Rapid Eye Movement Sleep
B.N. Mallick and S. Inoue (Eds)


# 5. Muscle Atonia in REM Sleep

**Yuan-Yang Lai and Jerome M. Siegel**

Dept. Psychiat., Sch. Med., UCLA., VAMC, Sepulveda, CA, 91343, USA

## SUMMARY

Rapid eye movement (REM) sleep is characterized by skeletal muscle atonia. The neural substrates participating in REM atonia have been identified in the pons and medulla. Electrical and chemical stimulations in these areas induces muscle atonia in both the intact and the decerebrate animals. Cholinergic, glutamatergic and corticotropin-releasing factor (CRF) mechanisms have been found to be involved in muscle atonia. In the medial pons, cholinergic, glutamatergic and CRF agonist injection induces muscle atonia. In the medial medulla, 2 distinct atonia inducing areas, a rostroventral medulla glutamatergic/CRF and a caudal medulla cholinoceptive system mediating muscle atonia have been identified. Microdialysis studies find that acetylcholine release in the pons and caudal medulla increases during natural REM sleep in the intact cat. Active inhibition of motoneurons from the activation of neurons in the pontine inhibitory area and medial medullary reticular formation has a role in muscle atonia. The other systems, including locus coeruleus complex, ventral paralemniscal tegmental field and retrorubral nucleus, may also contribute to muscle tone suppression via inhibitory or disfacilitatory effects on motoneurons.

*Key Words:* locus coeruleus, medulla, pons, midbrain, glutamate, acetylcholine, microdialysis, motor control.

## Introduction

This review concerns experimental studies of REM sleep atonia and the mechanisms underlying atonia. The majority of studies have been done on the cat, a few experiments on the rat are also included. Muscle atonia in REM sleep was first discovered by Jouvet and Michel (1959). REM sleep can be subdivided into two phases—tonic and pahsic. Tonic REM sleep includes sustained muscle atonia, whereas phasic REM refers to the occurrence of muscle twitches superimposed on tonic atonia. An understanding of supraspinal regulation of muscle activity in sleep may be relevant to sleep related disorders, such as periodic leg movement, REM behavior disorder and obstructive sleep apnea.

## Supraspinal Structures Involved in the Inhibition of Motor Activity

In natural sleep, a complete loss of muscle tone (Jouvet and Michel, 1959) and a suppression of spinal reflexes (Gassel et al., 1964, 1965) in REM sleep have been reported. These muscle atonia and reflexes suppression could be attributed to supraspinal structures. Two areas of the brainstem, the medial pons and medulla, have been extensively studied. Electrophysiological studies on either intact unanesthetized or decerebrate animals have shown that the pontine inhibitory area (PIA) and medial medullary reticular formation play a critical role in postural suppression. A physiological role of muscle tone regulation for 2 other areas, ventro-caudal midbrain and locus coeruleus (LC) complex, have been also discussed.

### *Pons-midbrain*

*Pontine inhibitory area*

The PIA (Fig. 1) extends from the nucleus reticularis pontis oralis (PoO) and the rostral portion of the nucleus reticularis pontis caudalis (PoC) according to Taber (1961). Sprague et al. (1948) first reported that electrical stimulation of the PoC dorsal to the trapezoid body, produced reflex inhibition bilaterally in the decerebrate cat. In the more rostral pons, electrical stimulation in the PoO produces muscle tone suppression in neck (Lai and Siegel, 1988) and hindlimb muscles (Iwakiri et al. 1994). Fig. 1 shows that inhibitory sites are widely diffused from the dorsal to the ventral portion at the junction of PoO and PoC while a restricted localized area in the medial portion could be found in PoO in the cat. Similar to the cat, electrical stimulation in the PoO and PoC also induced reduction of muscle tone in the decerebrate rat (Hajnik et al., 1995).

Lesion studies in intact animals have localized the neural structures participating in REM atonia. Jouvet (1962) and Carli and Zanchetti (1963) showed that lesions in the pontine reticular formation suppressed REM sleep. Thereafter, Jouvet and Delorme (1965) found that small lesions in this region produced REM sleep without atonia instead of REM sleep suppression. Extensive studies in lesions in the dorsolateral pons were performed by Morrison and colleagues and Sastre et al. (1978). They found that electrolytic lesion in the area ventromedial to the nucleus locus coeruleus (LC) produced REM sleep without atonia (Henley and Morrison, 1974; Sastre et al., 1978). Further experiments have shown that caudal medial pontine lesion produced REM sleep without atonia, while lesions extending more rostroventrally not only produced REM sleep without atonia but also expressed different behaviors (Hendricks et al., 1982; Morrison, 1988). This pontine lesion-induced REM sleep without atonia has been confirmed by other studies using radiofrequency thermal lesion (Friedman and Jones, 1984; Jones, 1979; Shouse and Siegel, 1992). In contrast, neurotoxic kainate lesion in the caudomedial pons fails to produce REM sleep without atonia (Sastre et al., 1981).

The proto-oncogene c-fos is an immediate-early gene expressed in cells in response to stimulation. Fos expressing neurons could be identified by immunohistochemistry. This technique provides another evidence of brainstem participation in muscle atonia. In carbachol-induced REM sleep-like activity, fos-like immunoreactive neurons could be found in the PIA (Shiromani et al., 1992; Yamuy et al., 1993). This result indicates that neurons in the PIA may play an important role in the regulation of muscle activity or in other aspects of REM sleep.

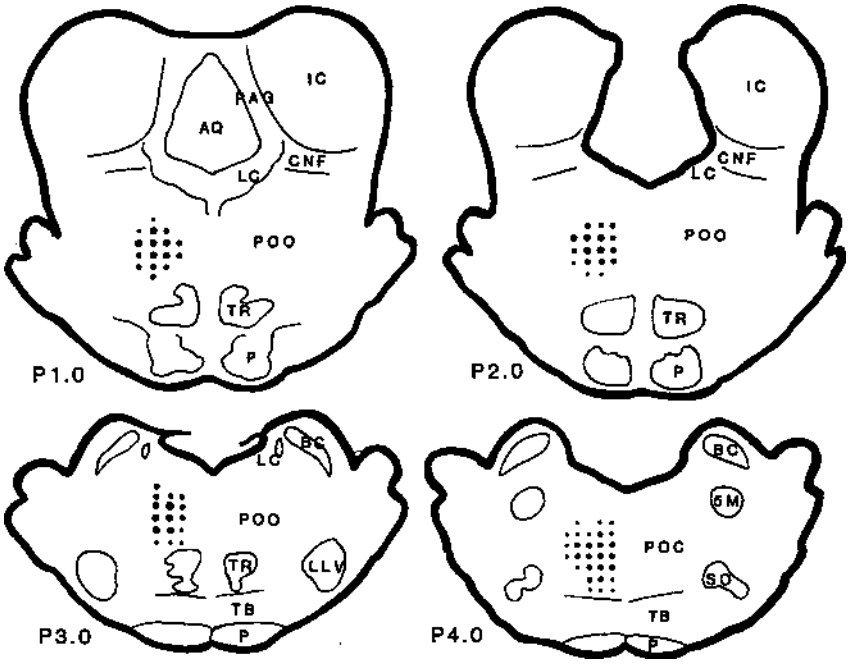


**Fig. 1. Sites of pontine-induced atonia by electrical stimulation. 500 msec trains**

been found in the *LCa*and peri-LCain natural sleep (Sakai, 1988; Sakai and Koyama, 1996). Some REM-on cells have a descending projection to the NMC suggesting these REM-on cells in the pons are involved in muscle atonia. Injection of cholinergic agonists into the area medioventral to the LC, induce postural atonia in unanesthetized (George et al]., 1964; van Dogen et al., 1978) and decerebrate animals (Lai and Siegel, 1988; Hajnik et al., 1996).

