Muscle tone regulation during REM sleep: neural circuitry and clinical significance

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ABSTRACT

Rapid eye movement (REM) sleep is a distinct behavioral state characterized by an activated cortical and hippo-campal electroencephalogram (EEG) and concurrent muscle atonia. Research conducted over the past 50 years has revealed the neuronal circuits responsible for the generation and maintenance of REM sleep, as well as the pathways involved in generating the cardinal signs of REM sleep such as cortical activation and muscle atonia. The generation and maintenance of REM sleep appear to involve a widespread network in the pons and medulla. The caudal laterodorsal tegmental nucleus (cLDT) and sublaterodorsal nucleus (SLD) within the dorsolateral pons contain REM-on neurons, and the ventrolateral periaqueductal grey (vlPAG) contains REM-off neurons. The inter-action between these structures is proposed to regulate REM sleep amounts. The cLDT-SLD neurons project to the basal forebrain via the parabrachial-precoeruleus (PB-PC) complex, and this pathway may be critical for the EEG activation seen during REM sleep. Descending SLD glutamatergic projections activating the premotor neurons in the ventromedial medulla and spinal cord interneurons bring about muscle atonia and suppress phasic muscle twitches in spinal musculature. In contrast, phasic muscle twitches in the masseter muscles may be driven by glu-tamatergic neurons in the rostral parvicellular reticular nucleus (PCRt); however, the brain regions responsible for generating phasic twitches in other cranial muscles, including facial muscles and the tongue, are not clear.

Key words
Atonia • Inhibition • Neural networks • Motoneurons • REM sleep behavior disorder

Introduction

Rapid eye movement (REM) sleep, a unique state in the sleep-wake cycle when vivid dreams occur, was originally discovered by Aserinsky and Kleitman who observed the periodic occurrence of eye move-ments during sleep in humans (Aserinsky and Kleitman, 1953). Following Dement's demonstra-tion of a similar phenomenon in cats, Jouvet and Michel showed that this stage of sleep is also accom-panied by a complete loss of tone in the somatic musculature (Dement and Kleitman, 1957a,b; Jouvet and Michel, 1959). Jouvet termed this stage of sleep 'paradoxical sleep' (PS), because central activation and peripheral inhibition occured simultaneously during this stage.

Central activation during REM sleep includes corti-cal (high frequency, low amplitude EEG) and hippo-campal activation (theta waves) and ponto-geniculo-occipital (PGO) waves (P-waves in rats). The mag-nitude of cortical and hippocampal activation during REM sleep is as great as, if not higher than, that observed during wakefulness. The prominent hip-pocampal theta rhythm (4-9 Hz oscillations) is also seen in rodents during active exploration, suggesting that the hippocampus and cortex are highly engaged

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(as in learning and memory processes) during REM sleep. Indeed, a variety of studies in humans and animals indicate that REM sleep and the hippocampal theta and P-waves observed during this state are involved in various aspects of learning and memory processes (Louie and Wilson, 2001; Stickgold et al., 2001; Datta et al., 2004, 2005; Poe et al., 2010). On the other hand, suppression of REM sleep by brain lesions or by pharmacological manipulations did not have any apparent effect on learning and memory in humans or animals (van Hulzen and Coenen, 1982; Lavie and Tzischinsky, 1985; Kaminer and Lavie, 1991; Parent et al., 1999; Vertes and Eastman, 2000; Rasch et al., 2009). Thus, the importance of REM sleep in learning and memory is not clear.

Peripheral inhibition during REM sleep consists of complete muscle atonia in the somatic musculature (except the ocular and inner ear muscles and diaphragm) (Jouvet and Michel, 1959; Jouvet, 1967; Siegel, 2011). However, the atonia is accompanied by brief phasic twitches in both cranial and spinal musculature. Under normal circumstances, phasic events rarely occur in the spinal musculature in rats, but they are very prominent in the cranial muscles of the jaw, eye, and tongue (Chase and Morales, 1990; Lavigne et al., 2001; Lu et al., 2005; Burgess et al, 2008; Anaclet et al., 2010; Fraigne and Orem, 2011). In addition to cortical activation and muscle atonia, REM sleep is accompanied by an increase in brain temperature, cessation of thermoregulation and autonomic fluctuation: irregularities in heart and respiratory rates, penile erection in men and clitoral enlargement in women (Kawamura and Sawyer, 1965; Walker et al., 1983; Hendricks et al., 1991; Murali et al., 2003; Hirshkowitz and Schmidt, 2005). However, in this review article, we will mainly focus on the neuronal mechanisms of REM sleep generation and muscle atonia, and briefly describe the other cardinal signs of REM sleep at the end.

REM sleep generation involves a widespread network in the brainstem

The dorsolateral pons is critical for REM sleep control

Although cats with complete midbrain transections (cerveau isolé) enter a coma-like state for a few days following transections, regular sleep-wake cycles eventually return in these animals (Bremer, 1935; Villablanca et al., 2001). This suggests that the forebrain is independently capable of regulating sleep-wake behavior. On the other hand, cats (and rats) with midbrain transections do not display signs of REM sleep in the forebrain (cortical EEG desynchronization, PGO and hippocampal theta waves), indicating that the isolated forebrain is incapable of producing REM and that the sites responsible for the generation of REM sleep are located in the brainstem. A series of transection studies from Michel Jouvet's lab, and later from Jerry Siegel's lab, showed that the REM sleep generating neurons are localized in the pontine tegmentum (Jouvet, 1965; Siegel et al., 1984, 1986; Siegel, 2011). In line with these findings, large electrolytic and cell-specific lesions of the dorsolateral pons consistently suppressed REM sleep in cats (Jouvet, 1962; Carli and Zanchetti, 1965; Jouvet and Delorme, 1965; Sastre et al., 1981; Webster and Jones, 1988). Cholinergic neurons in the pons were first proposed to be involved in REM sleep generation, as systemic administration of a cholinergic antagonist, atropine, suppressed REM sleep in cats (Jouvet, 1962). Experiments that followed further showed that microinjections of carbachol in several sites in the pons and medulla could induce REM sleep (George et al., 1964; Vanni-Mercier et al., 1989, 1991). These early studies, along with the observation that brainstem monoaminergic neurons cease firing during REM sleep, formed the basis for the development of McCarley and Hobson's (1975) 'reciprocal interaction' model of REM sleep generation. According to the model, the pontine cholinergic REM sleep generator is tonically inhibited by pontine REM-off monoaminergic neurons during wake, but during NREM sleep the inhibitory monoaminergic tone gradually wanes and cholinergic excitation waxes until eventually REM sleep is generated. It was then hypothesized that mesopontine cholinergic neurons, including the pedunculopontine tegmentum (PPT) and laterodosal pontine tegmentum (LDT), are involved in REM sleep generation. However, many studies that followed did not support this hypothesis. For example, although many neurons in the PPT and LDT region were found to contain neurons that are active during REM, most of them were also active during wake (Kayama et al., 1992; Datta and Hobson, 1994; Datta and Siwek, 2002). Moreover, there is no direct

evidence that those REM-active neurons were cholinergic. For example, Steriade and colleagues demonstrated that most pontine neurons projecting to the thalamus are active during both REM sleep and wake (Steriade et al., 1990a,b). As both cholinergic and non-cholinergic (presumably glutamatergic) neurons in the PPT and LDT project to the thalamus, this study could not confirm that the recorded neurons were cholinergic (Steriade et al., 1990b; Motts and Schofield, 2011). Similarly, a subpopulation of LDT neurons was shown to be maximally active during REM sleep but silent during wake (Kayama et al., 1992). Although these authors proposed that these neurons were "possibly" cholinergic based on their firing properties and localization of the recording sites using NADPH-diaphorase immunochemistry (which labels dorsomedial pontine cholinergic neurons), the neurons themselves were not identified as cholinergic by means of juxtacellular labeling. Thus, though it is possible that a subpopulation of mesopontine cholinergic neurons is active specifically during REM sleep, it has never been directly demonstrated. Moreover, very limited cFos expression was observed in the LDT-PPT cholinergic neurons following periods of enhanced REM sleep in rodents (Verret et al. 2005; Lu et al. 2006), and neurotoxic lesions of the PPT or LDT (which destroys both cholinergic and non-cholinergic neurons) did not reduce REM sleep (Deurveilher and Hennevin, 2001; Lu et al., 2006). On the other hand, neurotoxic lesions of the subcoeruleus in cats resulted in a reduction in REM sleep amounts (Shouse and Siegel, 1992). It has also been well established that this region contains a population of neurons firing only during REM sleep (REM-on or PS-on neurons) (Sakai et al., 1981, 2001; Sakai, 1986, 1988; Sakai and Koyama, 1996). These REM-on neurons are completely silent during wake, exhibit a significant increase in discharge rate prior to the onset of REM sleep, maintain their firing throughout REM sleep, and stop firing during the transition from REM to NREM or wake (Sakai, 1988). Moreover, small volumes of carbachol injected into the subcoeruleus produced REM sleep with the shortest latency compared to when injected in other brainstem regions, including the oral pontine nucleus and gigantoceullar tegmental field (FTG), the two most studied regions for the cholinergic control of REM sleep (Vanni-Mercier et al., 1989, 1991). These studies

indicate that the subcoeruleus neurons may form the 'REM generator' in the brainstem. The subcoeruleus has been the focus of many other sleep researchers investigating REM sleep mechanisms, although a variety of names such as peri-locus coeruleus alpha, peribrachial region and pontine inhibitory region were used to describe this region in cats (Hu et al., 1989; Lai and Siegel, 1991; Xi et al., 2001). The equivalent region in rats is described as the sublaterodorsal nucleus (SLD) (Swanson, 1998; Boissard et al., 2002, 2003; Lu et al., 2006; Luppi et al., 2006). As all of our results were obtained from rats and mice, we will use the term 'SLD' throughout this review to represent this pontine region critical for REM control in all species, including humans.

