies, noradrenergic neurons in the locus coeruleus have been shown to depolarize motoneurons and increase muscle tone (Parkis *et al,* 1995; Fung and Barries, 1987; Lai *et* al., 1989). Unilateral lesions of the

locus coeruleus produce an ipsilateral reduction of muscle tone (D'Ascanio *et al,* 1988). Noradrenergic cells of the locus coeruleus and of the more ventral and caudally located A5-A7 noradrenergic cell groups have projections to the brainstem, spinal motor, and cerebellar areas. One-third of locus coeruleus and a majority of non-locus coeruleus noradrenergic cells have spinal projections (Nygren and Olson, 1977; Satoh *et al,* 1977; Reddy *et al,* 1989; Jones, 1991), with terminals on spinal and brainstem motoneu-rons (Lyons *et al,* 1989; Jones, 1991). Locus coeruleus neurons in humans become active in response to inspiratory loading, which simulates obstructive apnea (Gozal *et al,* 1995).

Work has shown that locus coeruleus cells may not act through norepinephrine release alone. Eighty-six percent of the locus coeruleus neurons that project to spinal cord motoneuronal regions have glutamate as a co-transmitter (Liu *et al,* 1995). Thus, motor facilitation resulting from locus coeruleus activation may involve a synergistic interaction between norepinephrine and glutamate. The extent to which such an interaction occurs can best be determined by measurement of the release of both transmitters.

Sleep-related activity of serotonergic and noradrenergic neurons

Studies of amincrgic cells in behaving animals began with the work of McGinty and colleagues (McGinty and Sakai, 1973; McGinty and Harper, 1976). They found that serotonergic cells discharged regularly in waking, decreased discharge in non-REM sleep, and ceased discharge in REM sleep. Subsequent work showed that noradrenergic cells had a similar pattern of waking activity and cessation of discharge in REM sleep (McGinty and Sakai, 1973; Hobson *et al,* 1975). Whereas there is overwhelming evidence that most noradrenergic and serotonergic neurons cease discharge during REM sleep, other evidence suggests that a subset of caudal serotonergic neurons in the nucleus raphe magnus may not cease discharge in REM sleep (Cespuglio *et al,* 1981; Sakai *et al,* 1983). It is certainly possible that some portion of noradrenergic neurons, particularly those in medullary regions adjacent to the hypoglossal motoneurons (A5-A7), do not show the REM sleep-off pattern that characterizes the pontine locus coeruleus population, although recordings from this region suggest that at least some of these cells may show the REM sleep-off pattern (Eguchi and Satoh, 1980).

Monoamine neurotransmitter release has been shown to be regulated not only by action potentials in the cell soma (Jacobs, 1991; Rueter and

Jacobs, 1996), but also by presynaptic control of release (Di Chiara *et al,* 1996; Marshall *et al,* 1997). This presynaptic regulation can attenuate or even reverse the release patterns that might be expected based on action potential activity of the afferent cells. For example, it has been shown that despite the midline locations of serotonergic neurons and their bilateral projections, strong interhemispheric asymmetries in release are present and are readily altered by eye closure and behavioral variables (Baxter *et al,* 2001).

Role of glutamate in motoneuron facilitation during sleep

Current evidence indicates that the primary cell populations contributing to respiratory rhythmicity are glutamatergic, as are some cells projecting from respiratory centers to motoncurons (Bonham, 1995). Thus, the respiratory drive to the phrenic motoneurons. as well as that to the accessory respiratory musculature, such as the masseter muscle, may be due to gluta-matergic input. It is likely that changes in glutamate release contribute to the reduction in tone in non-REM sleep in respiratory and non-respiratory motoneurons.

In studies of unrestrained animals, we have reported that the population of reticular and reticulospinal pontine and medullary cells as a whole reaches its lowest discharge level in non-REM sleep. They reach their highest discharge levels, exceeding mean waking values, in REM sleep (Siegel, 1979; Siegel and Tomaszewski, 1983; Siegel *et al,* 1983). Much of this cell population is glutamatergic and sends axons both to other reticular and reticulospinal neurons, and to cranial and ventral horn motoneurons (Lai and Siegel, 1991; Lai *et al,* 1993, 1999). Thus, the cessation or reduction of activity in glutamatergic neurons of the pontine and medial medullary reticular formation during non-REM sleep may contribute to the non-REM sleep related hypotonia that figures so prominently in sleep apnea, and the dysfunction of these cells may cause disorders of excessive motor activity in non-REM sleep.

Increased discharge of glutamatergic cells in REM sleep, to the extent that it changes levels of glutamate release onto respiratory motor systems, may ordinarily compensate for the loss of noradrenergic and serotoner-gic facilitation (and the likely co-release of glutamate from aminergic neurons) in this state. Silent respiratory-related reticular interneurons are converted into neurons with clear respiratory rhythmicity by iontophoresis of increased levels of glutamate (Foutz *et al.,* 1987). Glutamate delivery was Particularly effective in non-REM sleep (Foutz *et al,* 1987), a time when we

would expect glutamate release to be minimal. In contrast, delivery of glutamate during REM sleep, a time when presumptive glutamatergic neurons are already active, produced little change in their respiratory rhythmicity. The level of glutamate release may be a key determinant of upper airway motoneuron activity and may contribute to non-REM sleep parasomnias, yet the pattern of release and the effects of glutamate agonists and antagonists at the motoneuronal level in both respiratory and non-respiratory related motoneurons is unknown.