*Locus coeruleus complex*

Physiologically, LC has been known to modulate the spinal motor system (FungandBarnes, 1981, 1987), nociception (Jones, 1991; Margalit and Segal, 1979; Mokha et al., 1985; West et al., 1993), sensory (Foote et al., 1980; Swick et al., 1994), EEG activation (Foote et al., 1980), cardiovascular regulation (Ward and Gunn, 1976; Chalmers et al., 1981; Gurtu et al., 1984), fear and anxiety (Aston-Jones et al., 1994) and memory (Sara et al., 1988). However, the functional aspects of the LC effect on muscle atonia have been neglected. Extracellular recording from LC neurons has shown these neurons tend to be silent during cholinergic induced muscle atonia/REM sleep in the decerebrate cat (Pompeiano and Hoshino, 1976a, 1976b). The decrease of neural activity of the LC neurons starts prior to the onset of slow wave sleep, and there is a complete absence of activity in REM sleep (Hobson et al., 1975; Steriade and Hobson, 1976). Further study by Sakai (1980) has demonstrated that REM-off neurons which ceases firing during REM sleep in the LC, markedly increase in activity during REM sleep-waking transition period, just prior to the return of muscle activity. This REM-off neuron has been identified as noradrenergic (Aston-Jones and Bloom, 1981). Extracellular recording from the narcoleptic dog demonstrates that all REM-off neurons in LC complex cease firing during cataplexic attacks (Wu et al., 1996). Clonidine which is an $a_2$ receptor agonist and inhibits noradrenergic neuron activity, microinjected into the LC produces muscle tone suppression (Pompeiano et al., 1987).

*Other systems (pedunculoponline nucleus, ventral paralemniscal tegmental field and retrorubral nucleus)*

The most rostral part of the pontine reticular formation, paralemniscal tegmental field (FTP) according to Berman's Atlas (1968) and pedunculopontine nucleus (PPN) of the mesopontine junction may play a role in the control of muscle tone. Electrical stimulation of the ventral portion of the FTP (VFTP) and PPN generates muscle tone suppression bilaterally in the decerebrate animal (Lai and Siegel, 1990; Hajnik et al., 1995). The latency (Table 1) of VFTP—(31 msec) and PPN-induced (27.1 msec) muscle tone suppression is short and comparable to those of the pons (18.7 msec) and medulla (16.5 msec). Injection of cholinergic agonists into the VFTP induces increases in REM sleep in the intact animals (Reinoso-Suarez et al.; 1990). Non-NMDA agonists injection into the VFTP produces reduction of muscle tone in the decerebrate

rat (Hajnik, et al., 1996). At the midbrain level, the so called A8 area of the retrorubral nucleus (RRN), located in between the substantia nigra and ventral tegmental area, has also been found to be involved in muscle tone regulation. The caudal portion of the RRN forms a continuation of the VFTP. Electrical stimulation in the RRN elicits muscle tone suppression with a latency of 36.5 msec (Lai and Siegel, 1990).

**Table 1. Latency of muscle tone suppression by electrical stimulation in midbrain, pons and medulla**

| Nucleus | RRN | VFTP | PPN | PIA | NMC | NPM |
|---|---|---|---|---|---|---|
| Latency (ms) | 36.5 | 31.0 | 27.1 | 18.7 | 16.5 | 15.4 |

NMC: nucleus magnocellularis;NPM:nucleus paramedianus; PIA: pontine inhibitory area; PPN: pedunculopontine nucleus; RRN: retrorubral nucleus; VFTP: ventral paralemniscal tegmental field.

We have found that repetitive electrical stimulation in the VFTP and PPN elicits reduction of muscle tone during stimulation, while elicited locomotion could be seen during the inter-stimulation interval (Lai and Siegel, 1990). Neurotoxic NMDA lesions of the ventral mesopontine junction including the VFTP and the caudal RRN, induces muscle twitching in decerebrate animals (Lai and Siegel, 1997a). We have hypothesized that this ventral mesopontine junction area may participate in the regulation of phasic events of REM sleep mediated through the nucleus magnocellularis (NMC) in the medulla (detail discussed below).

***Medulla***

In 1946, Magoun and Rhines described a global inhibitory effect from the medullary reticular formation on spinal motor activity in the decerebrate cat. Unilateral electrical stimulation in the medial medulla suppressed spinal reflexes of both hindlimbs. The bulbar sites which produce reflex inhibition are located in the NMC, nuclei gigantocellularis (NGC) and paramedianus (NPM). Further studies have found that stimulation in this medial medulla region inhibits visceral reflexes (Alderson and Downman, 1966), sensory-induced reciprocal inhibition (Bach, 1950), basal muscle tone (Lai et al., 1987), muscle twitches (Lai and Siegel, 1997b), and movement in the intact cat (Schenkel et al., 1998), movement in the anesthetized animal evoked by cortical stimulation (Niemer and Magoun, 1947) and in the decerebrate cat (Noga et al., 1988; Kinjo et al., 1990). In the rodent, electrical stimulation in the medial medulla of nuclei dorsal paragigantocelluaris, gigantocellularies and gigantocellularis ventralis also elicits muscle tone suppression (Hajnik et al., 1995).

The most potent inhibitory area in the medial medulla in the cat has been reported to be located in the rostral medial medulla. However, whether the dorsal medulla of the NGC or the ventral NMC generates the maximal effect

on muscle activity remains unclear. Using orthodromic stimulation and extracellular recording techniques, Mori and colleagues find that NGC neurons respond to stimulation of the pontine-induced postural suppression area, while NMC neurons respond to stimulation applied to the mesencephalic locomotor region (Iwakiri et al., 1995). In contrast, Magoun (1950) and Engberg et al. (1968a) have reported that the maximal suppression effect on spinal reflexes was originated from NMC stimulation. Our work in the decerebrate cat has been consistent that of Magoun (1950) and Engberg et al., (1968a). As shown on Table 2, the lowest threshold area to induce muscle atonia has been found to be located in the NMC by electrical stimulation.

**Table 2. Threshold for eliciting muscle tone suppression in the medial medulla**

| | Threshold ($\mu$A) |
|---|---|
| NGC | 32 ± 14 |
| NMC | 21 ± 10 |
| NPM | 27 ± 12 |

Electrical stimulation studies have shown that muscle tone suppression and reflex inhibition were "state-dependent" in intact animals. Stimulation in the NGC produces facilitation of masseteric reflex in waking and quiet sleep, while the same stimulation in the same site produces reflex inhibition in REM sleep (Chase and Wills, 1979). A recent study in our laboratory has found that medial medullary stimulation induces either no effect or a short inhibition followed by facilitation of muscle tone in waking, while the same stimulation produces muscle tone suppression in non-REM sleep (Schenkel et al., 1990). In decerebrate animals, stimulation in the NGC produced no effect on monosynaptic reflex and membrane potential of the motoneuron before intrapontine carbachol injection. However, suppression of monosynaptic reflex and hyperpolarization of spinal motoneuron could be seen after carbachol injection into the pons (Pereda et al., 1990).

Neuronal activity in the NGC and NMC increases during pontine carbachol-induced atonia and natural REM sleep. Extracellular recording study demonstrates that increases in firing rate in NGC neurons parallel the decreases in soleus muscle activity during intrapontine carbachol injection (Takakusaki et al., 1994). REM-on neurons have been identified in NMC in the cat (Sakai et al., 1981). Cataplexy-REM-on neurons have been found in the NMC in the narcoleptic dog (Siegel et al., 1991). Proto-oncogene c-fos immunoreactive neurons could be found in the medial medulla, especially in the NMC, in pontine carbochol-induced atonia (Yamuy et al., 1993). On the other hand, lesions in the medial medulla produces REM sleep without atonia (Sastre et al., 1978; Schenkel and Siegel, 1989), indicating that the medial medulla is a

final common pathway to regulate muscle atonia in REM sleep.

*Neural pathway*

Figure 2 summarizes the hypothesized neural pathway in control of muscle atonia. Neurons from the limbic system including bed nucleus of the stria terminalis, amygdala, hypothalamus-preoptic region and the anterior and mediodorsal thalamic nuclei (Holstege, 1991) project to the RRN, VFTP, periaqueductal gray (PAG), PPN, LC complex and NMC (Hopkins and Holstege, 1978; Saper et a l., 1979; Price and Amaral, 1981;Chiba and Murata, 1985; Holstege et al., 1985; Hosoya, 1985; Holstege, 1987, 1991; Deutch et al., 1988; Wallace et al., 1989; Shammah-Lagnado et al., 1993; Lai et al., 1994; Zardetto-Smith and Johnson, 1995; Rizvi et al., 1996). A direct projection from the limbic system to the spinal cord have also been found (Kuypers and Maisky, 1975; Holstege, 1987). Neurons from the RRN, VFTP, PPN and PAG have been found projecting to the PIA and NMC by retrograde transport tracing studies (Lai et al., 1993a, 1993b).