Consistent with the results of subcoeruleus lesions in cats, small ibotenic acid lesions of the dorsolateral pons, including the SLD and caudal LDT (cLDT) but sparing most of the LDT and PPT, resulted in about 60% reduction in REM sleep in rats (Lu et al., 2006). However, there was a marked increase in NREM-to-REM transitions and a dramatic reduction in average REM bout duration, indicating severe fragmentation of REM sleep. These changes in REM sleep architecture suggest that the maintenance, but not initiation, of REM sleep is disrupted after cLDT-SLD lesions. Interestingly, lesions of either the cLDT or SLD alone did not produce these REM sleep alterations, suggesting that these structures function as one unit in REM sleep control (Lu et al., 2006). In addition to this 'REM-on' region in the cLDT-SLD, the pons also has been found to contain a 'REM-off' region comprising the ventrolateral periaqueductal grey (vlPAG) and lateral pontine tegmentum (LPT). Injection of the GABA$_A$ receptor agonist muscimol into the vlPAG-LPT induces REM sleep in cats, rats and guinea pigs (Sastre et al., 1996; Crochet et al., 2006; Vanini et al., 2007; Sapin et al., 2009). In addition, lesions of the vlPAG and LPT increase REM sleep by increasing both the number and duration of REM bouts in rats and mice (Lu et al., 2006; Kaur et al., 2009). Hence, it was proposed that the GABAergic neurons in the vlPAG-LPT may gate REM sleep occurrence regardless of state, and loss of this gating control would result in REM sleep increase and its intrusion into wakefulness (Luppi et al., 2006, 2011; Benke, 2006; Vetrugno et al., 2009). Our tracing studies indicate that there are extensive reciprocal, GABAergic connections between the

vlPAG-LPT and SLD in rats (Lu et al., 2006). As the vlPAG-LPT GABAergic neurons project to the cLDT-SLD, and GABAergic neurons in the cLDT-SLD express cFos following enhanced REM sleep, we proposed that these two neuronal populations inhibit each other, and that this mutual inhibition produces state transitions into and out of REM sleep. These observations formed the basis for a flip-flop model of REM regulation (Lu et al., 2006). In addition, it was recently shown that about 84% of the SLD neurons expressing cFos after REM sleep hypersomnia contained vesicular glutamate transporter 2 (VGLUT2) mRNA, suggesting that the SLD glutamatergic neurons may also play a critical role in REM generation (Clement et al., 2011). As glutamate and GABA are intermingled in the cLDT-SLD, it has been difficult to characterize the respective *in vivo* roles of these neurotransmitters in the regulation of REM sleep using traditional methods. However, by using conditional knockout mice, we focally and selectively eliminated glutamate or GABA release from the cLDT-SLD neurons. Consistent with the cFos experiments, loss of glutamatergic neurotransmission from the cLDT-SLD neurons resulted in a major reduction in REM sleep and increase in REM fragmentation (increased number of shorter REM bouts) similar to that observed after cLDT-SLD lesions in rats (Krenzer et al., 2010). Thus, these results indicated that cLDT-SLD glutamatergic neurons are critical for the maintenance of REM sleep.

Collectively, the currently available evidence indicates that the GABAergic neurons in the vlPAG/LPT and the glutamatergic and GABAergic neurons in the cSLD-LDT are the cell groups primarily involved in the control of REM sleep, and that their interactions may be critical for transitioning into and maintaining REM sleep. Thus, these three cell groups may be the main participants in the 'switch' of the flip-flop model of REM regulation (Fig. 1). As lesions of the cholinergic and mono-aminergic cell groups in the brainstem did not alter the amount of spontaneous REM sleep, these cell groups were not considered a part of this switch (Lu et al., 2006). However, these cell groups may influence the main REM switch and produce changes in REM sleep or its specific aspects. For example, both the 'REM-on' cLDT-SLD and the 'REM-off' vLPAG-LPT receive afferents from the cholinergic

and monoaminergic cell groups in the brainstem, and receptors for acetylcholine and monoamines are vastly expressed in these regions. SLD neurons are excited by carbachol and inhibited by norepinephrine both *in vivo* and *in vitro*, although serotonin has no effect on the REM-on neurons in the SLD (Sakai and Koyama, 1996; Sakai et al., 2001; Brown et al., 2006). In addition, cholinergic and monoaminergic agents injected systemically or locally into these regions consistently produced REM sleep changes (Vanni-Mercier et al., 1989; Sakai & Onoe, 1997; Crochet and Sakai, 1999a,b; Kubin, 2001; Crochet et al., 2006). Moreover, antidepressant drugs that increase monoaminergic tone completely suppress REM sleep and induce cFos immunoreactivity in the vlPAG/LPT region (Chang and Lu, unpublished observations). The antidepressants may directly activate the REM-off vlPAG/LPT neurons and/or inactivate the REM-on SLD-cLDT neurons in order to produce REM suppression.

Neurons in the caudal medulla may contribute to REM sleep regulation

Although the dorsolateral pons has been considered to be the primary control center for the generation of REM sleep, many studies have also indicated an important role for the medullary structures in this process. For example, transections at the caudal pontine levels or pontomedullary junction in cats and rats completely abolished REM sleep, whereas spinal transections did not affect REM sleep (Webster et al., 1986; Siegel et al., 1986; Vanni-Mercier et al., 1991; Gottesmann et al., 1995;). Pontine carbachol was not able to induce REM sleep in cats after transections at the pontomedullary junction (Vanni-Mercier et al., 1991). Moreover, electrolytic lesions in the rostroventral medulla (RVM) that sever the fiber pathways connecting the pons and caudal medulla eliminate REM sleep without altering NREM sleep (Sastre et al., 1981). Thus, when the pons and medulla are separated from each other, REM sleep is no longer evident, suggesting that the pons alone is insufficient for REM sleep generation and that the connections between the pons and the medulla are necessary for the appearance of this sleep stage. In addition, REM sleep-active neurons are found to be widely distributed throughout the caudal medulla, including the magnocellular reticular field, parvocellular reticular formation (PCRt)
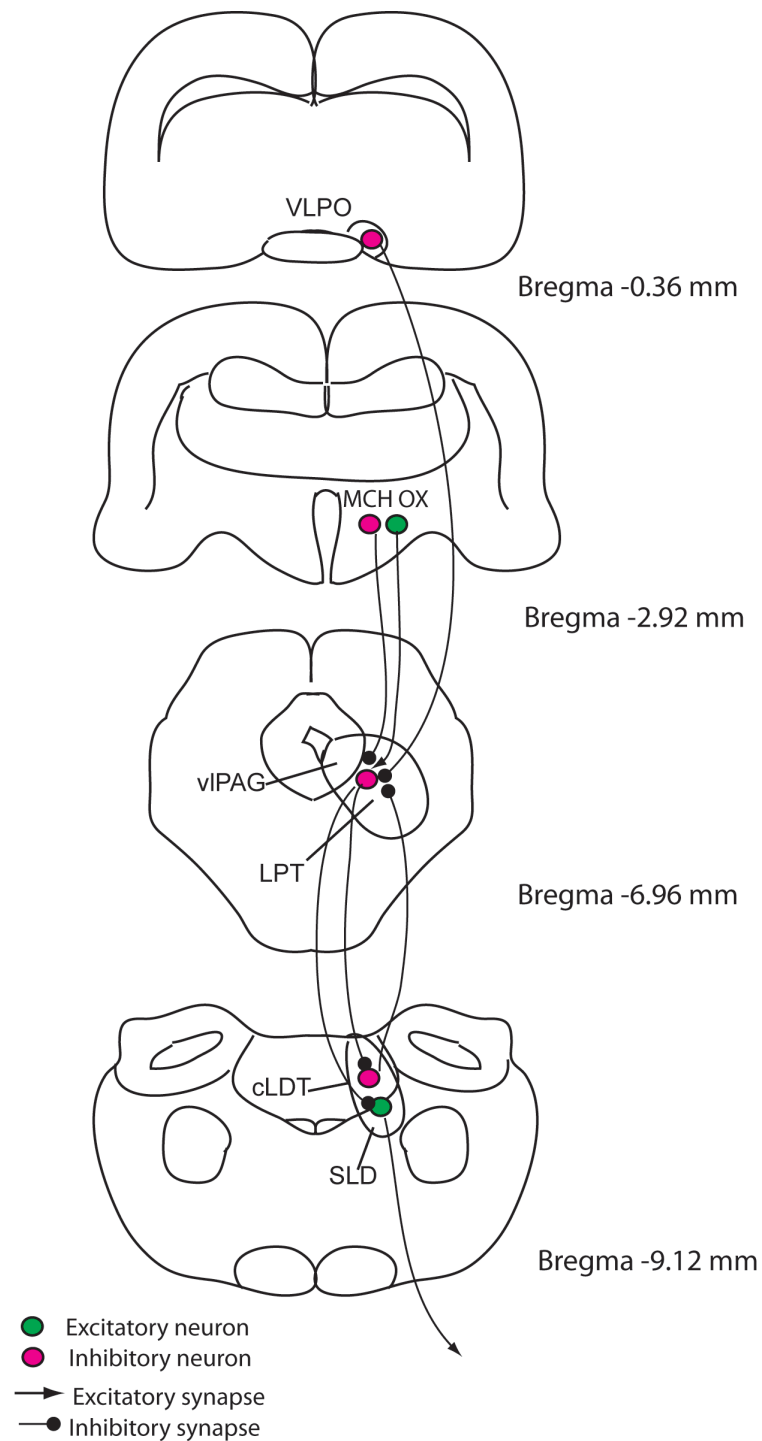
Fig. 1. - The key neurons for the regulation of REM sleep are located in the cLDT-SLD in the dorsolateral pons. In the flip-flop circuit model of REM sleep regulation (Lu et al., 2006), the REM-on GABAergic neurons located in this region and the REM-off GABAergic neurons in the vlPAG-LPT inhibit each other. This mutual inhibition may explain the sharp transitions into and out of REM sleep. The REM-off neurons in the vlPAG-LPT also inhibit the glutamatergic neurons in the cLDT-SLD that control REM amounts and generate the cardinal signs of REM sleep (see also Figs. 2 and 4). These neurons are under the control of sleep-active, anterior hypothalamic neurons of the eVLPO and orexin (OX) and melanin-concentrating hormone (MCH) neurons of the posterior, lateral hypothalamus. Monoaminergic and cholinergic neurons in the brainstem (not shown in the figure) are not part of this circuitry, but may modulate it. The antero-posterior levels of the sections are from the rat atlas of Paxinos and Watson (2009). Abbreviations: eVLPO = extended ventrolateral preoptic nucleus; vlPAG = ventrolateral periaqueductal gray; LPT = lateral pontine tegmentum; SLD = sublaterodorsal nucleus; cLDT = caudal laterodorsal tegmental nucleus; BF = basal forebrain.

and lateral and dorsal paragigantocellularis (LPGi and DPGi) (Netick et al., 1977; Steriade et al., 1984; Sakai, 1988; Yamuy et al., 1993; Boissard et al., 2002; Goutagny et al., 2008). A large number of GABAergic neurons in the above-mentioned cell groups in the caudal medulla expressed cFos following periods of REM sleep hypersomnia (Sapin et al., 2009). More importantly, neurotoxic lesions in the ventromedial medulla (VMM) lying dorsal to the inferior olive resulted in major reductions in REM sleep in cats and rats (Holmes and Jones, 1994; Vetrivelan et al., 2009). Cell-specific lesions of other medullary regions, including the parvicellular reticular formation (PCRt) (Anaclet et al., 2010) and nucleus of the solitary tract (NTS) also consistently produced moderate reductions of REM sleep amounts (Anaclet and Lu, unpublished results). These findings suggest that the caudal medulla may also contain neurons critical for controlling REM sleep, and that the interaction between these neurons and the pontine REM-on regions may play a major role in the generation and maintenance of REM sleep. Alternatively, these neurons may be critical for inhibiting the 'REM-off' monoaminergic neurons in the pons, so that REM sleep may occur (permissive role). Characterization of the medullary REM-active neurons, the neurotransmitters involved and their interaction with the pontine REM sleep network requires further research.

