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7. Brainstem Systems Mediating the Control of Muscle Tone

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During rapid eye movement (REM) sleep, muscle tone in the "anti-gravity" muscles is suppressed. This "atonia" prevents one from "acting out" his dreams. Pathology in the systems producing REM sleep suppression of tone is responsible for cataplexy, a loss of muscle tone in waking triggered by environmental variables that produce sudden excitement. The REM sleep without atonia syndrome, which in humans is termed the REM behavior disorder, is also believed to result from abnormal operations of this system. This chapter will review the current state of knowledge about the atonia system.

Medial Medulla and the Suppression of Muscle Tone

Magoun and his colleagues [41,42] discovered that stimulation of the medial medulla of the decerebnte cat and monkey produces an immediate and complete loss of reflex response and muscle tone. In contrast to Sherington's principle of reciprocal changes in the activity; in extensor and flexor muscles around a joint, Magoun reported a non-reciprocal suppression of tone occurring simultaneously in flexors and extensors. At the time of this discovery, there was no known physiological state in which such changes occurred. In 1962, Jouvet discovered that REM sleep, in both the intact and decerebrate cat, is accompanied by a complete and sustained loss of muscle tone. Morrison and Pompeiano [52,58] and Pompeiano [57] found that not only was muscle tone absent, but reflex response was totally suppressed during this state. Since the medial medulla was the only area whose stimulation was known to produce suppression of muscle tone, it was hypothesized that this region mediated the muscle tone suppression of REM sleep.

Subsequent work has supported this idea. A population of neurons in the medial medulla has been shown to be selectively active during the REM sleep state in intact animals [11, 31, 53, 72, 77]. Two such "REM-on" cells were antidromically identified and found to be reticulospinal, conducting at 6-8 m/sec [31]. Many REM-on cells, while silent in active waking, show increased activity in quiet waking in conjunction with reductions in muscle tone [77]. This increased discharge in quiet waking is the opposite of the pattern seen in the vast majority of pontine and medullary medial reticular formation cells [74, 76, 77]. *These cells may therefore mediate reductions in tone in waking and slow wave sleep, in addition to the abolition of tone in REM sleep.* Studies in the intact cat and dog have localized the REM-on (waking-off) cells to the ventral portions of medial medulla [31, 73], a region that has been named the nucleus magnocellularis (NMC) [6,8, 84]. Intracellular

recordings from spinal motoneurons have demonstrated that *both* REM sleep atonia and atonia elicited by stimulation of the medulla are produced by hyperpolarization of motoneurons [9, 10, 19, 28].

Mori's group has investigated the role of nucleus gigantocellularis (NGC) in postural control and locomotion. The NGC region is located just dorsal to NMC. Using spike triggered averaging, they found postsynaptic motoneuron inhibition of hindlimb motoneurons 5 msec after action potentials in NGC, indicating a conduction velocity of 70-90 m/sec [85]. They suggest that inhibition of motoneurons results from the action of a spinal interneuron rather than the direct action of a reticulospinal projection. The REM sleep activity of these NGC cells was not characterized. It remains unclear if the system that Mori's group is studying has the same function and transmitter mechanisms as the more ventral system in the NMC that has been implicated in cataplexy and REM sleep control. If not involved in the nonreciprocal inhibition of REM sleep, Mori's system could be involved in reciprocal changes in tone, and in waking postural control.

Lesions of the dorsolateral pons produce a disruption of the muscle atonia of REM sleep [23, 29]. Animals with these lesions have all the major signs of REM sleep except muscle atonia, and show complex motor behaviors during a state that otherwise resembles REM sleep. The region whose destruction produces this syndrome projects monosynaptically to the mediaUmedullary region identified by Magoun and his colleagues, but has no direct spinal projection [63]* Therefore, it has been hypothesized that the dorsal pontine output is relayed in the medial medulla. We have found that lesions of the medial medulla produce a syndrome of REM sleep without atonia comparable to that seen after pontine lesions [65].

In the spinal cord, the transmitter responsible for motoneuron hyperpolarization has been identified as glycine [12,78]. The source of the glycine responsible for motoneuron hyperpolarization is unknown. There are glycinergic neurons in both the spinal cord, and medulla [16]. Holstege and Bongers [24] have identified a glycinergic projection from the NMC to spinal motoneurons. This could represent a direct pathway for glycinergic motor inhibition. Therefore, the atonia related medial medullary neurons may be glycinergic. However, glycinergic projections to the spinal cord may be involved in other aspects of spinal signal processing including reflex facilitation [20]. Non-glycinergic NMC cells could produce REM sleep atonia by activating glycinergic interneurons within the cord.