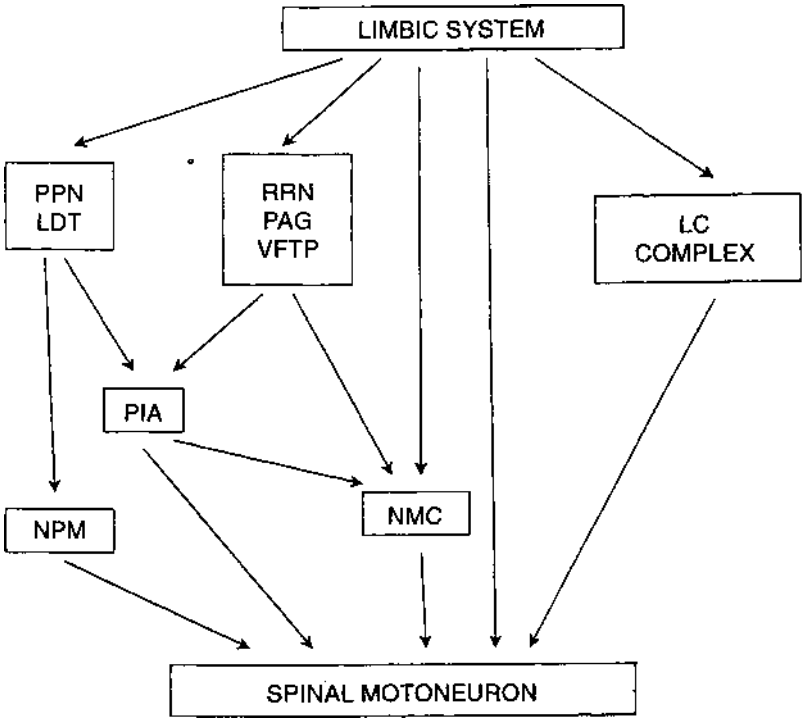


**Fig. 2. Hypothesized neural structures and pathways involved in muscle atonia. Neurons in the limbic system project to the bainstem and exert either facilitatory or inhibitory effects on the target neurons, which in turn project to the medullary relay nuclei and spinal cord. Spinal motoneurons receive multiple innervations from pontomedullary neural structures. Muscle atonia resulted from the summation of input fiber activity. LDT: dorsolateral tegmental nucleus; PAG: Periagueductal gray.**

Neurons in the pons project to the NGC (Matsuyama et al., 1993), NMC

(Sakai et ah, 1979; Lai and Siegel, 1988; Lai et al., 1993) and NPM (Shiromani et al., 1988) which in turn project to the spinal cord (Tohyama et al., 1979; Newman, 1985). However, a direct projection from the PIA to the spinal cord has also been reported (Nyberg-Hansen, 1966; Kuypers and Maisky, 1975, 1977; Matsuyama et al., 1997). Anatomical and electrophysiological studies find the neurons in the pons send their fibers through the dorsal tegmental field and terminate in the NGC (Ohta et al., 1988). Nucleus magnocellularis neurons also receive fiber inputs from the pons. Orthodromic stimulation in the pons excitates NMC neurons (Kanamori et al., 1980), and pontine neurons can be antidromically activated from the NMC (Sakai et al., 1981) indicating neurons from pons project to the NMC. Labelled neurons have been found in the pons (Sakai et al., 1979; Luppi et al., 1988; Lai et al., 1993b) when retrograde tracers were injected into the NMC in the cat, as well as in the nucleus gigantocellularis alpha and ventralis in the rat (Gallager and Pert, 1978; Bayev et ah, 1988). Anterograde PHA-L and autoradiographic studies have demonstrated that the nucleus gigantocellularis alpha and ventralis in the rat receive afferents from the pons (Jones and Yang, 1985). In our physiological study in the decerebrate cat, we found that pontine carbachol-induced muscle atonia could be reversed by unilateral injection of the glutamate antagonist, gamma-D-glutamyglycine, into the NMC (Lai and Siegel, 1988). This result indicates that the NMC is the relay nucleus for the pons in inducing muscle atonia.

Funicular trajectories of descending fibers from the brainstem nuclei have been identified. The pioneer study on funicular trajectory was done using degeneration and silver impregnation techniques. After lesions in different brainstem regions, degenerating fibers, terminal arborizations and terminal boutons in the spinal cord could be identified by silver impregnation. Using these techinques, Nyberg-Hansen (1965, 1966) was able to identify neurons from the PoC that send fibers descending through the ventral and ventrolateral funiculi and terminate in laminae VII and VIII. This finding was confirmed by anterograde autoradiographic tracing study (Holstege and Kuypers, 1982). Anterograde autoradiographic and PHA-L tracing studies have also identified fibers from the PoO that descend through the ventral funiculus and terminate in laminae VII and VIII of the spinal cord (Holstege and kuypers, 1982; Matsuyama et ah, 1993). In the dorsolateral pontine tegmentum, including LC and subcoeruleus, descending fibers can be seen in the dorsal, dorsolateral ventrolateral and ventral funiculi (Holstege et ah, 1979; Bjorklund and Skagerberg, 1982; Kuypers and Huisman, 1982; Carlton et ah, 1985). These dorsolateral pontine projection fibers terminate in laminae V-VIII and X, throughout all levels of the spinal cord (Holstege et ah, 1979).

In the medial medulla, neurons from both the NGC and NMC send descending fibers through the ventral and ventrolateral funiculi through all levels of the spinal cord, and terminate in laminae VI-IX in the cat (Nyberg-Hansen, 1965,1966; Tohyama et ah, 1979; Johannessen et ah, 1984; Matsuyama

et al., 1988, 1995; Mitani et al., 1988). However, a different spinal pathway from the NMC has been reported. Descending fibers from the NMC travel through ventral and ventrolateral funiculi at the cervical and thoracic, cord and then over the dorsolateral funiculus at the lumbosacral level, terminate in all levels of spinal cord in laminae V-VIII and X (Holstege et al., 1979; Holstege and Kuypers, 1982, 1987). Finally, descending projections from the NPM pass via dorsal and lateral funiculi in the spinal cord (Tohyama et al., 1979).

***Mechanism of supraspinal inhibition of motor activity***

Stimulation in the medial medulla produces IPSP in both of the extensor and flexor motoneurons (Llinas and Terzuolo, 1964,1965; Jankowska et al., 1968). Since a long slow positive potential in the motoneuronal pool accompanying with the suppression has been recorded, Lettvin and Dell (1950) suggest that this medullary inhibitory effect on motoneurons is mediated via the interneurons in the spinal cord. Subsequent studies by either intracellular or extracellular recording from spinal interneurons have confirmed this hypothesis (Lungberg and Vyklicky 1966; Engberg et al., 1968a, 1968b; Jankowska et al., 1968). Using the spike-trigger averaging technique, Takakusaki et al. (1989) found that stimulation in the medial medulla generated IPSPs in spinal motoneurons with a segmental delay of 1.3 ms, indicating at least one interneurons is involved.

Electrical stimulation in the medial pons (Fung et al., 1982) and NGC (Chase et al., 1986) induces hyperpolarization of spinal motoneuron in intact animals. This brainstem-induced hyperpolarization of spinal motoneuron has been hypothesized to be "state-dependent". In waking and quiet sleep, stimulation in the pons produced a short latency of hyperpolarizing potential of hindlimb motoneuron. However, this same stimulation elicits not only a short latency IPSP but also a following longer latency IPSP in the same motoneuron during REM sleep (Fung et al., 1982). Similar findings have been reported from stimulation in the NGC. Chase et al., (1986) report that 59% of spinal motoneurons produced a small IPSP and another 41% of the cells produced no apparent change in membrane potential with NGC stimulation in waking and quiet sleep. On the other hand, the same NGC stimulation in REM sleep produced a potent IPSP in all recorded motoneurons.