Muscle tone regulation during REM sleep

Separating the muscle-related signatures of REM sleep into two processes, tonic (atonia) and phasic (muscle twitches), facilitates a better understanding of these events. While atonia occurs in almost all non-respiratory muscles during REM sleep, phasic activity occurs primarily in the cranial muscles and those of the extremities. Cranial muscle phasic events include rapid eye movements and twitching of the jaw, facial and tongue muscles during REM sleep (Chase and Morales, 1990; Burgess et al, 2008, Anaclet et al., 2010; Siegel, 2011). Although it is reasonable to hypothesize that the postural and cranial motor systems have a common mechanism of REM atonia, many differences are apparent. By simultaneously recording masseter EMG (jaw

muscles), electrooculogram, and neck EMG, we found that there is no apparent temporal synchronization among neck, jaw and ocular muscles during natural REM sleep in rats (Anaclet et al., 2010). These observations led us to hypothesize that the muscle twitches during REM sleep in cranial *vs.* postural muscles may be under independent control mechanisms; or even if there is a common upstream control, there must be multiple, discrete control processes for the individual cranial motor nuclei (Lu et al., 2005; Fraigne and Orem, 2011). Results from our laboratory and others further confirm this hypothesis (see below).

Regulation of muscle tone in spinal musculature during REM sleep

In the 1960s and 70s, two laboratories headed by Michel Jouvet and Adrian Morrison found that electrolytic lesions in the subcoeruleus region (ventral to the LC) resulted in REM sleep without atonia in cats (Jouvet and Mounier, 1960; Henley and Morrison, 1974; Hendricks et al., 1982). These cats showed disinhibited behaviors ranging from twitching and jerking to complex motor behaviors, such as appearing to chase a mouse. In 1986, Schenck and colleagues identified a similar human behavioral phenotype and named it REM sleep behavior disorder (RBD; Schenck et al., 1986). Recent studies from our laboratory and others have revealed the complex nature of the brainstem circuitry responsible for REM atonia (Lai and Siegel, 1998; Lu et al., 2006; Luppi et al., 2006; Siegel, 2011). Specifically, we showed that neurotoxic lesions of the SLD resulted in REM without atonia in rats. Using time-lock video recording synchronized with EEG and EMG, we found that rats with SLD lesions exhibit a wide range of behavior such as jerking, twitching, walking, running and 'leaping' while in REM sleep, similar to the behavioral phenotypes observed in humans with RBD and after large lesions in the dorsolateral pons in cats (Lu et al., 2006). Consistent with these observations, human patients with RBD were found to have lesions in the subcoeruleus (SLD equivalent in humans) region caused by either inflammation or stroke (Limousin et al., 2009; Xi and Luning, 2009). Thus, lesions in the subcoeruleus in humans appear to be the mostly likely cause of RBD (Arnulf et al., 2000; Boeve et al., 2007a,b; Scherfler et al., 2011). Following the demonstration that rats with SLD

lesions abolish muscle atonia, we then sought to determine the pathways by which the SLD may bring about muscle atonia during REM sleep. We traced the descending projections from the SLD by injecting an anterograde tracer, adeno-associated viral vector containing green fluorescent protein (AAV-GFP), into this region in rats. Consistent with previous reports, we traced axons through the medial pontine and medullary reticular formation to the spinal ventral horn (Lu et al., 2006). As most of these descending projections from the SLD are glutamatergic, we hypothesized that glutamatergic neurons in the SLD contribute to muscle atonia during REM sleep. Consistently, specific and focal elimination of glutamate neurotransmission from the SLD resulted in the loss of muscle atonia during REM sleep, which mimicked the SLD lesions in rats (Krenzer et al., 2010). Many studies have suggested that the ventromedial medulla (VMM), which receives glutamatergic inputs from the SLD, may be the relay site for the pontine inhibitory area on spinal motor neurons (Sakai et al., 1981; Chase and Morales, 1990). The VMM, as defined by Holstege (1996), comprises the ventral medullary region extending from the caudal part of the inferior olive to the caudal part of the trapezoid body. This region includes many subregions or nuclei such as the paramedian reticular nucleus, ventral gigantocellular nucleus (GiV, known as the magnocellular tegmental field in cats) and ventromedial part of the paragigantocellular nucleus at the level of the inferior olive. More rostrally, it comprises the gigantocellular nucleus-pars alpha (known as the magnocellular nucleus in cats) and the rostral part of the paragigantocellular nucleus (Andrezik and Beitz, 1985; Holstege, 1996). Using a variety of approaches, including cFos immunochemistry, electrical and pharmacological stimulation and cytotoxic and genetic lesions, each of these subregions has been implicated in the REM atonia process (see below). However, this entire region (VMM) contains premotor (ventral horn-projecting) neurons known to be responsible for the inhibition of spinal motor neurons (Holstege and Bongers, 1991; Fort et al., 1993; Rampon et al., 1996; Stornetta and Guyenet, 1999), and hence the term 'VMM' is used in this review and no attempt is made to further differentiate its subregions. On the other hand, the rostroventral medulla (RVM) that mainly contains

the neurons projecting to the spinal cord dorsal horn is not considered a part of the VMM. In general support of the hypothesis that the VMM is necessary for the pontine control of muscle atonia, electrical and pharmacological stimulation of this region in decerebrate rats and cats produced muscle atonia (Lai and Siegel, 1988, 1991, 1992, 1997; Hajnik et al., 2000). A subset of VMM neurons in dogs is active only during periods of complete muscle atonia (Siegel et al., 1991). Moreover, glycine-immunoreactive neurons in the VMM expressed cFos following carbachol-induced REM sleep atonia (Morales et al., 2006). Electrolytic and chemical lesions of this region produced REM without atonia in cats (Schenkel and Siegel, 1989; Holmes and Jones, 1994). Consistent with these observations, we found that orexin-saporin lesions in a restricted region of the VMM lying immediately dorsal to the inferior olive in rats also resulted in high amplitude phasic muscle activity during REM sleep (Vetrivelan et al., 2009). These muscle activities were rapid, jerky, and visible (by video) twitches that ranged in frequency from 0.5 to 16 per minute of REM sleep (on average 5 myoclonic jerks/min of REM sleep). Many of these animals also demonstrated abrupt, violent phasic activity, including accelerating themselves into the cage walls while in REM sleep. VMM lesions, however, did not result in any coordinated behavior (such as walking) while in REM sleep, such as those observed after SLD lesions (Lu et al., 2006; Vetrivelan et al., 2009). Whereas most of the movements seen in the VMM-lesioned rats were rapid and jerky, slow head rising or whole body movements were also occasionally observed. These studies indicate that VMM neurons may be the relay site for the SLD control of spinal motor neurons. To characterize the neurotransmitter(s) involved in this relay, we specifically eliminated glutamate or GABA/glycine neurotransmission from the VMM neurons. As glutamate knockout in the VMM produced more prominent phasic activity in the neck EMG than that produced by GABA/glycine knockout, we suggested that glutamate neurotransmission in the VMM may be more important than GABA/glycine for suppressing phasic motor activity during REM sleep (Vetrivelan et al., 2009).

One important point, however, to consider is that neither VMM lesions nor glutamate or GABA/glycine deletion from the VMM neurons resulted in

a complete loss of muscle atonia, as was observed after SLD lesions in rats or specific elimination of glutamate from SLD neurons in mice. Periods of complete muscle atonia (the tonic component) were observed in most of the REM episodes following these cytotoxic or genetic lesions (Vetrivelan et al., 2009). Thus, these studies collectively indicate that VMM neurons may contribute to but are not sufficient for generating muscle atonia during REM sleep. This idea is consistent with the previous observations that VMM stimulation was not able to produce REM atonia after inactivation of the pons by lidocaine in decerebrate cats (Kohyama et al., 1998). Thus, it is possible that a bidirectional communication between the SLD and VMM plays a crucial role in muscle atonia during REM sleep. These authors further hypothesized that the medial medulla may activate the pontine elements that directly or multisynaptically descend to the spinal cord to inhibit motoneurons (Kohyama et al., 1998). Accordingly, the SLD also has direct glutamatergic projections to the spinal ventral horn, and anterograde tracing studies have shown that SLD neurons form appositions with parvalbumin-immunoreactive cells in lamina VIII, most of which belong to the class VI interneurons that innervate spinal motor neurons (Lu et al., 2006). About 10% of these spinal cord-projecting SLD neurons expressed cFos after enhanced REM sleep in rats (Lu et al., 2006). These spinal projecting SLD neurons may be different from the ones that project to the VMM (Vetrivelan et al., 2009). Thus, the glutamatergic neurons in the SLD may directly act on GABA/glycinergic interneurons in the spinal cord in addition to relaying through the VMM to bring about muscle atonia during REM sleep (Fig. 2). Hence, specific elimination of GABA/glycinergic neurotransmission from both the VMM and spinal cord interneurons may be required to reverse REM atonia. In addition to GABA/glycinergic neurotransmission, monoaminergic, orexinergic and MCHergic neurons may play a role in REM atonia either by their direct projections to the spinal cord or by acting on the SLD and/or VMM neurons (Siegel, 2005; Hasani et al., 2009; Saper et al., 2010; Willie et al., 2011).

Taken together, the brainstem mechanisms controlling muscle atonia during REM sleep appears to be more complicated than presently understood. Active inhibition of the spinal motor neurons by GABA/glycine (Fig. 2) and disfacilitation resulting from the withdrawal of activating influences by noradrenergic, serotonergic and orexinergic neurons may underlie postural muscle atonia during REM sleep (Kubin et al., 1998; Fenik et al., 2005; Siegel, 2011). On the other hand, the cell group(s) responsible for the phasic twitches in spinal musculature during REM sleep is currently unknown. Karlsson and Blumberg (2005) have shown that caudal pontine but not midbrain transections in pups significantly reduce spinal motor phasic activity, indicating that the pons may contain the key neural elements for these events.