Approximately 15% of the spinal terminals labelled with orthograde transport from the medial medulla contained glycine. Since, most cells (> 90%) at the level of the NMC are reticulospinal [26, 86], it follows that somewhat less than 15% of NMC neurons may have descending glycinergic projections. This figure can be compared to our finding that 12% of NMC cells are REM-on-cataplexy-on [73] and our finding and the findings of Sakai and Netick et al. that less than 20% of the cells in the NMC of the behaving cat are selectively active during REM sleep [31, 53, 72, 77]. These numbers are

consistent with (but certainly do not prove) the hypothesis that NMC REM-on cells are glycinergic.

We emphasize that all this work demonstrates that the NMC is not a homogeneous cell group. Most NMC cells are not active in relation to atonia. Atonia related cells are likely to be intermixed and coordinated with cells having other functions. Our prior work indicates that these other functions include control of lateralized head movement and other movements of the axial column [70,71,74,76]. The synchronous activation of the atonia related cells and the larger group of movement related cells in the medulla, may underlie the combination of motor activation and inhibition that characterizes REM sleep [38].

Holstege [25] reports evidence for a GABA-ergic projection from the NMC region to motoneurons. This projection constitutes 40% of the NMC reticulospinal projection. However, GABA does not appear to be involved in the motoneuron hyperpolarization of REM sleep [9]. In addition, the 40% figure is much higher than the percentage of NMC REM sleep-on cells. Therefore, it is unlikely that the REM sleep population is identical to the GABA population, in contrast to the situation with glycine. It remains possible that some NMC neurons contain both GABA and glycine, but this would be a minority of either group [24],

Our recent work has indicated that non-NMDA glutamate receptors in the NMC are responsible for atonia. This, combined with our other work and analysis of the literature, leads to our hypothesis that glycinergic reticulospinal cells, exited by non-NMDA glutamate agonists, and localized to the ventral NMC, are responsible for atonia and cataplexy.

Narcolepsy

Narcolepsy was first recognized over a century ago by Gilineau [54]. The symptoms of narcolepsy include excessive daytime sleepiness, hypnagogic hallucinations, cataplexy and sleep paralysis (an inability to move at sleep onset or awakening) [21 j. Approximately 200,000 Americans have narcolepsy [1]. After the discovery of REM sleep, it was hypothesized that the symptoms of narcolepsy might be dissociated elements of REM sleep [59]. In particular, cataplexy and sleep paralysis resemble the loss of muscle tone and reflex response that, in the normal individual, happens only during REM sleep. Seventy five percent of narcoleptics with cataplexy have more than one attack per day with some having four or more per day. Attacks last for as little as a few seconds to as long as 20 minutes. In certain individuals, a condition of "status cataplecticus" can develop [55]. During cataplectic attacks, consciousness is preserved, but muscle tone and the ability to contract skeletal muscles is lost.

Narcolepsy in humans is linked to the histocompatibility factor HLA-DQB1-0602 [27, 44]. However, genetic factors do not appear to be sufficient, since monozygotic twins are usually discordant for narcolepsy [14, 51, 56], and most narcoleptics do not have narcoleptic family members [22]. The

genetic and environmental factors can be reconciled with the autoimmune hypothesis. According to this hypothesis, an autoimmune process, triggered by environmental insults in susceptible individuals, produces damage to a critical CNS cell group. However, direct tests of this hypothesis, looking for indications of autoimmune activity in narcoleptics, have so far been negative [1, 17, 62, 81], suggesting that any autoimmune activity is short lived or limited to a small CNS region.

After the first case study reports of narcolepsy in dogs, Miller, Dement and their co-workers were able to gather enough such animals to start a breeding colony [33, 49, 50]. The trait was found to be transmitted through an autosomal recessive gene [3], and linked to a /u immunoglobin chain switch [47], suggesting that canine, like human narcolepsy may have an autoimmune etiology. These animals have most of the symptoms defining narcolepsy in humans. They have dramatic episodes of cataplexy, which are triggered by play, novel foods and other arousing activities. They also exhibit excessive sleepiness [30] and respond to the same drugs that are effective in human narcoleptics [3]. Drugs which suppress REM sleep, particularly antidepressants, are employed to treat cataplexy in humans, while high doses of stimulants, which also have a REM sleep suppressant effect, are used to treat the excessive daytime sleepiness of narcolepsy [2, 13]. While drug treatments reduce symptoms, side effects of chronic administration limit usage.

Neuropathological examinations of the brains of narcoleptics have not produced consistent findings. While there have been some reports of cortical abnormalities, cysts and brainstem gliosis [15, 33, 49] other studies have found no morphological abnormalities [3]. However, studies in narcoleptic dogs have shown major changes in the levels of transmitters and transmitter metabolites. Dopamine, epinephrine and norepinephrine levels were elevated and dopamine turnover decreased in several brainstem regions [3]. Cholinergic receptor concentrations were elevated in most of the medial reticular nuclei [3]. It is not known if these receptor changes cause, or result from narcolepsy. Glutamate receptor levels have not been examined in the narcoleptic.