For decades, muscle tone inhibition has been hypothesized due to active inhibition instead of disfacilitation (Giaquinto et al., 1964; Gottesmann, 1997). Glenn and Dement (1981) found that an increases in IPSPs but no decreases in EPSP in the spinal motoneurons in REM sleep. This finding led them to suggest that muscle atonia during REM sleep is mediated by the activation of the medial medullary inhibitory system. However, monoaminergic neurons in the pons may play a role in muscle tone suppression through a disfacilitatory effect on spinal motoneurons. It has been shown that blockage of LC neuron activity by local injection of clonidine produced muscle tone suppression,

ipsilateral to the injection side (Pompeiano et al, 1987). Unilateral electrolytic lesion of the LC also produces a reduction of muscle tone ipsilateral to the lesion side (D'Ascanio et al., 1989). This LC effect on muscle activity led

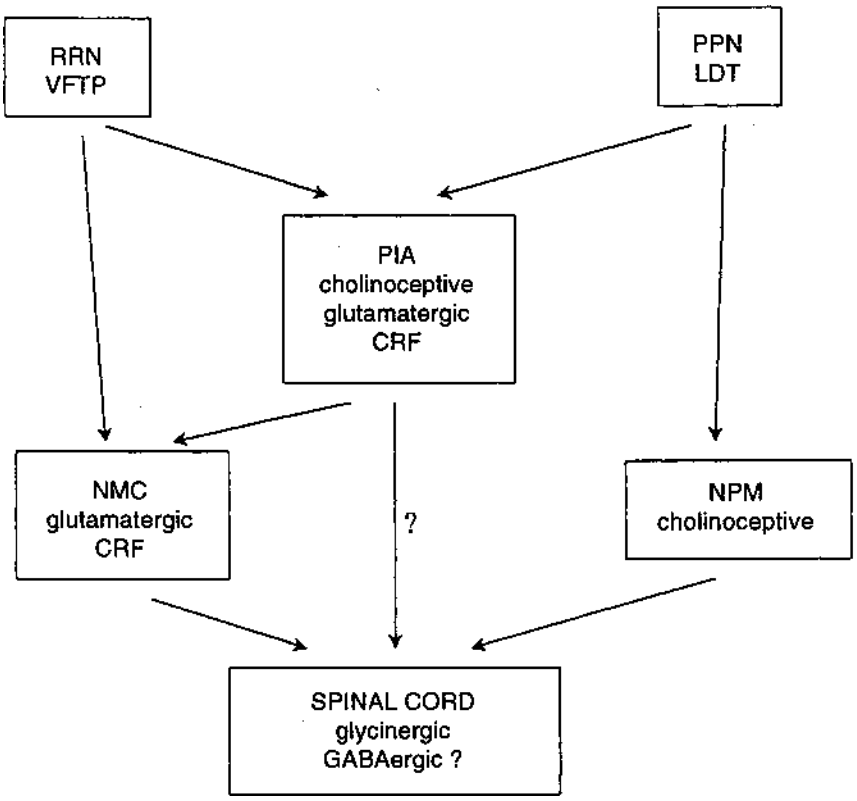


**Fig. 3. Putative neurotransmitters involved in muscle atonia. The PIA received glutamatergic fibers from the RRN, VFTP, PPN and LDT, while cholinergic and CRF input fibers may originate from PPN and LDT. The PPN and LDT also send fibers to NPM. In NMC, glutamatergic innervation comes from RRN, VFTP and PIA. In spinal cord, both glycinergic and GABAergic inputs originate from NMC, and also possible from PIA. The question mark from PIA to spinal cord represents an unknown inhibitory pathway.**

injection into the area ventromedial to the LC produced waking with atonia. Similar findings have been also reported in the cat and rat (Baghdoyan et al., 1984; Katayama et al.; 1984; Gnadt and Pegram, 1986; Taguchi et al., 1992; Lopez-Rodriguez et al., 1995), These results indicate that muscarinic cholinergic receptors are involved in pontine-induced atonia. Further studies using specific agonists and antagonists microinjected into the pons, have determined that the $M_2$ muscarinic system plays a critical role in pontine-induced atonia (Velazquez-Moctezuma et al., 1989, 1991; Imeri et al., 1992). In the more rostroventral pons, carbachol injection not only produces long lasting muscle atonia but also increases in REM sleep (Reinoso-Suarez et al., 1990). Atonia with waking will be found when cholinergic agonists injected into the dorsal pons, while ventral pontine injection produces REM sleep with atonia (Rodrigo-Angulo et al., 1994).

The NPM of the caudomedial medulla also generates muscle tone

suppression when cholinergic agonists are injected into it (Lai and Siegel, 1988). This cholinergic induced muscle atonia could be blocked by prior local injection of atropine, suggesting that a muscarinic receptor is involved (Lai and Siegel, 1988). The NPM area has been demonstrated to receive cholinergic innervation from the PPN (Shiromani et al., 1988).

The microdialysis technique has provided another line of evidence regarding the neurotransmitters involving in REM sleep and atonia. In the free moving animals, acetylcholine release in the pons is increased during natural REM sleep (Kodama et al., 1990) or pontine carbachol-induced muscle atonia (Lydic et al., 1991). Acetylcholine release in the NPM is also increased during muscle atonia induced by either pontine electrical stimulation or carbachol injection in both intact and decerebrate animals (Kodama et al., 1992).

### *Excitatory amino acids andpeptide*

Our experiments on the decerebrate animals have demonstrated that non-cholinergic mechanism also participates in muscle atonia in the medial pons. Microinjection of corticotropin-releasing factor (CRF; Lai and Siegel, 1992) and glutamate (Lai and Siegel, 1988) agonists into the PIA, in which carbachol and acetylcholine injection induced atonia, produces muscle tone suppression. Further study has determined that nonNMDA but not NMDA glutamate agonists are involved in muscle tone suppression (Lai and Siegel, 1991). The latency and duration of CRF, glutamate nonNMDA agonists-induced muscle atonia are comparable to that of acetylcholine injection (Table 4). In the decerebrate rat, the area responsible for cholinergic-induced muscle tone suppression in the pons is also responsible for nonNMDA agonists inducing atonia (Hajnik et al., 1996). This pontine nonNMDA effect on muscle activity has been confirmed by Onoe and Sakai (1995). They find that the nonNMDA agonists, kainate and AMPA, but not NMDA agonists microinjected into the pons induce increases in REM sleep and atonia in intact animals.

**Table 4. Latency and duration of muscle tone suppression induced by agonist injection in the pons and medulla**

| | Latency (sec) | | | Duration (min) | | |
|---|---|---|---|---|---|---|
| | Pons | NMC | NPM | Pons | NMC | NPM |
| Ach | 25 | — | 34 | 7.7 | _ | 4.1 |
| CRF | 27 | 19 | — | 10.6 | 4.1 | — |
| Glut | 24 | 18 | — | 12.9 | 4.2 | — |
| KA | 37 | 29 | — | 9.7 | 4.5 | — |
| QA | 26 | 21 | — | 14.3 | 13.3 | — |

Glut: glutamate; KA: kainic acid; QA: quesqualic acid.

In the medial medulla, we have identified 2 distinct areas, a rostral NMC glutamatergic/CRF and a caudal NPM cholinoceptive (see above), participating

in muscle tone suppression (Lai and Siegel, 1988; 1992). As in the pons, the NMC area also responses to glutamate and CRF injection. Glutamate agonists injected into the NMC but not the NPM produce muscle tone suppression bilaterally, and this effect can be blocked by glutamate antagonists, L-glutamic acid diethylester and gamma-D-glutamyglycine. As in the pons, nonNMDA agonists kainate, quisqualate and willardine but not NMDA agonists microinjected into the NMC elicit muscle atonia (Lai and Siegel, 1991). This nonNMDA agonist-induced atonia can be blocked by specific nonNMDA antagonists, 6-cyano-7-nitroquinoxaline-2, 3-dione and 6,7-dinitroquinoxaline-2, 3-dione. As with the nonNMDA agonist, CRF injected into the NMC but not the NPM elicits muscle tone suppression (Lai and Siegel, 1992). On the other hand, cholinergic agonists microinjected into the NMC fails to induce muscle tone suppression (Lai and Siegel, 1988).

In contrast to the nonNMDA agonist-induced muscle atonia, NMDA agonists microinjected into the PIA and NMC produced either increases in muscle tone or locomotion (Lai and Siegel, 1991). We have hypothesized that imbalance of NMDA and nonNMDA receptor activity in the NMC could contribute to increases in the generation of phasic events superimposed on the muscle atonia of REM sleep. Further support for this hypothesis has come from our recent study showing that ventral mesopontine junction lesion-induced muscle twitches (Lai and Siegel, 1997a) can be attenuted or blocked by nonNMDA agonists injection into the NMC (Lai and Siegel, 1997b). Anatomically, the NMC received glutamatergic afferent projections from the ventral mesopontine junction (Lai et al., 1993b).

***Inhibitory amino acid***

At the spinal cord level, extensive studies on neurotransmitters participating in motoneuron inhibition has been performed by Chase and colleagues. With intracellular recording from the lumbar motoneurons and iontophoretic application of chemicals, they found that the medulla-induced IPSPs in the motoneurons during active sleep were abolished or partially suppressed by strychnine, a glycine antagonist (Soja et al., 1987, 1991). This glycinergic effect in spinal motoneurons could be also seen in decerebrate animals during carbachol-induced REM-like activity (Morales et al., 1987). On the other hand, GABA antagonists failed to block these motoneuron IPSPs.