Studies of transmitter release in decerebrate animals

Amino acids

We have used the acute decerebrate preparation to conduct the first studies of the release of amino acids and monoamines in the REM sleep-like atonic state that can be elicited by pontine stimulation.

We hypothesized that cessation of brainstem monoaminergic systems and an activation of brainstem inhibitory systems are both involved in pontine inhibitory area (PIA) stimulation-induced muscle atonia. Kodama *et al.* (2003) demonstrated an increase in inhibitory amino acid release in motor nuclei during electrical and chemical PIA stimulation in the decerebrate cat using *in vivo* microdialysis and high-performance liquid chromatography analysis techniques. Microinjection of acetylcholine into the PIA elicited muscle atonia and simultaneously produced a significant increase in both glycine and GABA release in the hypoglossal nucleus and in the lumbar ventral horn. Glycine release increased by 74% in the hypoglossal nucleus and by 50% in the spinal cord. GABA release increased by 31% in the hypoglossal nucleus and by 64% in the ventral horn during atonia induced by cholinergic stimulation of the PIA. Glutamate release in the motor nuclei was not significantly altered during atonia induced by electrical or acetylcholine stimulation of the PIA. We suggest that both glycine and GABA play important roles in the regulation of upper airway and postural muscle tone in REM sleep. A combination of decreased monoamine and increased inhibitory amino acid release in motoneuron pools causes PIA-induced atonia and may be involved in atonia linked to REM sleep (see below).

Monoamines

Lai *et al.* (2001) wanted to examine further the neurotransmitter environment of motoneurons during REM sleep. In this study, we addressed

the issue of whether monoamine release was greater in hypoglossal than in ventral horn motoneurons in atonic states induced by pontine stimulation, using microdialysis in the decerebrate animal. Electrical stimulation and cholinergic agonist injection into the mesopontine reticular formation produced a suppression of tone in the postural and respiratory muscles and simultaneously caused a significant reduction of norepinephrine and serotonin release that was of similar magnitude in both the hypoglossal nucleus and the spinal cord. Norepinephrine and serotonin release in these motoneuron pools was unchanged when the stimulation was applied to brainstem areas that did not generate bilateral suppression of muscle tone. No change in dopamine release in the motoneuron pools was seen during mesopontine stimulation-induced atonia. We hypothesize that the reduction of monoamine release that we observe exerts a disfacilitatory effect on both ventral horn and hypoglossal motoneurons, and that this disfacilitatory mechanism contributes to the muscle atonia elicited in the decerebrate animal and in the intact animal during REM sleep. A combination of decreased norepinephrine and serotonin and increased glycine and GABA release is linked to pontine-triggered atonia. These changes in release occur to equal extents in the ventral horn and the hypoglossal nucleus.

The reduced release of serotonin and norepinephrine and simultaneous increase in release of glycine and GABA in the REM sleep-like state induced by pontine stimulation raises the issue of how these monoamine and amino acid changes are coupled. Mileykovskiy *et al.* (2000) determined the response of locus coeruleus cells to brainstem stimulation that suppressed muscled tone. Activation of the PIA or the medullary inhibitory area (gigantocellular reticular nucleus) (Gi) suppresses muscle tone in decerebrate animals (Lai and Siegel, 1988). Both PIA and Gi stimulation produced inhibition of locus coeruleus discharge. We conclude that activation of pontine and medullary inhibitory regions produces a coordinated reduction in the activity of LC units (and of cells in the midbrain locomotor region, which also facilitates muscle tone). This relation is particularly striking in the case of PIA stimulation, since stimulating electrodes that were effective in suppressing muscle tone reduced locus coeruleus activity, even though in many cases these stimulation electrodes were within a millimeter or two of the locus coeruleus, and therefore might be expected to excite these cells.

This study demonstrates a surprising inhibitory connection between Pontine inhibitory regions, which work by triggering the release of inhibitory amino acids onto motoneurons, and the locus coeruleus, whose neurons release norepinephrine, which facilitates activity in motoneurons. disturbance of the inhibitory coupling between these two systems may be

a factor in motor disorders of REM sleep, but their role in non-REM sleep is unknown.

In a study of the physiology of the descending inhibitory system, we determined the conduction velocity of the descending inhibitory projections (Koliyama *et al,* 1998a). In further work we showed that there is an ascending projection from the medullary inhibitory region to the region of the locus coeruleus (as suggested above). When we blocked this ascending pathway with lidocaine, sites in the medulla that had been inhibitory produced a net excitation. This work demonstrated the importance of the ascending pathway to locus coeruleus for motor inhibition (Kohyama *et* al., 1998b).

Summary

The suppression of muscle tone during sleep involves a complex interplay of disfacilitatory and inhibitory processes. Although the normal mechanisms regulating this suppression in REM sleep arc becoming understood, the factors regulating tone in non-REM sleep are less well known. The disruptions responsible for sleep motor pathologies are poorly understood.

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