REM Behavior Disorder

While REM sleep without atonia had been described after pontine lesions in cats in 1965 [29], it was not until 1986 [64], that it was appreciated that a similar syndrome exists in humans. These patients vocalize and make violent movements during REM sleep. Some of them have lesions resembling those that produce REM without atonia in cats. However, gross lesions are absent in most [43]. Receptor assays and detailed histopathology has not been performed on the brains of REM behavior disorder patients.

Sleep Apnea

The reduction of muscle tone seen in the postural muscles in REM sleep also affects the accessory respiratory musculature. The intercostal muscles are completely silenced in REM sleep, and tone in the oropharynx and genioglossus

muscles is minimal [60,88]. This reduction in tone increases airway resistance in REM sleep compared to nonREM sleep. In people with small airways, this leads to sleep apnea [46]. Apnea produces a relatively selective REM sleep deprivation, leading to a progressive increase in REM sleep pressure. It has been concluded that the expression of this REM sleep pressure as attempted nonREM-REM transitions, triggers most episodes of sleep apnea [82]. This sets up a positive feedback loop that progressively worsens the problem (Fig. 1). CPAP (Continuous Positive Airway Pressure) treatment, which holds the airway open, results in a huge REM sleep rebound, reflecting this intense REM sleep pressure. By breaking the cycle of apnea -» REM sleep deprivation —> increased REM sleep pressure —» REM transition induced atonia of the upper airway, CPAP can temporarily relieve apnea. However, a few

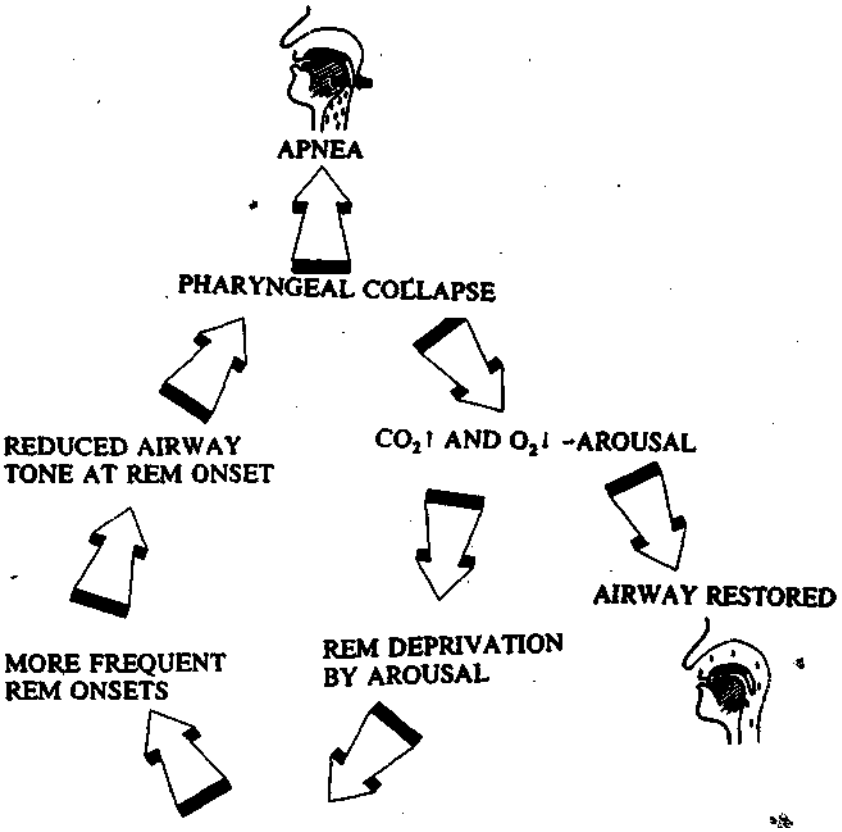

Fig. 1. The apnea cycle. Individuals with small airways have airway diameter further reduced by muscle atonia during sleep, and in particular during REM sleep. Collapse of the airway reduces arousal which restores the patency of the airway. However, frequent arousals interrupt sleep and block REM sleep. A progressive REM sleep debt results which causes more frequent REM sleep onsets and more frequent airway collapse. This cycle can be broken by inflating the airway with Continuous Positive Airway Pressure (CPAP) [84].

days after discontinuance of CPAP, the cycle of reduced airway size, REM sleep atonia and REM sleep deprivation reinstates the apnea. Manipulation of the REM sleep atonia mechanism might be an effective means of extending the remissions produced by CPAP.