Spinal interneurons including Renshaw cells and $I_a$ inhibitory neurons exert inhibitory effect on motoneurons mediated by GABA and glycine (Cullheim and Kellerth, 1981). Glycinergic spinal Renshaw cells and $I_a$ inhibitory interneurons have been identified (Fyffe, 1991). However, the glycinergic mechanism involved in motoneuron IPSP generation in REM sleep may primarily originate from supraspinal structures since activity of the majority of Renshaw cell (85%) was suppressed (Morales et al., 1988), and only a few glycinergic spinal interneurons were double labelled with c-fos (Rampon et al., 1997) by carbachol administered into the pons which induced muscle

Carli, G. and Zanchetti, A. A study of pontine lesions suppressing deep sleep in the cat, Arch. ital. Biol., 103 (1965) 751-788. Carlton, S.M., Chung, J.M., Leonard, R.B. and Willis, W.D. Funicular trajectories of brainstem neurons projecting to the lumbar spinal cord in the monkey *(Macaca fascicularis):* A retrograde labeling study, J. Comp. Neurol., 241 (1985) 382-404. Chalmers, J.R, Blessing, W.W., West, M.J., Howe, P.R.C., Costa, M. and Fumes, J.B. Importance of new catecholamine pathway in control of blood pressure, Clin. Exp. Hypertension, 3 (1981) 393-416. Chase, M.H., Morales, F.R., Boxer, P.A., Fung, S.J. and Soja, P.J. Effect of stimulation of the nucleus reticularis gigantocellularis on the membrane potential of cat lumbar motoneurons during sleep and wakefulness, Brain Res., 386 (1986) 237-244. Chase, M.H. and Wills, N. Brain stem control of masseteric reflex activity during sleep and wakefulness: Medulla, Exp. Neurol., 64 (1979) 118-131. Chiba, T. and Murata, Y. Afferent and efferent connections of the medial preoptic area in the rat: A WGA-HRP study, Brain Res. Bull., 14 (1985) 261-272. Cullheim, S. and Kellerth, J.O. Two kinds of recurrent inhibition of cat spinal alpha-motoneurones as differentiated pharmacologically, J. Physiol., 312 (1981) 209-224. D'Ascanio, P., Pompeiano, M. and Tononi, G. Inhibition of vestibulospinal reflexes during the episodes of postural atonia induced by unilateral lesion of the locus coeruleus in the decerebrate cat, Arch. ital. Biol., 127 (1989) 81-97. Deutch, A.Y., Goldstein, M., Baldino, R, Jr. and Roth, R.H. Telencephalic projections of the A8 dopamine cell group. In: P.W. Kalivas and C.B. Nemeroff (Eds.), *The mesocorticolimbic dopamine system, Ann. New York Acad. Sci. Vol. 537,* New York, 1988, pp. 27-50. Engberg, L, Lundberg, A. and Ryall R.W. Reticulospinal inhibition of transmission in reflex pathways, J. Physiol., 194 (1968a) 201-233. Engberg, I., Lundberg, A. and Ryall, R.W. Reticulospinal inhibition of interneurones, J. Physiol., 194 (1968b) 225-236. Foote, S.L., Aston-Jones, G. and Bloom, F.E. Impulse activity of locus coeruleus neurons in awake rats and monkeys is a function of sensory stimulation and arousal, Proc. Natl. Acad. Sci. USA, 77 (1980) 3033-3037. Fort, P., Luppi, PH. and Jouvet, M. Glycine-immunoreactive neurones in the cat brain stem reticular formation, NeuroReport, 4 (1993) 1123-1126. Friedman, L. and Jones, B. E. Computer graphics analysis of sleep-wakefulness state changes after pontine lesions, Brain Res. Bull., 13 (1984) 53-68. Fung, S.J. and Barnes, C.D. Evidence of facilitatory coerulospinal action in lumbar motoneurons of cats, Brain Res., 216 (1981) 299-311. Fung, S.J. and Barnes, C.D. Membrane excitability changes in hindlimb motoneurons induced by stimulation of the locus coeruleus in cats, Brain Res., 402 (1987) 230-242. Fung, S.J., Boxer, PA., Morales, F.R. and Chase, M.H. Hyperpolarizing membrane responses induced in lumber motoneurons by stimulation of the nucleus reticularis pontis oralis during active sleep, Brain Res., 24: (1982) 267-273. Fung, S.J., Reddy, V.K., Zhuo, H., Liu, R.-H. and Barnes, C.D. Anatomical evidence for the presence of glutamate or enkephalin in noradrenergic projection neurons of the locus coeruleus, Microscopy Res. Tech., 29 (1994) 219-225. Gallager, D.W. and Pert, A., Afferents to brain stem nuclei (brain stem raphe, nucleus reticularis pontis caudalis and nucleus gigantocellularis) in the rat as demonstrated by microiontophoretically applied horseradish peroxidase, Brain Res., 144 (1978) 257-275. Gassel, M.M., Marchiafava, PL. and Pompeiano, O. Tonic and phasic inhibition of spinal reflexes during deep, desynchronized sleep in unrestrained cats, Arch. ital. Biol., 102 (1964)471-499.

Gassel, M.M., Marchiafava, RL. and Pomeiano, O. An analysis of the supraspinal influences acting on motoneurons during sleep in the unrestrained cat. Modification of the recurrent discharge of the alpha motoneurons during sleep, Arch. ital. Biol., 103 (1965) 25-44. George, R., Haslett, W.L. and Jenden, D.J. A cholinergic mechanism in the brainstem reticular formation: Induction of paradoxical sleep, Int. J. Neuropharmacol., 3 (1964) 541-552. Giaquinto, S., Pompeiano, O. and Somogyi, I. Descending inhibitory influences on spinal reflexes during natural sleep, Arch. ital. Biol., 102 (1964) 282-307. Glenn, L.L. and Dement, W.C. Membrane resistance and rheobase of hindlimb motoneurons during wakefulness and sleep, J. Neurophysiol., 46 (1981) 1076-1088. Gnadt, J.W. and Pegram, G.V. Cholinergic brainstem mechanisms of REM sleep in the rat, Brain Res., 384 (1986) 29-41. Gottesmann, C. Introduction to the neurophysiological study of sleep: Central regulation of skeletal and ocular activities, Arch. ital. Biol., 135. (1997) 279-314. Gurtu, S., Pant, K.K., Sinha, J.N. and Bhargava, K.R An investigation into the mechanism of cardiovascular responses elicited by electrical stimulation of locus coeruleus and subcoemleus in the cat, Brain Res., 301 (1984) 59-64. Hajnik, T., Lai, Y.Y. and Siegel, J.M. Atonia related regions in the rodent pons and medulla, Sleep Res., 24A (1995) 26. Hajnik, T., Lai, Y.Y. and Siegel, J.M. The atonia related regions in the rodent pons are glutamate sensitive, APSS Abstr., (1996) 133. Hancock, M.B. and Fougerousse, C.L. Spinal projections from the nucleus locus coeruleus and nucleus subcoeruleus in the cat and monkey as demonstrated by the retrograde transport of horseradish peroxidase, Brain Res. Bull., 1 (1976) 229-234. Hendricks, J.C., Morrison, A.R. and Mann, G.L. Different behaviors during paradoxical sleep without atonia depend on pontine lesion site, Brain Res., 239 (1982) 81-105. Henley, K. and Morrison, A.R. A re-evaluation of the effects of lesions of the pontine tegmentum and locus coeruleus on phenomena of paradoxical sleep in the cat, Acta Neurobiol. Exp., 34 (1974) 215-232. Hobson, J.A., McCarley, R.W. and Wyzinski, P.W. Sleep cycle oscillation: Reciprocal discharge by two brainstem neuronal groups, Science, 189 (1975) 55-58. Holstege, G. Some anatomical observations on the projections from the hypothalamus to brainstem and spinal cord: An HRP and autoradiographic tracing study in the cat, J. Comp. Neurol., 260 (1987) 98-126. Holstege, G., Descending motor pathways and the spinal motor system: Limbic and non-limbic components. In: G. Holstege (Ed.), *Role of the forebrain in sensation and behavior, Prog. Brain Res., 87,* Elsevier, Amsterdam, 1991, pp.307-421. Holstege, G. and Kuypers, H.G.J.M. The anatomy of brain stem pathways to the spinal cord in cat. A labeled amino acid tracing study. In: H.G.J.M. Kuypers and G.F. Martin (Eds.), *Descending pathways to the spinal cord, Prog. Brain Res., 57,* Elsevier, Amsterdam, 1982, pp. 145-175. Holstege, G., Kuypers, H.G.J.M. and Boer, R.C. Anatomical evidence for direct brain stem projections to the somatic motoneuronal cell groups and autonomic preganglionic cell groups in cat spinal cord, Brain Res., 171 (1979) 329-333. Holstege, G., Meiners, L. and Tan, K. Projections of the bed nucleus of the stria terminalis to the mesencephalon, pons, and medulla oblongata in the cat, Exp. Brain Res., 58 (1985)379-391. Holstege, J.C. Ultrastructural evidence for GABAergic brain stem projections to spinal motoneurons in the rat. J. Neurosci., 11 (1991) 159-167. Holstege, J.C. and Bongers, C.M.H.A glycinergic projection from the ventromedial lower brainstem to spinal motoneurons. An ultrastructural double labeling study in rat, Brain Res.,