Muscle tone regulation in the cranial muscles during REM sleep

We will first describe the mechanisms responsible for generating phasic twitches in the cranial muscles before discussing cranial muscle atonia. The trigeminal motor nucleus (Mo5) is the largest among the cranial motor nuclei and relatively easy to approach, so the Mo5 motor system has been widely used as a model system for studying the REM muscle twitches in cranial muscles. The Mo5 has two functional divisions: a ventromedial region containing motoneurons innervating the jaw-opening muscles, and a dorsolateral region containing the motoneurons of jaw closure (Fay and Norgren, 1997). The jaw-closing masseter muscles exhibit prominent phasic activity during REM sleep (Lavigne et al., 2001). Using a reverse microdialysis approach, Peever and colleagues have shown that functional glutamatergic drive is responsible for generating the phasic twitches in masseter muscles during REM sleep (Brooks and Peever, 2008a,b; Burgess et al., 2008), as initially proposed by Chase and colleagues (Chase and Morales, 1990). However, loss of this glutamatergic drive was not sufficient for triggering REM motor atonia, i.e., tonic process, as activation of neither AMPA nor NMDA receptors on trigeminal motoneurons reversed masseter atonia.

Mo5 receives glutamatergic projections predominantly from the parvocellular reticular nucleus (PCRt), but also a less dense input from the paramedian reticular area (PMnR) (Travers and Norgren, 1983, Travers et al., 2005). To determine if the PCRt and PMnR drive masseter phasic activity in REM sleep, we made cell-body lesions in these nuclei and other control sites surrounding these regions. We found that lesions in the rostral PCRt (rPCRt) and
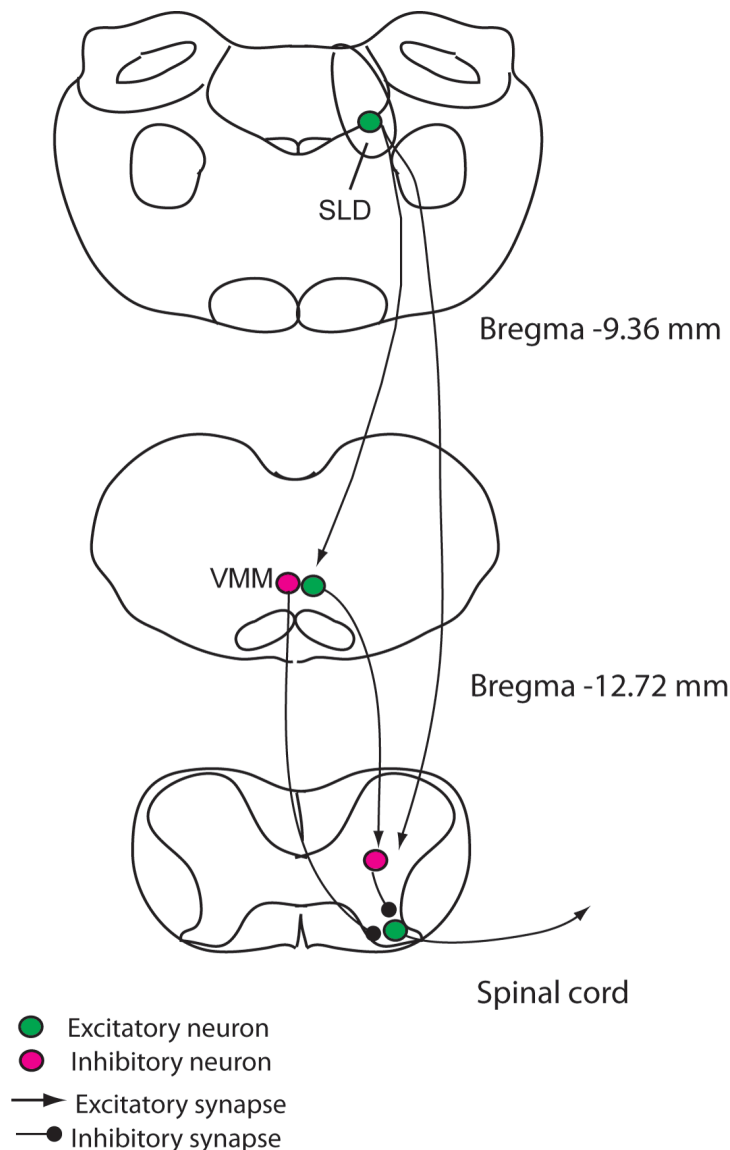
Fig. 2. - Neural circuitry proposed for muscle atonia in the spinal muscles during REM sleep. The REM-on glutama-tergic neurons in the cLDT-SLD send descending projections to the ventromedial medulla (VMM) and spinal cord interneurons (GABA-ergic/glycinergic). The glutamatergic neurons in the VMM project to spinal interneurons, while GABA-ergic/glycinergic neurons in this region project directly to spinal motor neurons. Thus, glutamatergic cLDT-SLD neurons, by directly or indirectly activating these three neuronal populations, cause enhanced release of GABA/glycine onto spinal motor neurons and cause atonia of postural muscles during REM sleep. In addition, withdrawal of activating influences exerted onto motor neurons by monoaminergic and orexinergic neurons (dis-facilitation) may also play a key role in muscle atonia (not shown). The antero-posterior levels of the sections are from the rat atlas of Paxinos and Watson (2009). SLD = sublaterordorsal nucleus.

PMnR significantly reduced masseter phasic activity during REM sleep without affecting neck muscle activity (Anaclet et al., 2010). In contrast, although lesions of the SLD produced jerking and twitching of postural muscles, they did not affect masseter (tonic or phasic) activity during REM sleep. These lesions also did not affect ocular activity during REM sleep, lending support to the hypothesis that differential regulatory systems exist for REM atonia in the cranial and spinal muscles (Kubin et al., 1993; Anaclet et al., 2010).

As the Mo5 receives glutamatergic afferents from the rPCRt and lesions in this region substantially reduced masseter phasic activity, we further hypothesized that specific loss of glutamatergic neurotransmission in the rPCRt would abolish masseter phasic

twitches during REM sleep. Hence, we focally and selectively eliminated glutamate neurotransmission from the rPCRt (Fig. 3) using specific conditional knockout mice and adeno-associated viral vectors. As expected, loss of glutamate release from rPCRt neurons resulted in near complete elimination of masseter twitches during REM sleep (Anaclet et al., 2010). Although we did not study the phasic twitches in the facial and tongue muscles in these animal models, it has been shown that the PCRt also projects to the facial (Mo7) and hypoglossal (Mo12) nuclei in addition to the Mo5 (Travers et al., 2005). Thus, we hypothesize that glutamatergic neurons in the PCRt may be responsible for driving phasic twitches in the facial and hypoglossal muscles as well. Studies are ongoing in our laboratory to confirm this hypothesis. Moreover, the upstream site controlling the PCRt glutamatergic neurons in the generation of these phasic twitches is not currently known, although we have ruled out the possibility of the SLD being this control center.

Our current understanding of the mechanisms controlling atonia (tonic) in the cranial muscles is surprisingly limited despite that significant work has been done in this field. Classical work by Chase and his colleagues first showed that, as in the spinal motor neurons, glycine-mediated postsynaptic inhibition occurs in cranial musculature because administration of a glycine antagonist, strychnine, abolished inhibitory postsynaptic potentials in the Mo5 and Mo12 motor neurons (Chase et al., 1989; Kohlmeier et al., 1996, 1997; Yamuy et al., 1999). However, *in vivo* microdialysis of strychnine or bicuculline (GABA-A antagonist) into the Mo5 motor pool had no effect on REM masseter atonia (Brooks and Peever, 2008a,b). In addition, antagonism of both glycine and $GABA_A$ receptors had no effect on masseter muscle atonia during REM sleep (Brooks and Peever, 2008a,b). Similarly, microinjections of strychnine or bicuculline into the Mo12 had little effect on the suppression of hypoglossal nerve activity during carbachol-induced REM sleep atonia in decerebrate cats, and during natural REM sleep in rats (Kubin et al., 1993; Morrison et al., 2003), indicating a limited role for inhibitory amino acid neurotransmitters in cranial muscle atonia. On the other hand, multiple lines of evidences support a role for monoamines, particularly serotonin and norepinephrine, in cranial muscle atonia (Kubin et al.,

1998; Kodama et al., 2003; Fenik et al., 2005). For example, extracellular levels of norepinephrine and serotonin decrease in the Mo12 neuronal pool during carbachol-induced REM sleep (Kubin et al., 1994; Lai et al., 2001), and noradrenergic and serotonergic agonists excite Mo12 neurons (Kubin et al., 1998). Although noradrenaline did not directly modulate masseter muscle tone, it indirectly increased it by amplifying the prevailing glutamate-driven excitation of the trigeminal motoneurons in anesthetized rats (Schwarz et al., 2008). More importantly, the combined blockade of excitatory adrenergic and serotonergic receptors was both necessary and sufficient to abolish the REM sleep-like depression of Mo12 motoneuronal activity in rats (Fenik et al., 2005). Collectively, these results indicate a major role for monoaminergic disfacilitation in mediating REM atonia (tonic) in cranial muscles.