Sleep apnea is perhaps the most significant health problem treated in sleep disorders centers. It greatly impairs waking alertness. It has effects on cardiovascular variables and life expectancy comparable to those produced by heavy cigarette smoking [66].

Recent Work in Our Laboratory

Work in our laboratory has led us to create the model of REM sleep atonia circuits displayed in Fig. 2. The evidence for this model is presented below.

While many studies had reported that electrical stimulation of the medial medulla of the decerebrate animal produced atonia, electrical stimulation of

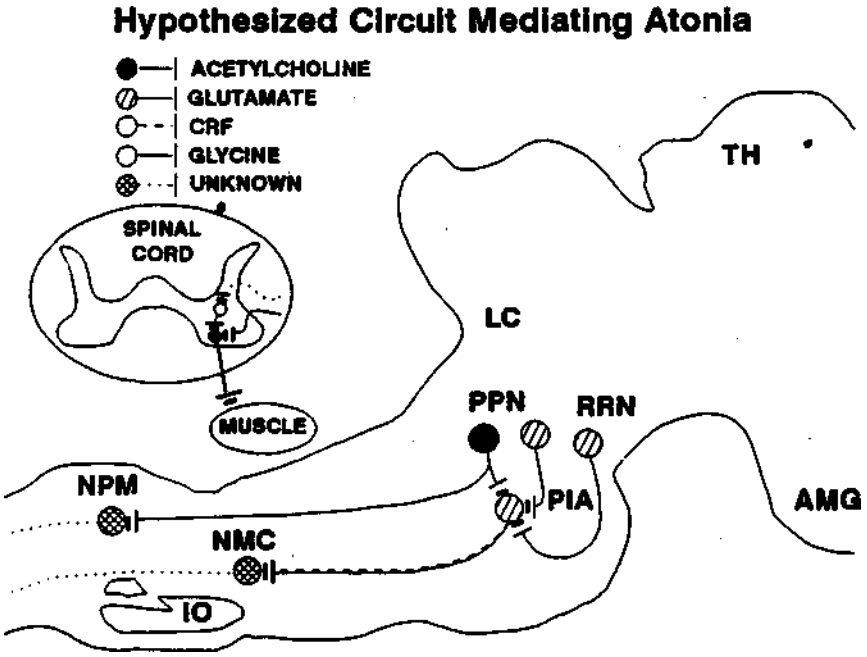

Fig. 2. Model of the circuit producing atonia in REM sleep and cataplexy. Sagittal view of the brainstem of the cat, with pontomedullary areas, transmitters and pathways implicated in atonia. We have demonstrated the glutamate and CRF sensitivities of PIA (the Pontine /nhibitory Area). Ponto-medullary neurons containing bout CRF and glutamate have been described. We identified a glutamatergic projection from PIA to MC. We have demonstrated the cholinergic sensitivities of both PIA and PM. We have shown that PPN Ach neurons project to PM and that Ach release in PM is increased in REM sleep. The work of Chase's group indicating glycinergic hvperpolarization of motoneurons is shown in the spinal cord section. The model depicts two possible sources of glycine for motoneuron hyperpolarization, a,direct glycinergic medullo-spinal projection and a glycinergic spinal intemeuron. TH, thalamus; AMG, amygdala; IO, inferior olive; L*C,* locus coeruleus; MC = NMC, nucleus magnocellularis; PM = NPM, nucleus paramedianus; PPN, pedunculopontine nucleus; RRN, retrorubral nucleus.

more rostral regions had not been shown to cause atonia. We explored the mesopontine brainstem and found that stimulation of the midbrain retrorubral (RRN), ventral paralemniscal tegmental field (vFIP), reticular tegmental (TRN) and pedunculopontine tegmental (PPN) nuclei produced bilateral suppression of muscle tone. The RRN is the most rostral area in the brain found to produce such suppression. Stimulation intensities in RRN, vFTP, TRN and PPN were comparable to or lower than those required in the "classic" atonia region of the medial medulla (Fig. 3),

Mesopontine muscle tone suppression is frequency and intensity dependent, as is medullary atonia. At low stimulus intensities, bilateral suppression was produced. At higher current and frequency levels, two types of muscle responses were found: excitation in PPN and RRN and suppression followed by excitation