Holstege, J.C. and Kuypers, H.G.J.M. Brainstem projections to spinal motoneurons: An update, Neurosci., 23 (1987) 809-821. Hopkins, D.A. and Holstege, G. Amygdaloid projections to the mesencephalon, pons and medulla oblongata in the cat, Exp. Brain Res., 32 (1978) 529-547. Horn, E., D'Ascanio, P., Pompeiano, O. and Stampacchia, G. Pontine reticular origin of cholinergic excitatory afferents to the locus coeruleus controlling the gain of vestibulospinal and cervicospinal reflexes in decerebrate cats, Arch. ital. Biol., 125 (1987)273-304. Hosoya, Y. Hypothalamic projections to the ventral medulla oblongata in the rat, with special reference to the nucleus raphe pallidus: A study using autoradiographic and HRP techniques, Brain Res., 344 (1985) 338-350. Imeri, L., Bianchi, S., Angeli, P. and Mancia, M. Differential effects of $M_2$ and $M_3$ muscarinic antagonists on the sleep-wake cycle, NeuroReport, 2 (1992) 383-385. Iwakiri, H., Oka, T. and Mori, S. Multi-segmental and generalized suppression of postural muscle tone evoked by stimulating the dorsal tegmental field and the medial pontine reticular formation in acute decerebrate cats, Neurosci. Lett., 182 (1994) 83-86. Iwakiri, H., Oka, T., Takakusaki, K. and Mori, S. Stimulus effects of the medial pontine reticular formation and the mesencephalic locomotor region upon medullary reticulospinal neurons in acute decerebrate cats, Neurosci. Res., 23 (1995) 47-53. Jankowska, E., Lund, S., Lundberg, A. and Pompeiano, O. Inhibitory effects evoked through ventral reticulospinal pathways, Arch. ital. Biol., 106 (1968) 124-140. Johannessen, J.N., Watkins, L.R. and Mayer, D.J. Non-serotonergic origins of the dorsolateral funiculus in the rat ventral medulla, J. Neurosci., 4 (1984) 757-766. Jones, B.E., Elimination of paradoxical sleep by lesions of the pontine gigantocellular tegmental field in the cat, Neurosci. Lett., 13 (1979) 285-293. Jones, B.E. and Yang, T.-Z. The efferent projections from the reticular formation and the locus coeruleus studied by anterograde and retrograde axonal transport in the rat, J. Comp. Neurol., 242 (1985) 56-92. Jones, S.L., Descending noradrenergic influences on pain. In: C.D. Bames and O. Pomeiano (Eds.), *Neurobiology of the locus coeruleus, Prog. Brain Res. Vol 88,* Elsevier, Amsterdam, 1991, pp. 381-394. Jouvet, M. Recherches sur les structures nerveuses et les mecanismes responsables des differentes phases du sommeil physiologique, Arch. ital. Biol., 100 (1962) 125-206. Jouvet, M. and Delorme, F. Locus coeruleus et sommeil paradoxal, C.R. Soc. Biol., 159 (1965)895-899. Jouvet, M. and Michel, F. Correlations electromyographiques du sommeil chez le chat, C.R. Soc. Biol., Paris, 153 (1959) 422-425. Kanamori, N., Sakai, K. and Jouvet, M. Neuronal activity specific to paradoxical sleep in the ventromedial medullary reticular formation of unrestrained cats, Brain Res., 189 (1980)251-255. Katayama, Y., DeWitt, D.S., Becker, D.P. and Hayes, R.L. Behavioral evidence for a cholinoceptive pontine inhibitory area: Descending control of spinal motor output and sensory input, Brain Res., 296 (1984) 241-262. Kinjo, N., Atsuta, Y, Webber, M., Kyle, R., Skinner, R.D. and Garcia-Rill, E. Medioventral medulla-induced locomotion, Brain Res. Bull., 24 (1990) 509-516. Kodama, T., Lai, Y.Y. and Siegel, J.M. Enhancement of acetylcholine release during REM sleep in the caudomedial medulla as measured by in vivo microdialysis, Brain Res., 580(1992)348-350. Kodama, T., Takahashi, Y. and Honda, Y. Enhancement of acetylcholine release during paradoxical sleep in the dorsal tegmental field of the cat brain stem, Neuronsci. Lett., 144(1990)277-282.

Kuypers, H.G.J.M. and Huisman, A.M. The new anatomy of the descending brain pathways. In: B. Sjolund and A. Bjorklund (Eds.), *Brain stem control of spinal mechanisms,* Elsevier, Amsterdam, 1982, pp. 29-54. Kuypers, H.G.J.M. and Maisky, V.A. Retrograde axonal trasport of horseradish peroxidase from spinal cord to brain stem cell groups in the cat, Neurosci. Lett., 1 (1975) 9-14. Kuypers, H.G.J.M. and Maisky, V.A. Funicular trajectories of descending brain stem pathways in cat, Brain Res., 136 (1977) 159-165. Lai, Y.Y. and Barnes, C.D. A spinal projection of serotonergic neurons of the locus coeruleus in the cat, Neurosci. Lett., 58 (1985) 159-164. Lai, Y.Y. and Siegel,, J.M. Medullary regions mediating atonia, J. Neurosci., 8 (1988) 4790-4796. Lai, Y.Y. and Siegel, J.M. Muscle tone suppression and stepping produced by stimulation of midbrain and rostral pontine reticular formation, J. Neurosci., 10 (1990) 2727-2734. Lai, Y.Y. and Siegel, J.M. Pontomedullary glutamate receptors mediating locomotion and muscle tone suppression, J. Neurosci., 11 (1991) 2931-2937. Lai, Y.Y. and Siegel, J.M. Corticotropin-releasing factor mediated muscle atonia in pons and medulla, Brain Res., 575 (1992) 63-68. Lai, Y.Y. and Siegel, J.M. Brainstem-mediated locomotion and myoclonic jerks. I. Neural substrates, Brain Res., 745 (1997a) 257-264. Lai, Y.Y. and Siegel, J.M. Brainstem-mediated locomotion and myoclonic jerks. II. Pharmacological effects, Brain Res., 745 (1997b) 265-270. Lai, Y.Y, Clemente, J.R. and Siegel, J.M. Glutamatergic and cholinergic projections to the pontine inhibitory area identified with horseradish peroxidase retrograde transport and immunohistochemistry, J. Comp. Neurol., 336 (1993a) 321-330. Lai, Y.Y., Clemente, J.R. and Siegel, J.M. Afferents to the nucleus magnocellularis of the medulla, Soc. Neurosci. Abstr., 19 (1993b) 1437. Lai, Y.Y., Siegel, J.M. and Wilson, W.J. Effect of blood pressure on changes in muscle tone poduced by stimulation of the medial medulla, Am. J. Physiol., 252 (1987) H1249-H1257. Lai, Y.Y., Strahlendorf, H.K., Fung, S.J. and Barnes, C.D. The actions of two monoamines on spinal motoneurons from stimulation of the locus coeruleus in the cat, Brain Res., 484 (1989) 268-272. Lai, Y.Y., Wu, J.-P, Horng, H.T., Wang, S.D., Chai, C.Y., Kuo, J.S. and Siegel, J.M. Projections to the pontine reticular formation from the diencephalon and medulla: WGA-HRP and catecholamine immunohistochemistry studies, Sleep Res., 23 (1994) 50. Lettvin, J. Y. and Dell, PC. Positivity in ventral horn during bulbar reticular inhibition of motoneurons, Fed. Proc., 9 (1950) 77. Liu, R.-H., Fung, S.J., Reddy, V.K. and Barnes, C.D. Localization of glutamatergic neurons in the dorsolateral pontine tegmentum projecting to the spinal cord of the cat with a proposed role of glutamate on lumbar motoneuron activity, Neurosci., 64 (1995) 193-208. Llinas, R. andTerzuolo, C.A. Mechanisms of supraspinal actions upon spinal cord activities. Reticular inhibitory mechanisms on alpha-extensor motoneurons, J. Neurophysiol., 27(1964)579-591. Llinas, R. and Terzuolo, C.A. Mechanisms of supraspinal actions upon spinal cord activities. Reticular inhibitory mechanisms upon flexor motoneurons, J. Neurophysiol., 28 (1965) 413-422, Lopez-Rodroguez, F, Kohlmeier, K.A., Yamuy, J., Morales, F.R. and Chase, M.H. Muscle atonia can be induced by carbachol injections into the nucleus pontis oralis in cats anesthetized with a-chloralose, Brain Res., 699 (1995) 201-207. Lungberg, A. and Vyklicky, L. Inhibition of transmission to primary afferents by electrical stimulation of the brain stem, Arch, ital. Biol., 104 (1966) 86-97,