Neural pathways controlling the other signs of REM sleep

In addition to muscle atonia, REM sleep is also accompanied by cortical activation, autonomic fluctuations (irregularities in heart rate, respiratory rate) and penile erection in men. The thalamocortical system has widely been considered a major source of cortical activation (Steriade et al., 1993; Llinas and Steriade, 2006), and is believed to be regulated by the ascending reticular activating system (ARAS) as originally proposed by Moruzzi and Magoun (1949). However, a recent study from our lab demonstrated that the ascending projections from the parabrachial nucleus and precoeruleus region (PB-PC), relayed by the basal forebrain (BF) to the cerebral cortex, may be critical for behavioral or electrocortical arousal, whereas the previously described reticulo-thalamo-cortical pathway may play a very limited role in this process (Fuller et al., 2011). Furthermore, retrograde tracing from the PB, BF and intralaminar thalamus in mice showed that only the PB received significant glutamatergic inputs from the cLDT-SLD (Krenzer and Lu, unpublished observations). Thus, these evidences indicate that cortical activation during REM sleep may involve activation of PB-PC ascending projections to the BF (Fig. 4). While the neural mechanisms responsible for cortical activation is relatively well understood, those controlling penile erections and autonomic fluc-
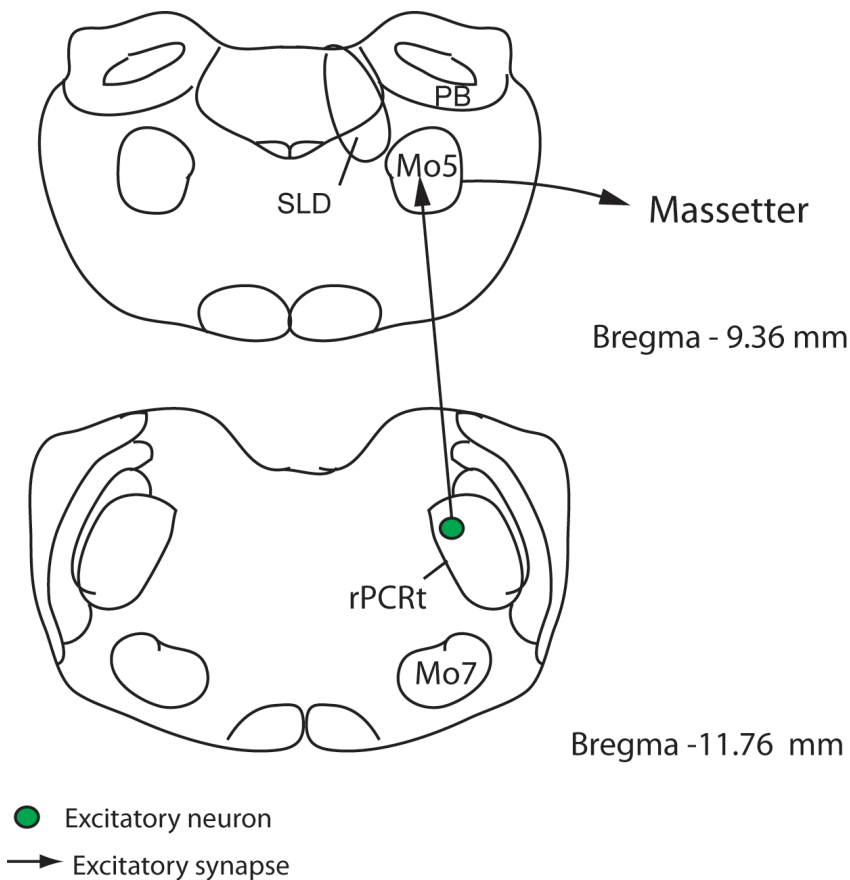
Fig. 3. - Proposed neural circuitry for phasic muscle twitches in the masseter muscles. Glutamatergic neurons in the rostral parvicellular reticular nucleus (rPCRt) project to the trigeminal motor nuclei. These neurons are critical for generating the phasic muscle twitches in masseter muscles during REM sleep. As the rPCRt neurons also project to the facial and hypoglossal nuclei, it is possible that these neurons are responsible for generating phasic twitches in the facial and tongue muscles as well. The antero-posterior levels of the sections are from the rat atlas of Paxinos and Watson (2009). Abbreviations: SLD = sublaterordorsal nucleus; Mo5 = trigeminal motor nucleus; Mo7 = facial motor nucleus; PB = parabrachial nucleus.

tuations are far from clear. Nevertheless, studies by Schmidt and colleagues showed that the brainstem is not sufficient to generate penile erections during REM sleep, as rostral midbrain transections abolished REM-related erections (Schmidt et al., 1999). The studies that followed revealed a critical role for the lateral preoptic region (LPOA) in this process. Chemical lesions of the LPOA specifically disrupt REM-related penile erections while leaving wake-related erections intact (Schmidt et al., 2000). Moreover, electrical stimulation of the dorsal pontine tegmentum, specifically the LDT and the surrounding regions, induced penile erections in rats (Salas et al., 2008). These studies indicate that REM-on neurons in the cLDT may activate the LPOA for controlling REM-related erections. The LPOA may activate the paraventricular nucleus of hypothalamus (PVH), which contains pre-autonomic neurons that project to the intermediolateral column in the spinal cord and thus may mediate REM-erections. However, confirmatory evidence for a role of the PVH in REM-related erections is still lacking. Moreover, it is not clear whether the pathway from the REM-on regions in the pons to the hypothalamic regions is also responsible for phasic autonomic events (autonomic fluctuations) such as irregular heart rate and respiration during REM sleep. However, while pure autonomic failure (absence of the phasic autonomic events) is observed in RBD patients (Braak et al., 2006; Gagnon et al., 2006a,b; Boeve et al., 2007a,b; Postuma et al., 2011), penile erection still occurs during REM sleep in several RBD patients (Oudiette et al., 2010), indicating that different pathways may be involved in these two processes.
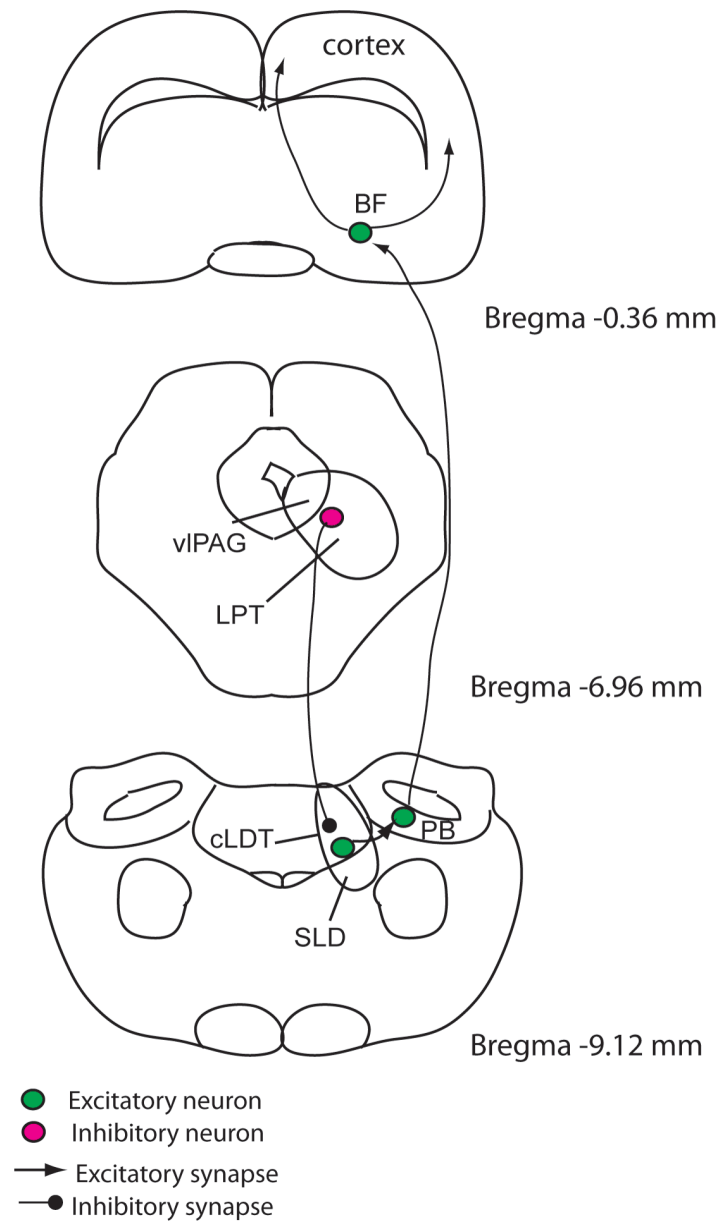
Fig. 4. - The neural circuitry proposed for REM EEG control. The REM-on glutamatergic neurons in the cLDT-SLD project to the basal forebrain (BF) via a relay in the parabrachial-precoeruleus complex (PB). In turn, the BF cholinergic and non-cholinergic neurons project extensively to the cortex. This circuit may play a key role in cortical activation during REM sleep. The antero-posterior levels of the sections are from the rat atlas of Paxinos and Watson (2009). Abbreviations: vlPAG = ventrolateral periaquaductal gray; LPT = lateral pontine tegmentum; SLD = sublaterordorsal nucleus; cLDT = caudal laterodorsal tegmental nucleus.

Summary and clinical implications

From a clinical viewpoint, understanding the neural circuitries regulating REM sleep and muscle atonia may provide a framework for understanding the pathophysiology of RBD. RBD is a parasomnia that is typically manifested as 'dream enactment' behavior, i.e., involuntary nocturnal movements such as kicking, punching, shouting, and screaming during REM sleep (for a review, see Boeve et al., 2007a,b). From long-term epidemiological studies, RBD is now recognized as an early sign of neural degenera-

tive disease, such as Parkinson's disease (PD). RBD often precedes Parkinsonian symptoms by a decade (Schenck and Mahowald, 2005; Boeve et al., 2007; Mahowald et al., 2007). Thus, the diagnosis of RBD may provide an early therapeutic window for delaying or preventing the full development of PD (Olson et al., 2000; Boeve et al., 2001; Gagnon et al., 2006a,b). Although the brainstem is clearly implicated in RBD pathogenesis, the identity of the neural networks that become dysfunctional in RBD is currently unknown. The above-mentioned findings from animal models suggest a possible critical role for the glutamatergic SLD neurons in RBD and subsequent PD. Interestingly, several case reports indicate that lesions restricted to the dorsal pontine tegmentum (presumably involving the SLD region) can cause RBD (Mathis et al., 2007; Xi and Luning, 2009; Limousin et al., 2009). Distinct structural tissue abnormalities (identified via MRI) were found in the pontine tegmentum in idiopathic RBD subjects (Scherfler et al., 2011). Moreover, secondary RBD is associated with PD, dementia with Lewy bodies and multiple system atrophy and prominent alpha synuclein pathology and neuronal loss in the midbrain and pontomedullary brainstem areas, presumably including the SLD and/or the VMM, were observed in these neurodegenerative disorders (Braak et al., 2001, 2006; Iranzo et al., 2005). One additional observation in RBD patients is that while the RBD gets progressively worse over time, the total amount of REM sleep is typically not altered (Iranzo et al., 2009). Thus, it seems that the reticulospinal neurons in the VMM and/or SLD may be affected in these cases, while the SLD-cLDT glutamatergic neurons that control REM sleep amounts are either minimally affected or intact. However, the mechanisms underlying the selective vulnerability of these reticulospinal glutamatergic neurons in RBD are not currently known.

Acknowledgements

References

Anaclet C., Pedersen N.P., Fuller P.M., Lu J. Brainstem circuitry regulating phasic activation of trigeminal motoneurons during REM sleep. *PLoS One*, **5**: e8788, 2010.

Andrezik J.A., Beitz A.J. Reticular formation, central gray and related tegmental nuclei. In: Paxinos G. (Ed.) *The Rat Nervous System. Vol. 2*. Sydney, Academic Press: 1-28, 1985.

Arnulf I., Bonnet A.M., Damier P., Bejjani B.P., Seilhean D., Derenne J.P., Agid Y. Hallucinations, REM sleep, and Parkinson's disease: a medical hypothesis. *Neurology*, **55**: 281-288, 2000.

Aserinsky E. and Kleitman N. Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science*, **118**: 273-274, 1953.

Benke T. Peduncular hallucinosis: a syndrome of impaired reality monitoring. *J. Neurol.*, **253**: 1561-1571, 2006.