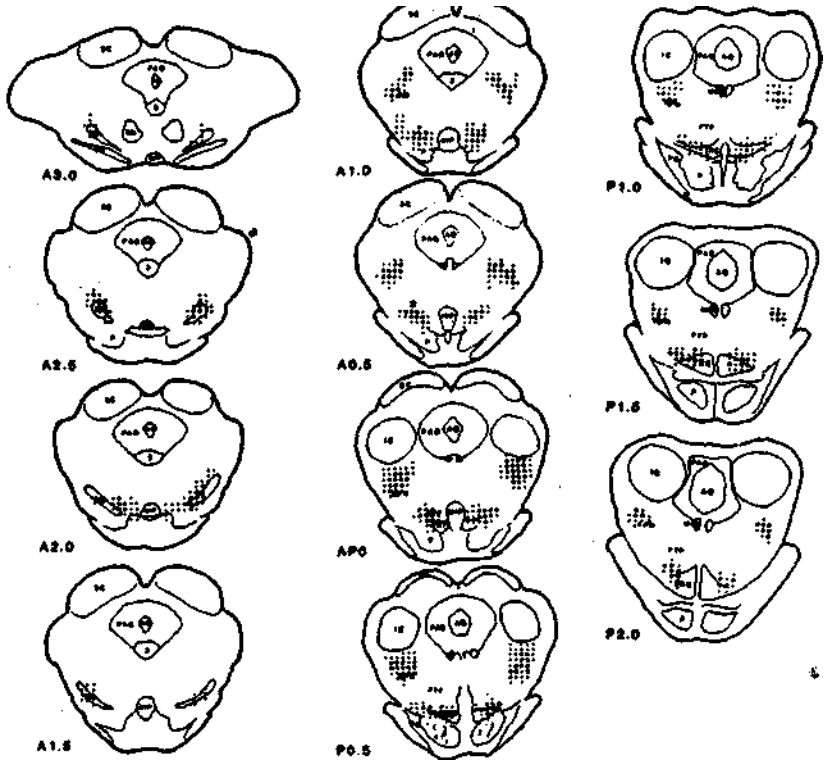

Fig. 3. Location of the ponto-mesencephalic inhibitory area in decerebrated cats. Large and small dots represent the stimulating points that produced > or < than 70% inhibition of neck muscle tone (compared with to 60 sec baseline values, as determined by 10 sec integrations of rectified EMG activity). 3: oculomotor nucleus; 4: trochlcar nucleus; AQ: aqueduct; 1C: inferior colliculus; FTP: paralemniscal tegmental field; MLB: medial longitudinal bundle; NIP: interpeduncular nucleus; P: pyramidal tract; PAG: periaqueductal gray; PG: pontine gray; PPN: pedunculopontine tegmental nucleus; RD: red nucleus; RR: retrorubral nucleus; SC: superior colliculus; SN: substantia nigra; TRC: TRN (tegmental reticular nucleus), central division; TRP: TRN, peri-central division; from [37].

in TRN and vFTP. Stepping-like activity could be elicited at the same points by rapid consecutive train stimulations in PPN and single train stimulation in TRN and vFTP. Thus, systems producing locomotion can be activated, at longer latencies, at the same sites as those producing atonia. The .mean latency to atonia was not significantly different in TRN (36.8 msec) and RRN (36.5 msec). However, muscle tone suppression latency was significantly shorter as we moved caudally to vFTP (31 msec) and PPN (27 msec). Atonia latency after NMC stimulation is 16 msec [39].

The latency of our NMC stimulation studies can be used to estimate the conduction velocity of the inhibitory pathway descending from the medial medulla. We assume a direct descending pathway, a utilization time of 0.2 msec, a minimum of two synapses (NMC-motoneuron and motoneuron-muscle) with 0.5 msec delay at each, and a 16 msec delay from the stimulation of the medial medulla to the onset of neck muscle atonia. We calculate the medulla-motoneuron distance at 0.075 m, and the motoneuron-splenius muscle distance at 0.05 m. If motoneuron conducts at 100 m/sec, then 14.3 msec is left for the NMC-motoneuron portion of the circuit. These calculations yield a minimum conduction velocity of 5.2 m/sec for the atonia circuit descending from NMC. This value is in approximate agreement with the conduction velocity measured for two REM sleep-on cells in NMC (6 and 8 m/sec) [31], but not with those'of the NGC inhibitory motoneurons studied by Mod's group (70-90 m/sec) [85].

Since Magoun's original work, many electrical stimulation studies have mapped the medullary region from which atonia can be elicited. But since such stimulation can activate axons and their collaterals as well as cell bodies, one cannot, with this technique, locate the somas of the neurons responsible. We therefore microinjected transmitter agonists and antagonists to determine the precise location of neurons mediating muscle tone suppression and the nature of the receptors involved [36].

We found that glutamate and Ach produced suppression of muscle tone in different regions of the medial medulla. The glutamate sensitive region is the anatomically defined NMC, while the Ach sensitive region is the more caudal nucleus paramedianus (NPM). More dorsal and rostral regions, where electrical stimulation is effective, do not respond to chemical stimulation. This suggests that axons are being activated by electrical stimulation or that other, as yet untested, transmitters are involved. Using both agonist and antagonist microinjections, we found that non-NMDA glutamate receptors mediate the glutamate induction of atonia by the NMC, while muscarinic Ach receptors mediate the cholinergic induction of atonia by the NPM.