Lydic, R., Baghdoyan, H.A. and Lorinc, Z. Microdialysis of cat pons reveals enhanced acetylcholine release during state-dependent respiratory depression, Am. J. Physiol., 261 (1991) R766-R770. Luppi, P.-H., Sakai, K., Fort, P., Salvert, D. and Jouvet, M. The nuclei of origin of monoaminergic, peptidergic, and cholinergic afferents to the cat nucleus reticularis magnocellularis: A double-labeling study with cholera toxin as a retrograde tracer, J. Comp. Neurol., 277 (1988) 1-20. Magoun, H.W. Caudal and cephalic influences of the brain stem reticular formation, Physiol. Rev., 30. (1950) 459-474. Magoun, H.W. and Rhines, R. An inhibitory mechanism in the bulbar reticular formation, J. Neurophysiol., 9 (1946) 165-171. Margalit, D. and Segal, M. A pharmacologic study of analgesia produced by stimulation of the nucleus locus coeruleus, Psychopharmacol., 62 (1979) 169-183. Matsuyama, K., Kobayashi, Y., Takakusaki, K., Mori, S. and Kimura, H. Termination mode and branching patterns of reticuloreticular and reticulospinal fibers of the nucleus reticularis ponds oralis in the cat: an anterograde PHA-L tracing study, Neurosci. Res., 17(1993)9-21. Matsuyama, K., Nakajima, K., Miyashita, E. and Mori, S. Spinal innervation patterns of the nucleus reticularis magnocellularis in the cat, Fourth IBRO World Congr. Neurosci., (1995)331. Matsuyama, K., Ohta, Y. and Mori, S. Ascending and descending projections of the nucleus reticularis gigantocellularis in the cat demonstrated by the anterograde neural tracer, Phaseolus vulgaris leucoagglutinin (PHA-L), Brain Res., 460 (1988) 124-141.
Matsuyama, K., Takakusaki, K., Nakajima, K. and Mori, S. Multi-segmental innervation of single pontine reticulospinal axons in the cervico-thoracic region of the cat: Anterograde PHA-L tracing study, J. Comp. Neurol., 377 (1997) 234-250. Matsuzaki, M. Differential effects of sodium butyrate and physostigmine upon the activities of para-sleep in acute brain stem preparations, Brain Res., 13 (1969) 247-265.
Matsuzaki, M., Okada, Y and Shuto, S. Cholinergic agents related to para-sleep state in acute brain stem preparations, Brain Res., 9 (1968) 253-267. Mitani, A., Ito, K., Mitani, Y and McCarly, R.W Descending projections from the gigantocellular tegmental field in the cat: Cells of origin and their brainstem and spinal cord trajectories, J. Comp. Neurol., 268 (1988) 546-566. Mokha, S.S., McMillan, J.A. and Iggo, A. Descending control of spinal nociceptive transmission: actions produced on spinal multireceptive neurons from the nuclei locus coeruleus (LC) and raphe magnus (NRM), Exp. Brain Res., 58 (1985) 213-225.
Morales, F.R., Engelhardt, J.K., Spja, PJ., Pereda, A.E. and Chase, M.H. Motoneuron properties during motor inhibition produced by microinjection of carbachol into the pontine reticular formation of the decerebrate cat, J. Neurophysiol., 57 (1987) 1118-1129. Morales, F.R., Engelhardt, J.K., Pereda, E.P, Yamuy, J. and Chase, M.H. Renshaw cells are inactive during motor inhibition elicited by pontine micorinjection of carbachol, Neurosci, Lett., 86 (1988) 289-295.
Morrison, A.R, Paradoxical sleep without atonia, Arch. ital. Biol., 126 (1988) 275-289.
Newman, D.B., Distinguishing rat brainstem reticulospinal nuclei by their neuronal morphology. I. Medullary nuclei, J. Hirnforsch., 26 (1985) 187-226. Niemer, W.T. and Magoun, H.W Reticule-spinal tracts influencing motor activity, J. Comp. Neurol .,87(1947) 367-379.
Noga, B.R., Kettler, J. and Jordan, L.M. Locomotion produced in mesencephalic cats by injections of putative transmitter substances and antagonists into the medial reticular formation and the pontomedullary locomotor strip, J. Neurosci., 8 (1988) 2074-2086.

Nyberg-Hansen, R. Sites and mode of termination of reticulo-spinal fibers in the cat. An experimental study with silver impregnation methods, J. Comp. Neurol., 124 (1965) 71-100. Nyberg-Hansen, R. Functional organization of descending supraspinal fibre systems to the spinal cord. Anatomical observations and physiological correlations, Ergebn, Anat. Entwickl., 39 (1966) 6-47. Nygren, L.-G. and Olson, L. A new major projection from locus coeruleus: The main source of noradrenergic nerve terminals in the ventral and dorsal coulmns of the spinal cord, Brain Res., 132 (1977) 85-93. Ohta, Y., Mori, S. and Kimura, H. Neuronal structures of the brainstem participating in postural suppression, Neurosci. Res., 5 (1988) 181-202. Onoe, H. and Sakai, K. Kainate receptors: A novel mechanism in paradoxical (REM) sleep generation, NeuroReport, 6 (1995) 353-356. Pereda, A.E., Morales, F.R. and Chase, M.H. Medullary control of lumbar motoneurons during carbachol-induced motor inhibition, Brain Res., 514 (1990) 175-179. Pompeiano, O. and Hoshino, K. Central control of posture: reciprocal discharge by two pontine neuronal groups leading to suppression of decerebrate rigidity, Brain Res., 116(1976a) 131-138. Pompeiano, O. and Hoshino, K. Tonic inhibition of dorsal pontine neurons during the postural atonia produced by an anticholinesterase in the decerebrate cat, Arch. ital. Biol., 114 (1976b) 310-340. Pompeiano, O., D' Ascanio, P., Horn, E. and Stampacchia, G. Effects of local injection of the $a_2$-adrenergic agonist clonidine into the locus coeruleus complex on the gain of vestibulospinal and cervicospinal reflexes in decerebrate cats, Arch. ital. Biol., 125 (1987) 225-289. Price, J.L. and Amaral, D.G. An autoradiographic study of the projections of the central nucleus of the monkey amygdala, J. Neurosci., 1 (1981) 1242-1259. Rampon, C., Morales, F.R., Fort, P., Luppi, PH., Sampogna, S. and Chase, M. H. Glysine immunohistochemistry and c-fos expression in the cervical spinal cord of cats during carbachol-induced active sleep, Soc. Neurosci. Abstr., 23 (1997) 795. Reinoso-Suraez, F, De Andres, I., Rodrigo-Angulo, M.L. and Rodriguez-Viega, E. Location and anatomical connections of a paradoxical sleep induction site in the cat ventral pontine tegmentum, Eur. J. Neurosci., 6 (1994) 1829-1836. Reinoso-Suarez, F, Rodrigo-Angulo, M.L., Rodriguez-Veiga, E. and De Andres, I. Thalamic connections of the oral pontine tegmentum sites whose cholinergic stimulation produces enhancement of paradoxical sleep signs. In: M. Mancia and G. Marini (Eds.), *The diencephalon and sleep,* Raven Press, New York, 1990, pp. 49-63. Rizvi, T.A., Murphy, A.Z., Ennis, M., Behbehani, M.M. and Shipley, M.T. Medial preoptic area afferents to periaqueductal gray medullo-output neurons: A combined fos and tract tracing study, J. Neurosci., 16 (1996) 333-344. Sakai, K., Some anatomical and physiological properties of ponto-mesencephalic tegmental neurons with special references to the PGO waves and postural atonia during paradoxical sleep in the cat. In: J.A. Hobson and M.A.B. Brazier (Eds.), *The reticular formation revisited,* Raven Press, New York, 1980, pp. 427-447. Sakai, K., Executive mechanisms of paradoxical sleep, Arch. ital. Biol., 126 (1988) 239-257. Sakai, K. and Koyama, Y. Are there cholinergic and non-cholinergic paradoxical sleep-on neurones in the pons?, NeuroReport, 7 (1996) 2449-2453. Sakai, K., Sastre, J.P., Salvert, D., Touret, M., Tohyama, M. and Jouvet, M. Tegmentoreticular projections with special reference to the muscular atonia during paradoxical sleep in the cat: An HRP study, Brain Res., 176 (1979) 233-254.