Boeve B.F., Silber M.H., Ferman T.J., Lucas J.A., Parisi J.E. Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. *Mov. Disord.*, **16**: 622-630, 2001.

Boeve B.F., Dickson D.W., Olson E.J., Shepard J.W., Silber M.H., Ferman T.J., Ahlskog J.E., Benarroch E.E. Insights into REM sleep behavior disorder pathophysiology in brainstem-predominant Lewy body disease. *Sleep Med.*, **8**: 60-64, 2007a.

Boeve B.F., Silber M.H., Saper C.B., Ferman T.J., Dickson D.W., Parisi J.E., Benarroch E.E., Ahlskog J.E., Smith G.E., Caselli R.C., Tippman-Peikert M., Olson E.J., Lin S.C., Young T., Wszolek Z., Schenck C.H., Mahowald M.W., Castillo P.R., Del Tredici K., Braak H. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. *Brain*, **130**: 2770-2788, 2007b.

Boissard R., Gervasoni D., Schmidt M.H., Barbagli B., Fort P., Luppi P.H. The rat ponto-medullary network responsible for paradoxical sleep onset and maintenance: a combined microinjection and functional neuroanatomical study. *Eur. J. Neurosci.*, **16**: 1959-1973, 2002.

Boissard R., Fort P., Gervasoni D., Barbagli B., Luppi P.H. Localization of the GABAergic and non-GABAergic neurons projecting to the sublaterodorsal nucleus and potentially gating paradoxical sleep onset. *Eur. J. Neurosci.*, **18**: 1627-1639, 2003.

Braak E., Sandmann-Keil D., Rub U., Gai W. P., de Vos R.A., Steur E.N., Arai K., Braak H. Alpha-synuclein immunopositive Parkinson's disease-related inclusion bodies in lower brain stem nuclei. *Acta Neuropathol.*, **101**: 195-201, 2001.

Braak H., Muller C.M., Rub U., Ackermann H., Bratzke H., de Vos R.A., Del Tredici K. Pathology

associated with sporadic Parkinson's disease - where does it end? *J. Neural. Transm. Suppl.*, **70**: 89-97, 2006.

Bremer F. Cerveau "isolé" et physiologie du sommeil. *C.R. Soc. Biol. (Paris)*, **118**: 1235-1242, 1935.

Brooks P.L. and Peever J.H. Unraveling the mechanisms of REM sleep atonia. *Sleep*, **31**: 1492-1497, 2008a.

Brooks P.L. and Peever J.H. Glycinergic and GABA$_A$-mediated inhibition of somatic motoneurons does not mediate rapid eye movement sleep motor atonia. *J. Neurosci.*, **28**: 3535-3545, 2008b.

Brown R.E., Winston S., Basheer R., Thakkar M.M., McCarley R.W. Electrophysiological characterization of neurons in the dorsolateral pontine rapid-eye-movement sleep induction zone of the rat: Intrinsic membrane properties and responses to carbachol and orexins. *Neuroscience*, **143**: 739-755, 2006.

Burgess C., Lai D., Siegel J., Peever J. An endogenous glutamatergic drive onto somatic motoneurons contributes to the stereotypical pattern of muscle tone across the sleep-wake cycle. *J. Neurosci.*, **28**: 4649-4660, 2008.

Carli G. and Zanchetti A. A study of pontine lesions suppressing deep sleep in the cat. *Arch. Ital. Biol.*, **103**: 751-788, 1965.

Chase M.H., Soja P.J., Morales F.R. Evidence that glycine mediates the postsynaptic potentials that inhibit lumbar motoneurons during the atonia of active sleep. *J. Neurosci.*, **9**: 743-751, 1989.

Chase, M.H. and Morales, F.R. The atonia and myoclonia of active (REM) sleep. *Annu. Rev. Psychol.*, **41**: 557-584, 1990.

Clement O., Sapin E., Berod A., Fort P., Luppi P.H. Evidence that neurons of the sublaterodorsal tegmental nucleus triggering paradoxical (REM) sleep are glutamatergic. *Sleep*, **34**: 419-423, 2011.

Crochet S. and Sakai K. Effects of microdialysis application of monoamines on the EEG and behavioural states in the cat mesopontine tegmentum. *Eur. J. Neurosci.*, **11**: 3738-3752, 1999a.

Crochet S. and Sakai K. Alpha-2 adrenoceptor mediated paradoxical (REM) sleep inhibition in the cat. *NeuroReport*, **10**: 2199-2204, 1999b.

Crochet S., Onoe H., Sakai K. A potent non-monoaminergic paradoxical sleep inhibitory system: a reverse microdialysis and single-unit recording study. *Eur. J. Neurosci.*, **24**: 1404-1412, 2006.

Datta S. and Hobson J.A. Neuronal activity in the caudolateral peribrachial pons: relationship to PGO waves and rapid eye movements. *J. Neurophysiol.*, **71**: 95-109, 1994.

Datta S. and Siwek D.F. Single cell activity patterns of pedunculopontine tegmentum neurons across the sleep-wake cycle in the freely moving rats. *J. Neurosci. Res.*, **70**: 611-621, 2002.

Datta S., Mavanji V., Ulloor J., Patterson E.H. Activation of phasic pontine-wave generator prevents rapid eye movement sleep deprivation-induced learning impairment in the rat: a mechanism for sleep-dependent plasticity. *J. Neurosci.*, **24**: 1416-1427, 2004.

Datta S., Saha S., Prutzman S.L., Mullins O.J., Mavanji V. Pontine-wave generator activation-dependent memory processing of avoidance learning involves the dorsal hippocampus in the rat. *J. Neurosci. Res.*, **80**: 727-737, 2005.

Dement W. and Kleitman N. Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming. *EEG Clin. Neurophysiol.*, **9**: 673-690, 1957.

Dement W. and Kleitman N. The relation of eye movements during sleep to dream activity: an objective method for the study of dreaming. *J. Exp Psychol*, **53**: 339-346, 1957.

Deurveilher S. and Hennevin E. Lesions of the pedunculopontine tegmental nucleus reduce paradoxical sleep (PS) propensity: evidence from a short-term PS deprivation study in rats. *Eur. J. Neurosci.*, **13**: 1963-1976, 2001.

Fay R.A. and Norgren R. Identification of rat brainstem multisynaptic connections to the oral motor nuclei using pseudorabies virus. I. Masticatory muscle motor systems. *Brain. Res. Brain. Res. Rev.*, **25**: 255-275, 1997.

Fenik V.B., Davies R.O., Kubin L. REM sleep-like atonia of XII motoneurons is caused by loss of noradrenergic and serotonergic inputs. *Am. J. Resp. Crit. Care Med.*, **172**: 1322-1330, 2005.

Fort P., Luppi P.H., Jouvet M. Glycine-immunoreactive neurones in the cat brain stem reticular formation. *NeuroReport*, **4**: 1123-1126, 1993.

Fraigne J.J. and Orem J.M. Phasic motor activity of respiratory and non-respiratory muscles in REM sleep. *Sleep*, **34**: 425-434, 2011.

Fuller P., Sherman D., Pedersen N.P., Saper C.B., Lu J. Reassessment of the structural basis of the ascending arousal system. *J. Comp. Neurol.*, **519**: 933-956, 2011.

Gagnon J.F., Postuma R.B., Mazza S., Doyon J., Montplaisir J. Rapid-eye-movement sleep behav-

iour disorder and neurodegenerative diseases. *Lancet Neurol*, **5**: 424-432, 2006a.

Gagnon J.F., Postuma R.B., Montplaisir J. Update on the pharmacology of REM sleep behavior disorder. *Neurology*, **67**: 742-747, 2006b.

George R., Haslett W.L., Jenden D.J. A Cholinergic Mechanism in the Brainstem Reticular Formation: Induction of Paradoxical Sleep. *Int. J. Neuropharmacol.*, **3**: 541-552, 1964.

Gottesmann C., Gandolfo G., Zernicki B. Sleep-waking cycle in chronic rat preparations with brain stem transected at the caudopontine level. *Brain Res. Bull.*, **36**: 573-580, 1995.

Goutagny R., Luppi P.H., Salvert D., Lapray D., Gervasoni D., Fort P. Role of the dorsal paragigantocellular reticular nucleus in paradoxical (rapid eye movement) sleep generation: a combined electrophysiological and anatomical study in the rat. *Neuroscience*, **152**: 849-857, 2008.

Hajnik T., Lai Y.Y., Siegel J.M. Atonia-related regions in the rodent pons and medulla. *J. Neurophysiol.*, **84**: 1942-1948, 2000.

Hassani O.K., Lee M.G., Jones B.E. Melanin-concentrating hormone neurons discharge in a reciprocal manner to orexin neurons across the sleep-wake cycle. *Proc. Natl. Acad. Sci. USA*, **106**: 2418-2422, 2009.

Hendricks J.C., Morrison A.R., Mann G.L. Different behaviors during paradoxical sleep without atonia depend on pontine lesion site. *Brain Res.*, **239**: 81-105, 1982.

Hendricks J.C., Kovalski R.J., Kline L.R. Phasic respiratory muscle patterns and sleep-disordered breathing during rapid eye movement sleep in the English bulldog. *Am. Rev. Respir. Dis.*, **144**: 1112-1120, 1991.

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. (Warsaw)*, **34**: 215-232, 1974.

Hirshkowitz M. and Schmidt M.H. Sleep-related erections: clinical perspectives and neural mechanisms. *Sleep Med. Rev.*, **9**: 311-329, 2005.

Holmes C.J. and Jones B.E. Importance of cholinergic, GABAergic, serotonergic and other neurons in the medial medullary reticular formation for sleep-wake states studied by cytotoxic lesions in the cat. *Neuroscience*, **62**: 1179-1200, 1994.

Holstege J.C. and Bongers C.M. A glycinergic projection from the ventromedial lower brainstem to spinal motoneurons. An ultrastructural double labeling study in rat. *Brain Res.*, **566**: 308-315, 1991.

Holstege J.C. The ventro-medial medullary projections to spinal motoneurons: ultrastructure, transmitters and functional aspects. *Prog. Brain Res.*, **107**: 159-181, 1996.

Hu B., Steriade M., Deschenes M. The cellular mechanism of thalamic ponto-geniculo-occipital waves. *Neuroscience*, **31**: 25-35, 1989.

Iranzo A., Santamaria J., Rye D.B., Valldeoriola F., Marti M.J., Munoz E., Vilaseca I., Tolosa E. Characteristics of idiopathic REM sleep behavior disorder and that associated with MSA and PD. *Neurology*, **65**: 247-252, 2005.

Iranzo A., Ratti P. L., Casanova-Molla J., Serradell M., Vilaseca I., Santamaria J. Excessive muscle activity increases over time in idiopathic REM sleep behavior disorder. *Sleep*, **32**: 1149-1153, 2009.