If cholinoceptive neurons in NPM mediate atonia, one would expect a selective augmentation of Ach release in this area during REM sleep. We conducted microdialysis studies in the intact freely moving animal to test this hypothesis. We found that Ach release is selectively increased in NPM during REM sleep, to an extent comparable to that seen in the cholinoceptive region of the dorsolateral pons [34].

Since immunohistochemical studies have identified corticotropin-releasing factor (CRF) as an important dorsolateral pontine and NMC transmitter [40, 83, 87], we studied the effect of this transmitter on muscle tone. CRF was microinjected into the dorsolateral pons and NMC in points at which electrical stimulation produced bilateral inhibition of muscle tone. CRF produced a dose-dependent muscle tone suppression, comparable to that seen after glutamate and Ach microinjection. This CRF-induced muscle inhibition was blocked by the specific CRF antagonist CRF 9-41. These results indicate that CRF may Interact with glutamate and Ach in the generation of muscle atonia.

As described above, we had determined that non-NMDA glutamate agonists produced atonia in both pons and medulla, while non-NMDA antagonists blocked this effect. We then examined the effect of NMDA agonists on muscle tone. We found that microinjection of NMDA agonists into the NMC and dorsolateral pons produced effects *opposite* to those of non-NMDA agonists. In every case, NMDA agonists produced increased tone or locomotion *at the same site* at which non-NMDA agonists produced atonia (Figs. 4 and 5). NMDA induction of locomotion in NMC has also been reported by Garcia-Rill, Skinner and colleagues [18, 32]. These workers did not test for

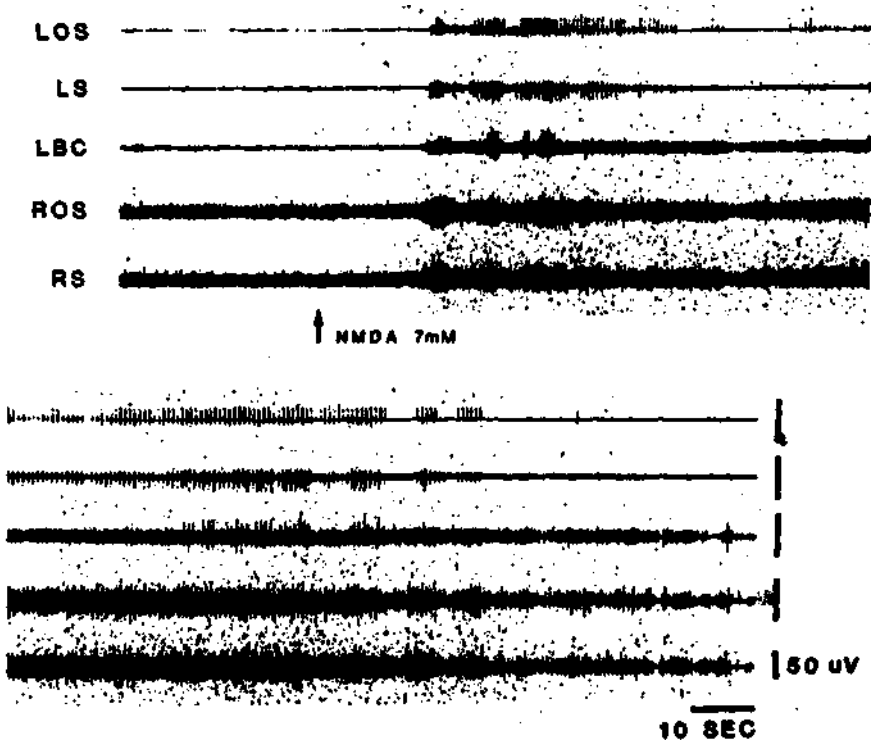

Fig. 4. Increased muscle tone with locomotion, produced by NMDA injection. 0.5 /ul of 7 mM NMDA microinjected into pontine inhibitory area not only produced an increase in tone but also induced stepping-like activity. LOS and ROS: left and right occipitoscapularis; LS and RS: left and right splenius; LBC: left biventer cervicis; from [40].

non-NMDA effects. We concluded that ponto-medullary non-NMDA receptors mediate muscle tone suppression, and that NMDA receptors mediate locomotion and muscle tone facilitation. NMDA receptors, which are voltage sensitive, would be potentiated by Ach and CRF mediated depolarization in REM sleep. The release of glutamate in REM sleep on these two populations of brainstem cells, cells with a predominant NMDA response and cells with a predominant non-NMDA response, can explain the "paradoxical" aspect of REM sleep, particularly the loss of muscle tone combined with brainstem motor activation that characterizes this state. To my knowledge, this is the first mechanistic explanation of this fundamental aspect of REM sleep.