Sakai, K., Sastre, J.-P, Kanamore, N. and Jouvet, M. State-specific neurons in the ponto-medullary reticular formation with special reference to the postural atonia during paradoxical sleep in the cat. In: O. Pqmpeiano and C. A. Marsan (Eds.), *Brain mechanisms of perceptual awareness and purposeful behavior,* Raven Press, New York, 1981, pp. 405-429. Saper, C.B., Swanson, L.W. and Cowan, W.M. An autoradiographic study of the efferent connections of the lateral hypothalamic area in the rat, J. Comp. Neurol., 183 (1979) 689-706. Sara, S.J., Devauges, V. and Segal, M. Locus coeruleus engagement in memory retrieval and attention. In: M. Sandier, A. Dahlstrom and R.H. Belmaker (Eds.), *Prog, in catecholamine research, part B: Central aspects,* Alan R Liss, New York, 1988, pp. 155-161. Sastre, J.-P, Sakai, K. and Jouvet, M. Bilateral lesions of the dorsolateral pontine tegmentum. II. Effects upon the muscle atonia, Sleep Res., 7 (1978) 44. Schenkel, E. and Siegel, J.M. REM sleep without atonia after lesions of the medial medulla, Neurosci. Lett., 98 (1989) 159-165. Schenkel, E., Lai, Y. Y. and Siegel, J.M. Cataplexy-like behavior after electrical or chemical stimulation of the medial medulla in the intact cat, APSS Abstr., (1990) 8. Shammah-Lagnado, S.J., Costa, M., Goto, M., Peracoli, A. and Canteras, N.S. Efferent connections of the retrorubral field (A8): A PHA-L study in the rat, Soc. Neurosci. Abstr., 19 (1993) 1434. Shiromani, P.J., Kilduff, T.S., Bloom, F.E. and McCarley, R.W. Cholinergically induced REM sleep triggers Fos-like immunoreactivity in dorsolateral pontine regions associated with REM sleep, Brain Res., 580 (1992) 351-357. Shiromani, P.J., Lai, Y.Y. and Siegel, J.M. Descending projections from the dorsolateral pontine tegmentum to the paramedian reticular nucleus of the caudal medulla in the cat, Brain Res., 517 (1988) 224-228. Shouse, M.N. and Siegel, J.M. Pontine regulation of REM sleep components in cats: Integrity of the pedunculopontine tegmentum (PPT) is important for phasic events but unnecessary for atonia during REM sleep, Brain Res., 571 (1992) 50-63. Siegel, J.M., Nienhuis, R., Fahringer, H.M., Paul, R., Shiromani, P., Dement, W.C., Mignot, E. and Chiu, C. Neuronal activity in narcolepsy: identification of cataplexy-related cells in the medial medulla, Science, 252 (1991) 1315-1318. Sprague, J.M., Schreiner, L.H., Lindsley, D.B., Magoun, H.W. Reticulo-spinal influences on stretch reflexes, J. Neurophysiol. 11: (1948) 501-507. Soja, PJ. Morales, F.R., Baranyi, A. and Chase, M.H. Effect of inhibitory amino acid antagonists on IPSPs induced in lumbar motoneurons upon stimulation of the nucleus reticularis gigantocellularis during active sleep, Brain Res., 423 (1987) 353-358. Soja, P.J., Lopez-Rodriquez, F., Morales, F.R. and Chase, M.H. The postsynaptic inhibitory control of lumbar motoneurons during the atonia of active sleep: Effect of strychnine on motoneuron properties, J. Neurosci., 11 (1991) 2804-2811. Steriade, M. and Hobson, J.A. Neuronal activity during the sleep-waking cycle, Prog. Neurobiol., 6 (1976) 155-376. Swick, D., Pineda, J.A., Schacher, S. and Foote, S.L. Locus coeruleus neuronal activity in awake monkeys: Relationship to auditory P300-like potentials and spontaneous EEC, Exp. Brain Res., 101 (1994) 86-92. Taal, W. and Holstege, J.C. GABA and glycine frequently colocalize in terminals on cat spinal motoneurons, NeuroReport, 5 (1994) 2225-2228. Taber, E. The cytoarchitecture of the brain stem of the cat. I. Brain stem nuclei of cat, J. Comp. Neurol., 116 (1961) 27-70. Taguchi, O., Kubin, L. and Pack, A.I. Evocation of postural atonia and respiratory depression by pontine carbachol in the decerebrate rat, Brain Res., 595 (1992) 107-115.

Takakusaki, K., Ohta, Y. and Mori, S. Single medullary reticulospinal neurons exert postsynaptic inhibitory effects via inhibitory interneurons upon alpha-motoneurons innervating cat hindlimb muscles, Exp. Brain Res., 74 (1989) 11-23. Takakusaki, K., Shimoda, N., Matsuyama, K. and Mori, S. Discharge properties of medullary reticulospinal neurons during postural changes induced by intrapontine injections of carbachol, atropine and serotonin, and their functional linkages to hindlimb motoneurons in cats, Exp. Brain Res., 99 (1994) 361-374. Tohyama, M, Sakai, K., Touret, M, Salvert, D. and Jouvet, M. Spinal projections from the lower brain stem in the cat as demonstrated by the horseradish peroxidase technique. I. Origins of the reticulospinal tracts and their funicular trajectories, Brain Res., 173 (1979)383-404. Van Dongen, P.A.M., Broekkamp, C.L.E. and Cools, A.R. Atonia after carbachol microinjections near the locus coeruleus in cats, Pharmacol. Biochem. Behav., 8 (1978) 527-532. Velazquez-Moctezuma, H., Gillin, J.C. and Shiromani, PJ. Effect of specific Ml, M2 muscarinic receptor agonists on REM sleep generation, Brain Res., 503 (1989) 128-131. Velazquez-Moctezuma, J., Shalauta, M. Gillin, J.C. and Shiromani, P.J. Cholinergic antagonists and REM sleep generation, Brain Res., 543 (1991) 175-179. Wallace, D.M., Magnuson, D.J. and Gray, T.S. The amygdalo-brainstem pathway: Selective innervation of dopaminergic, noradrenergic and adrenergic cells in the rat, Neurosci. Lett., 97 (1989) 252-258. Ward. D.G. and Gunn, C.G. Locus coeruleus complex: Elicitation of a pressor response and a brain stem region necessary for its occurrence, Brain Res., (1976) 401-406. West, W.L., Yeomans, D.C. and Proudfit, H.K. The function of noradrenergic neurons in mediating antinociception induced by electrical stimulation of the locus coeruleus in two different sources of Sprague-Dawley rats, Brain Res., 626 (1993) 127-135. Westlund, K.N. and Coulter, J.D. Descending projections of the locus coeruleus and subcoeruleus/medial parabrachial nuclei in monkey: Axonal transport studies and dopamine-/3-hydroxylase immunocytochemistry, Brain Res. Rev., 2 (1980) 235-264. Wu, W.-R, Gulyani, S., Mignot, E. and Siegel, J.M. Activity of REM-off cells during cataplexy in narcoleptic dog, APSS Abstr., (1996) 3. Yamuy, J., Mancillas, J.R., Morales, F.R. and Chase, M.H. C-fos expression in the pons and medulla of the cat during carbachol-induced active sleep, J. Neurosci., 13 (1993) 2703-2718. Zardetto-Smith, A.M. and Johnson, A.K. Chemical topography of efferent projections from the median preoptic nucleus to pontine monoaminergic cells groups in the rat, Neurosci. Lett., 199 (1995) 215-219. Zhuo, H., Fung, S.J., Reddy, V.K. and Barnes, C.D. Immunohistochemical evidence for coexistence of methionine-enkephalin and tyrosine hydroxylase in neurons of the locus coeruleus complex projecting to the spinal cord of the cat, J. Chem. Neuroanat., 5 (1992) 1-10.