Jouvet M. and Michel F. Corrélations électromyographiques du sommeil chez le chat de cortiqué et mésencéphalique chronique. *C.R. Soc. Biol.*, **153**: 422-425, 1959.

Jouvet M. and Mounier D. [Effect of lesions of the pontile reticular formation on sleep in the cat]. *C.R. Seances Soc. Biol. Fil.*, **154**: 2301-2305, 1960.

Jouvet M. [Research on the neural structures and responsible mechanisms in different phases of physiological sleep]. *Arch. Ital. Biol.*, **100**: 125-206, 1962.

Jouvet M. Paradoxical Sleep - a Study of Its Nature and Mechanisms. *Prog. Brain Res.*, **18**: 20-62, 1965.

Jouvet M. and Delorme F. Locus coeruleus et sommeil paradoxal. *C.R. Seances Soc. Biol.*, **159**: 895-899, 1965.

Jouvet M. Neurophysiology of the states of sleep. *Physiol. Rev.*, **47**: 117-177, 1967.

Kaminer H. and Lavie P. Sleep and dreaming in Holocaust survivors. Dramatic decrease in dream recall in well-adjusted survivors. *J. Nerv. Ment. Dis.*, **179**: 664-669, 1991.

Karlsson K.A. and Blumberg M.S. Active medullary control of atonia in week-old rats. *Neuroscience*, **130**: 275-283, 2005.

Kaur S., Thankachan S., Begum S., Liu M., Blanco-Centurion C., Shiromani P.J. Hypocretin-2 saporin lesions of the ventrolateral periaquadctal gray (vlPAG) increase REM sleep in hypocretin knock-out mice. *PLoS One*, **4**: e6346, 2009.

Kawamura H. and Sawyer C.H. Elevation in brain temperature during paradoxical sleep. *Science*, **150**: 912-913, 1965.

Kayama Y., Ohta M., Jodo E. Firing of 'possibly' cholinergic neurons in the rat laterodorsal tegmental nucleus during sleep and wakefulness. *Brain Res.*, **569**: 210-220, 1992.

Kodama T., Lai Y.Y., Siegel J.M. Changes in inhibitory amino acid release linked to pontine-induced atonia: an in vivo microdialysis study. *J. Neurosci.*, **23**: 1548-1554, 2003.

Kohlmeier K.A., Lopez-Rodriguez F., Liu R.H., Morales F.R., Chase M.H. State-dependent phenomena in cat masseter motoneurons. *Brain Res.*, **722**: 30-38, 1996.

Kohlmeier K.A., Lopez-Rodriguez F., Chase M.H. Strychnine blocks inhibitory postsynaptic potentials elicited in masseter motoneurons by sensory stimuli during carbachol-induced motor atonia. *Neuroscience*, **78**: 1195-1202, 1997.

Kohyama J., Lai Y.Y., Siegel J.M. Inactivation of the pons blocks medullary-induced muscle tone suppression in the decerebrate cat. *Sleep*, **21**: 695-699, 1998.

Krenzer M., Anaclet C., Lu J. Pontine glutamatergic circuit controls rapid eye movement sleep. *Sleep*, **33**: A52, 2010 (abstract).

Kubin L., Kimura H., Tojima H., Davies R.O., Pack A.I. Suppression of hypoglossal motoneurons during the carbachol-induced atonia of REM sleep is not caused by fast synaptic inhibition. *Brain Res.*, **611**: 300-312, 1993.

Kubin L., Reignier C., Tojima H., Taguchi O., Pack A.I., Davies R.O. Changes in serotonin level in the hypoglossal nucleus region during carbachol-induced atonia. *Brain Res.*, **645**: 291-302, 1994.

Kubin L., Davies R.O., Pack A.I. Control of upper airway motoneurons during REM sleep. *News Physiol. Sci.*, **13**: 91-97, 1998.

Kubin L. Carbachol models of REM sleep: recent developments and new directions. *Arch. Ital. Biol.*, **139**: 147-168, 2001.

Lai Y.Y. and Siegel J.M. Medullary regions mediating atonia. *J. Neurosci.*, **8**: 4790-4796, 1988.

Lai Y.Y. and Siegel J.M. Pontomedullary glutamate receptors mediating locomotion and muscle tone suppression. *J. Neurosci.*, **11**: 2931-2937, 1991.

Lai Y.Y. and Siegel J.M. Corticotropin-releasing factor mediated muscle atonia in pons and medulla. *Brain Res.*, **575**: 63-68, 1992.

Lai Y.Y. and Siegel J.M. Brainstem-mediated locomotion and myoclonic jerks. I. Neural substrates. *Brain Res.*, **745**: 257-264, 1997.

Lai Y.Y. and Siegel J.M. Muscle atonia and REM sleep. In: Mallick B.N. and Inoue S. (Eds.) *Rapid eye movement sleep.* New Delhi, Narosa Publishing House: 69-90, 1998.

Lai Y.Y., Kodama T., Siegel J.M. Changes in monoamine release in the ventral horn and hypoglossal nucleus linked to pontine inhibition of muscle tone: an in vivo microdialysis study. *J. Neurosci.*, **21**: 7384-7391, 2001.

Lavie P. and Tzischinsky O. Cognitive asymmetry and dreaming: lack of relationship. *Am. J. Psychol.*, **98**: 353-361, 1985.

Lavigne G.J., Rompre P.H., Poirier G., Huard H., Kato T., Montplaisir J.Y. Rhythmic masticatory muscle activity during sleep in humans. *J. Dent. Res.*, **80**: 443-448, 2001.

Limousin N., Dehais C., Gout O., Heran F., Oudiette D., Arnulf I. A brainstem inflammatory lesion causing REM sleep behavior disorder and sleepwalking (parasomnia overlap disorder). *Sleep Med.*, **10**: 1059-1062, 2009.

Llinas R.R. and Steriade M. Bursting of thalamic neurons and states of vigilance. *J. Neurophysiol.*, **95**: 3297-3308, 2006.

Louie K., and Wilson M.A. Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. *Neuron*, **29**: 145-156, 2001.

Lu J.W., Mann G.L., Ross R.J., Morrison A.R., Kubin L. Differential effect of sleep-wake states on lingual and dorsal neck muscle activity in rats. *Respir. Physiol. Neurobiol.*, **147**: 191-203, 2005.

Lu J., Sherman D., Devor M., Saper C.B. A putative flip-flop switch for control of REM sleep. *Nature*, **441**: 589-594, 2006.

Luppi P.H., Gervasoni D., Verret L., Goutagny R., Peyron C., Salvert D., Leger L., Fort P. Paradoxical (REM) sleep genesis: the switch from an aminergic-cholinergic to a GABAergic-glutamatergic hypothesis. *J. Physiol. (Paris)*, **100**: 271-283, 2006.

Luppi P.H., Clement O., Sapin E., Gervasoni D., Peyron C., Leger L., Salvert D., Fort P. The neuronal network responsible for paradoxical sleep and its dysfunctions causing narcolepsy and rapid eye movement (REM) behavior disorder. *Sleep Med. Rev.*, **15**: 153-163, 2011.

Mahowald M.W., Schenck C.H., Bornemann M.A. Pathophysiologic mechanisms in REM sleep

behavior disorder. *Curr. Neurol. Neurosci. Rep.*, **7**: 167-172, 2007.

Mathis J., Hess C.W., Bassetti C. Isolated medio-tegmental lesion causing narcolepsy and rapid eye movement sleep behaviour disorder: a case evidencing a common pathway in narcolepsy and rapid eye movement sleep behaviour disorder. *J. Neurol. Neurosurg. Psych.*, **78**: 427-429, 2007.

McCarley R.W. and Hobson J.A. Neuronal excitability modulation over the sleep cycle: a structural and mathematical model. *Science*, **189**: 58-60, 1975.

Morales F.R., Sampogna S., Rampon C., Luppi P.H., Chase M.H. Brainstem glycinergic neurons and their activation during active (rapid eye movement) sleep in the cat. *Neuroscience*, **142**: 37-47, 2006.

Morrison J.L., Sood S., Liu H., Park E., Liu X., Nolan P., Horner R.L. Role of inhibitory amino acids in control of hypoglossal motor outflow to genioglossus muscle in naturally sleeping rats. *J. Physiol.*, **552**: 975-991, 2003.

Moruzzi G. and Magoun H.W. Brain stem reticular formation and activation of the EEG. *EEG Clin. Neurophysiol.*, **1**: 455-473, 1949.

Motts S.D. and Schofield B.R. Cholinergic cells in the tegmentum send branching projections to the inferior colliculus and the medial geniculate body. *Neuroscience*, **179**: 120-130, 2011.

Murali N.S., Svatikova A., Somers V.K. Cardiovascular physiology and sleep. *Front. Biosci.*, **8**: s636-652, 2003.

Netick A., Orem J., Dement W. Neuronal activity specific to REM sleep and its relationship to breathing. *Brain Res.*, **120**: 197-207, 1977.

Olson E.J., Boeve B.F., Silber M.H. Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. *Brain*, **123**: 331-339, 2000.

Oudiette D., Leclair-Visonneau L., Arnulf I. Video-clinical corners. Snoring, penile erection and loss of reflexive consciousness during REM sleep behavior disorder. *Sleep Med.*, **11**: 953-955, 2010.

Parent M.B., Habib M.K., Baker G.B. Task-dependent effects of the antidepressant/antipanic drug phenelzine on memory. *Psychopharmacology (Berlin)*, **142**: 280-288, 1999.

Paxinos G. and Watson C. *The Rat Brain in Stereotaxic Coordinates.* San Diego, CA, Academic Press, 2009.

Poe G.R., Walsh C.M., Bjorness T.E. Cognitive neuroscience of sleep. *Prog. Brain Res.*, **185**: 1-19, 2010.

Postuma R.B., Montplaisir J., Lanfranchi P., Blais H., Rompre S., Colombo R., Gagnon J.F. Cardiac autonomic denervation in Parkinson's disease is linked to REM sleep behavior disorder. *Mov. Disord.*, 2011, in press.

Rampon C., Luppi P.H., Fort P., Peyron C., Jouvet M. Distribution of glycine-immunoreactive cell bodies and fibers in the rat brain. *Neuroscience*, **75**: 737-755, 1996.

Rasch B., Pommer J., Diekelmann S., Born J. Pharmacological REM sleep suppression paradoxically improves rather than impairs skill memory. *Nat. Neurosci.*, **12**: 396-397, 2009.

Sakai K., Sastre J.P., Kanamori N., 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: Pompeiano O. and Ajmone Marsan C. (Eds.) *Brain mechanisms and perceptual awareness.* New York, Raven Press: 405-429, 1981.

Sakai K. Central mechanisms of paradoxical sleep. *Brain Dev.*, **8**: 402-407, 1986.