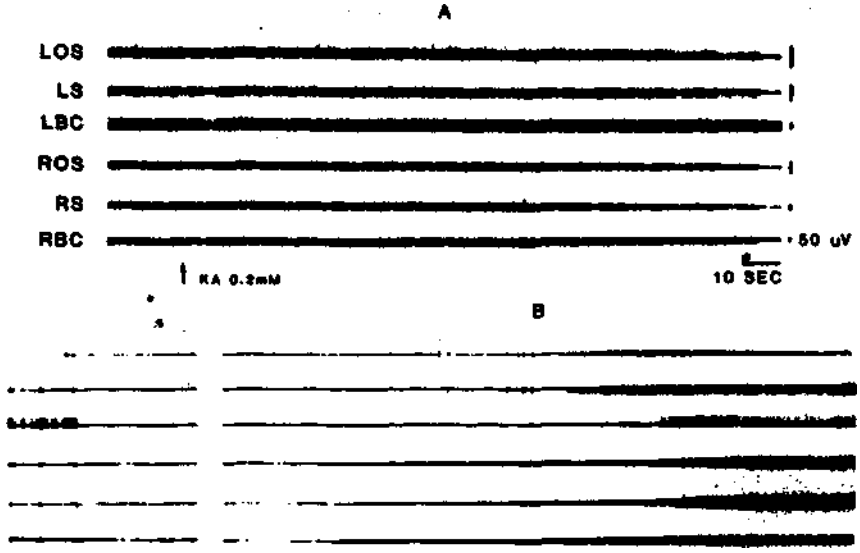

Fig. 5. Muscle tone suppression induced by kainic acid (KA) (a nonNMDA agonist) injection on muscle activity. LOS and ROS: left and right occipitoscapularis; LS and RS: left and right splenius; RBC: right biventer cervicis; from [40].

This work leads to the hypothesis that NMDA and non-NMDA receptors are differentially distributed on atonia and non-atonia related cells. There is a precedent for such a differential distribution of NMDA and non-NMDA receptors in the hippocampus [4]. In this study it was found that while most hippocampal synapses contained both receptor subtypes, 20% contained only non-NMDA and 10% only NMDA types. It is of course conceivable that atonia related and nonrelated cells would both have the same receptor mix, in which case one would have to focus on their membrane properties, projections, transmitters, morphology or inputs to differentiate them.

As described above, we found that glutamate microinjection into the NMC and the pontme inhibitory area and Ach injection into the NPM produce muscle tone suppression. We sought to determine the endogenous source of these transmitters. We mapped the distribution of glutamatergic cells in the brainstem using an antibody to glutamate conjugated to a carrier protein [45].

We found glutamatergic cell concentrations in the pedunculopontine nucleus, RRN, vFTP and the central and pericentral divisions of the ventrally located tegmental reticular nuclei [35].

We microinjected wheat germ agglutinated HRP at pontine sites where muscle tone suppression was induced by glutamate, to retrogradely label afferent cells. We used glutamate immunoreactivity to double label glutamate containing cells and NADPH diaphorase histochemistry to double label cells with NO synthase, a marker of cholinergic cells in the PPN/LDT region [35]. Glutamatergic cells projecting to the pontine inhibitory area were concentrated in the RRN, vFTP, rostral PPN and laterodorsal tegmental (LDT) nuclei. These are the same regions where we found that stimulation produced atonia [37].

We did similar studies using ChAT immunohistochemistry and HRP labelling to determine the source of the cholinergic projection to the NPM [68]. We found that this projection originated in the PPN and LDT. Adjacent non-Ach peribrachial neurons also project to NPM. Prior studies by others [48, 67], and our study [35] found that PPN and LDT were also the source of the Ach innervation of the pontine cholinoceptive atonia inducing regions. We hypothesize that tfye coordinated activation of these distinct glutamatergic and cholinergic cell populations in the PPN, RRN, vFTP and ventral tegmental regions of the pons, triggers the suppression of muscle tone in REM sleep.

Our electrical and chemical stimulation work described above bad identified a glutamate sensitive region in the medial medulla that could induce muscle atonia in the decerebrate cat. If, as we hypothesized, this medial medullary region mediated the suppression of muscle tone seen during REM sleep, then destruction of these neurons should disrupt REM sleep atonia. We tested this hypothesis by producing excitotoxic lesions of the medial medulla. These lesions produced a REM sleep without atonia syndrome, similar to that which results from pontine lesions. While the other phenomena of REM sleep such as pupillary miosis, inattention to surroundings, reversibility with stimulation, PGO activity and EEG desynchrony were present, muscle atonia was disrupted. The animal raised its head and made head movements during a state which otherwise resembled REM sleep.