Sakai K. Executive mechanisms of paradoxical sleep. *Arch. Ital. Biol.*, **126**: 239-257, 1988.

Sakai K. and Koyama Y. Are there cholinergic and non-cholinergic paradoxical sleep-on neurones in the pons? *NeuroReport*, **7**: 2449-2453, 1996.

Sakai K. and Onoe H. Critical role for M3 muscarinic receptors in paradoxical sleep generation in the cat. *Eur. J. Neurosci.*, **9**: 415-423, 1997.

Sakai K., Crochet S., Onoe H. Pontine structures and mechanisms involved in the generation of paradoxical (REM) sleep. *Arch. Ital. Biol.*, **139**: 93-107, 2001.

Salas J.C., Iwasaki H., Jodo E., Schmidt M.H., Kawauchi A., Miki T., Kayama Y., Otsuki M., Koyama Y. Penile erection and micturition events triggered by electrical stimulation of the mesopontine tegmental area. *Am. J. Physiol.*, **294**: R102-R111, 2008.

Saper C.B., Fuller P.M., Pedersen N.P., Lu J., Scammell T.E. Sleep state switching. *Neuron*, **68**: 1023-1042, 2010.

Sapin E., Lapray D., Berod A., Goutagny R., Leger L., Ravassard P., Clement O., Hanriot L., Fort P., Luppi P.H. Localization of the brainstem GABAergic neurons controlling paradoxical (REM) sleep. *PLoS One*, **4**: e4272, 2009.

Sastre J.P., Sakai K., Jouvet M. Are the gigantocellular tegmental field neurons responsible for paradoxical sleep? *Brain Res.*, **229**: 147-161, 1981.

Sastre J.P., Buda C., Kitahama K., Jouvet M. Importance of the ventrolateral region of the periaqueductal gray and adjacent tegmentum in the control of paradoxical sleep as studied by muscimol microinjections in the cat. *Neuroscience*, **74**: 415-426, 1996.

Schenck C.H., Bundlie S.R., Ettinger M.G., Mahowald M.W. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. *Sleep*, **9**: 293-308, 1986.

Schenck C.H. and Mahowald M.W. Rapid eye movement sleep parasomnias. *Neurol. Clin.*, **23**: 1107-1126, 2005.

Schenkel E. and Siegel J.M. REM sleep without atonia after lesions of the medial medulla. *Neurosci. Lett*, **98**: 159-165, 1989.

Scherfler C., Frauscher B., Schocke M., Iranzo A., Gschliesser V., Seppi K., Santamaria J., Tolosa E., Hogl B., Poewe W. White and gray matter abnormalities in idiopathic rapid eye movement sleep behavior disorder: a diffusion-tensor imaging and voxel-based morphometry study. *Ann. Neurol.*, **69**: 400-407, 2011.

Schmidt M.H., Sakai K., Valatx J.L., Jouvet M. The effects of spinal or mesencephalic transections on sleep-related erections and ex-copula penile reflexes in the rat. *Sleep*, **22**: 409-418, 1999.

Schmidt M.H., Valatx J.L., Sakai K., Fort P., Jouvet M. Role of the lateral preoptic area in sleep-related erectile mechanisms and sleep generation in the rat. *J. Neurosci.*, **20**: 6640-6647, 2000.

Schwarz P.B., Yee N., Mir S., Peever J.H. Noradrenaline triggers muscle tone by amplifying glutamate-driven excitation of somatic motoneurones in anaesthetized rats. *J. Physiol.*, **586**: 5787-5802, 2008.

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**: 50-63, 1992.

Siegel J.M., Nienhuis R., Tomaszewski K.S. REM sleep signs rostral to chronic transections at the pontomedullary junction. *Neurosci. Lett.*, **45**: 241-246, 1984.

Siegel J.M., Tomaszewski K.S., Nienhuis R. Behavioral states in the chronic medullary and midpontine cat. *EEG Clin. Neurophysiol.*, **63**: 274-288, 1986.

Siegel J.M., Nienhuis R., Fahringer H.M., Paul R., Shiromani P., Dement W.C., Mignot E., Chiu C. Neuronal activity in narcolepsy: identification of cataplexy-related cells in the medial medulla. *Science*, **252**: 1315-1318, 1991.

Siegel J.M. Control of muscle tone across the sleep-wake cycle. In: Parmeggiani P.L. and Velluti R.A. (Eds.) *The Physiologic Nature of Sleep.* London, Imperial College: 281-302, 2005.

Siegel J.M. REM sleep. In: Kryger M.H., Roth T., Dement W.C. (Eds.) *Principles and Practice of Sleep Medicine.* St. Louis, MI, Elsevier Saunders: 90-111, 2011.

Steriade M., Sakai K., Jouvet M. Bulbo-thalamic neurons related to thalamocortical activation processes during paradoxical sleep. *Exp. Brain Res.*, **54**: 463-475, 1984.

Steriade M., Datta S., Pare D., Oakson G., Curro Dossi R.C. Neuronal activities in brain-stem cholinergic nuclei related to tonic activation processes in thalamocortical systems. *J. Neurosci.*, **10**: 2541-2559, 1990a.

Steriade M., Pare D., Datta S., Oakson G., Curro Dossi R. Different cellular types in mesopontine cholinergic nuclei related to ponto-geniculo-occipital waves. *J. Neurosci.*, **10**: 2560-2579, 1990b.

Steriade M., McCormick D.A., Sejnowski T.J. Thalamocortical oscillations in the sleeping and aroused brain. *Science*, **262**: 679-685, 1993.

Stickgold R., Hobson J.A., Fosse R., Fosse M. Sleep, learning, and dreams: off-line memory reprocessing. *Science*, **294**: 1052-1057, 2001.

Stornetta R.L. and Guyenet P.G. Distribution of glutamic acid decarboxylase mRNA-containing neurons in rat medulla projecting to thoracic spinal cord in relation to monoaminergic brainstem neurons. *J. Comp. Neurol.*, **407**: 367-380, 1999.

Swanson L.W. *Brain Maps: Structure of the Rat Brain - A Laboratory Guide with Printed and Electronic Templates for Data, Models, and Schematics.* New York, Elsevier, 1998.

Travers J.B. and Norgren R. Afferent projections to the oral motor nuclei in the rat. *J. Comp. Neurol.*, **220**: 280-298, 1983.

Travers J.B., Yoo J.E., Chandran R., Herman K., Travers S.P. Neurotransmitter phenotypes of intermediate zone reticular formation projections to the motor trigeminal and hypoglossal nuclei in the rat. *J. Comp. Neurol.*, **488**: 28-47, 2005.

van Hulzen Z.J. and Coenen A.M. Effects of paradoxical sleep deprivation on two-way avoidance acquisition. *Physio.l Behav.*, **29**: 581-587, 1982.

Vanini G., Torterolo P., McGregor R., Chase M.H., Morales F.R. GABAergic processes in the mesen-

cephalic tegmentum modulate the occurrence of active (rapid eye movement) sleep in guinea pigs. *Neuroscience*, **145**: 1157-1167, 2007.

Vanni-Mercier G., Sakai K., Lin J.S., Jouvet M. Mapping of cholinoceptive brainstem structures responsible for the generation of paradoxical sleep in the cat. *Arch. Ital. Biol.*, **127**: 133-164, 1989.

Vanni-Mercier G., Sakai K., Lin J.S., Jouvet M. Carbachol microinjections in the mediodorsal pontine tegmentum are unable to induce paradoxical sleep after caudal pontine and prebulbar transections in the cat. *Neurosci. Lett*, **130**: 41-45, 1991.

Verret L., Leger L., Fort P., Luppi P.H. Cholinergic and noncholinergic brainstem neurons expressing Fos after paradoxical (REM) sleep deprivation and recovery. *Eur. J. Neurosci.*, **21**: 2488-2504, 2005.

Vertes R.P. and Eastman K.E. The case against memory consolidation in REM sleep. *Behav. Brain Sci.*, **23**: 867-876: discussion 904-1121, 2000.

Vetrivelan R., Fuller P.M., Tong Q., Lu J. Medullary circuitry regulating rapid eye movement sleep and motor atonia. *J. Neurosci.*, **29**: 9361-9369, 2009.

Vetrugno R., Vella A., Mascalchi M., Alessandria M., D'Angelo R., Gallassi R., Della Nave R., Ginestroni A., Antelmi E., Montagna P. Peduncular hallucinosis: a polysomnographic and spect study of a patient and efficacy of serotonergic therapy. *Sleep Med.*, **10**: 1158-1160, 2009.

Villablanca J.R., de Andres I., Olmstead C.E. Sleep-waking states develop independently in the isolated forebrain and brain stem following early postnatal midbrain transection in cats. *Neuroscience*, **106**: 717-731, 2001.

Walker J.M., Walker L.E., Harris D.V., Berger R.J. Cessation of thermoregulation during REM sleep in the pocket mouse. *Am. J. Physiol.*, **244**: R114-R118, 1983.

Webster H.H., Friedman L., Jones B.E. Modification of paradoxical sleep following transections of the reticular formation at the pontomedullary junction. *Sleep*, **9**: 1-23, 1986.

Webster H.H. and Jones B.E. Neurotoxic lesions of the dorsolateral pontomesencephalic tegmentum-cholinergic cell area in the cat. II. Effects upon sleep-waking states. *Brain Res.*, **458**: 285-302, 1988.

Willie J.T., Takahira H., Shibahara M., Hara J., Nomiyama M., Yanagisawa M., Sakurai T. Ectopic overexpression of orexin alters sleep/wakefulness states and muscle tone regulation during REM sleep in mice. *J. Mol. Neurosci.*, **43**: 155-161, 2011.

Xi M.C., Morales F.R., Chase M.H. Induction of wakefulness and inhibition of active (REM) sleep by GABAergic processes in the nucleus pontis oralis. *Arch. Ital. Biol.*, **139**: 125-145, 2001.

Xi Z. and Luning W. REM sleep behavior disorder in a patient with pontine stroke. *Sleep Med.*, **10**: 143-146, 2009.

Yamuy J., Mancillas J.R., Morales F.R., Chase M.H. C-fos expression in the pons and medulla of the cat during carbachol-induced active sleep. *J. Neurosci.*, **13**: 2703-2718, 1993.

Yamuy J., Mancillas J.R., Morales F.R., Chase M.H. C-fos expression in the pons and medulla of the cat during carbachol-induced active sleep. *J. Neurosci.*, **13**: 2703-2718, 1993.

Yamuy J., Fung S.J., Xi M., Morales F.R., Chase M.H. Hypoglossal motoneurons are postsynaptically inhibited during carbachol-induced rapid eye movement sleep. *Neuroscience*, **94**: 11-15, 1999.