In a father investigation of the pontine REM without atonia phenomenon, we compared the effects of dorsolateral pontine lesions with PPN/LDT lesions [69]. We found that relatively complete lesions of the cholinergic LDT/PPN were without any measurable effect on REM sleep atonia. However, these lesions produced an almost total elimination of REM sleep phasic events. Conversely, dorsolateral pontine lesions produced REM sleep without atonia without decreasing phasic events. We concluded that RRN and other non-Ach afferents to the dorsolateral pontine area are sufficient for the generation of REM sleep atonia.

We found that the effect of medullary stimulation on muscle tone was dependent on blood pressure [38]. When blood pressure in the decerebrate animal was lowered by pharmacologic or mechanical means, stimulation that

had produced atonia now produced increased tone or -reciprocal changes in muscle tone. EMG reductions cause a reduction in blood pressure. Therefore, "gating" of the atonia circuit by blood pressure prevents further blood pressure reductions in hypotensive states. This blood pressure dependence is probably responsible for the previous controversies surrounding the replicability of the Magoun phenomenon. Sprague and Chambers [79] and others (see [39] for references) had reported that medullary stimulation produced reciprocal changes in muscle tone, rather than the non-reciprocal effect reported by Magoun and his colleagues. Our work shows that reductions in blood pressure can block atonia and that elevation of blood pressure restores the atonia effect. The loss of the non-reciprocal atonia effect in certain preparations is due to hemorrhage or hypotension. Atonia is always elicited at lower current thresholds and shorter latency than the increased or reciprocal changes in tone reported by Sprague and Chambers.

This finding led us to investigate blood pressure relations to cataplexy in the narcoleptic dog. We found that blood pressure elevation increased the frequency of cataplexy and that blood pressure reductions blocked cataplexy. We found that spontaneous cataplexy onsets were not accompanied, by significant blood pressure changes, but were accompanied by marked heart rate acceleration [75].

We further examined the relations of blood pressure and heart rate changes to muscle tone in the decerebrate cat [37]. While much work has focused on the role of the lateral medulla in cardiovascular control, the contribution of transmitters in the medial medullary region to blood pressure control had not been investigated. We found that glutamate microinjection in the medial medulla produced hypotension without change of heart rate. At higher doses, glutamate induced hypotension with bradycardia. Glutamate also decreased muscle tone or produced complete atonia when microinjected into the pons and NMC. Both NMDA and non-NMDA receptor blockers attenuated or completely blocked the cardiovascular response, while only non-NMDA antagonists blocked muscle inhibition to glutamate injection, Microinjection of cholinergic agonists produced consistent hypotension but decreased muscle tone only when injected in the NPM. The time course of muscle atonia and cardiovascular change differed after most microinjections. We concluded that the muscle tone suppression and cardiovascular response to glutamate or Ach agonists are mediated by distinct neuronal populations. The co-localization of these effects suggests that neuronal networks in the medial medulla and dorsolateral pons interact in the coordination of motor and cardiovascular responses.

We found that a subset of cells in the NMC of the narcoleptic dog discharged at high rates only in cataplexy and REM sleep (REM-cataplexy-on cells) [73]. These cells were silent in active waking and had low levels of discharge in quiet waking. REM-cataplexy on cells were non-cholinergic and were localized to the ventral NMC, the precise area identified as glutamate sensitive in our decerebrate preparations. All medullary REM-on cells were active prior to and during cataplexy. The localization and discharge pattern of these

cells is consistent with the hypothesis that cataplexy results from waking activity in neurons normally responsible for the suppression of muscle tone in REM sleep.

While a population of REM-cataplexy-on cells was found, most medullary cells were *inactive* during cataplexy, but were *active* during REM sleep and waking. They discharged in the pre-cataplexy period and *ceased discharge* with the onset of cataplexy. The "cataplexy-on" cells in the NMC were intermixed with these "cataplexy-off' cells.

We hypothesize that cataplexy is a result of the pathological waking activity of medullary REM-cataplexy-on neurons. If these medullary cells are being driven by pontine cells, REM-cataplexy-on neurons may be present in lateral pontine regions. If cataplexy-on cells are absent from these pontine regions it would suggest that cataplexy is triggered by medullary mechanisms. The NMC is the natural starting point for any analysis of cataplexy, and might actually be the locus of the pathology of narcolepsy. In addition to its involvement in muscle tone control, the region of the NMC has long been known to modulate cortical arousal [5,7,61, 80] and therefore could produce the sleepiness that characterizes narcolepsy.

4

Conclusion

Using unit recording, microstimulation and lesion techniques, a brainstem network involved in the suppression of muscle tone control has been identified. This network can be triggered by environmental factors that provoke sudden excitement, leading to cataplectic attacks. Further analysis of the normal and abnormal operation of this system will shed light on the etiolgy of narcolepsy, sleep apnea and the REM sleep behaviour disorder.

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