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TOPICAL REVIEW

The anatomical, cellular and synaptic basis of motor atonia during rapid eye movement sleep

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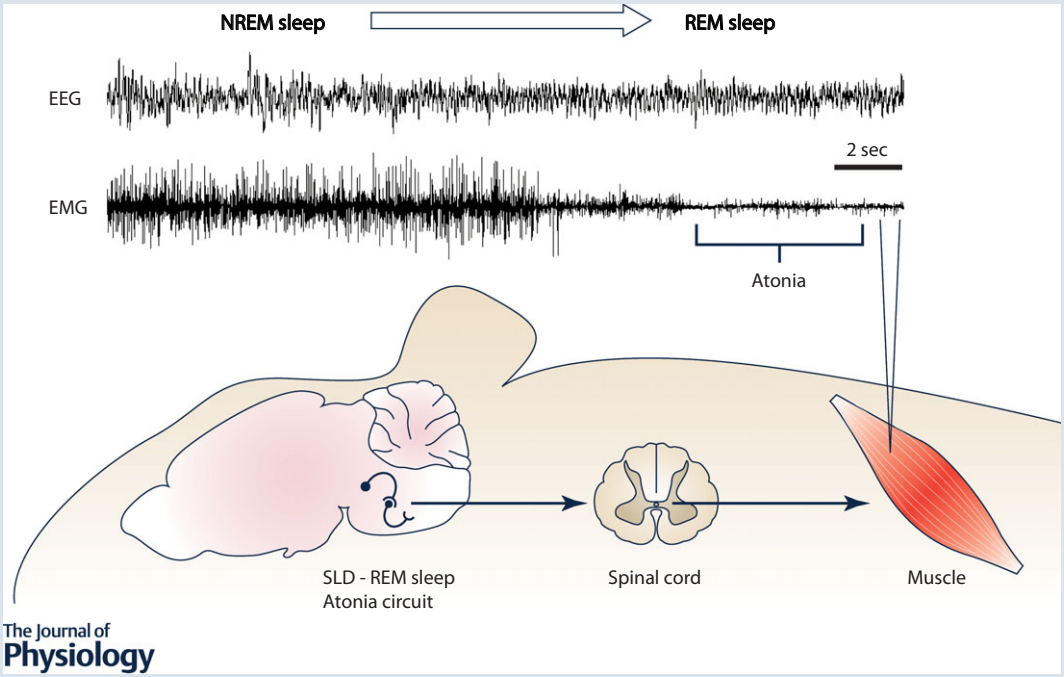

Abstract Rapid eye movement (REM) sleep is a recurring part of the sleep–wake cycle characterized by fast, desynchronized rhythms in the electroencephalogram (EEG), hippocampal theta activity, rapid eye movements, autonomic activation and loss of postural muscle tone (atonia). The brain circuitry governing REM sleep is located in the pontine and medullary brainstem and includes ascending and descending projections that regulate the EEG and motor components of REM sleep. The descending signal for postural muscle atonia during REM sleep

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And his eyes have all the seeming of a demon's that is dreaming – Edgar Allan Poe, *The Raven*

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is thought to originate from glutamatergic neurons of the sublaterodorsal nucleus (SLD), which in turn activate glycinergic pre-motor neurons in the spinal cord and/or ventromedial medulla to inhibit motor neurons. Despite work over the past two decades on many neurotransmitter systems that regulate the SLD, gaps remain in our knowledge of the synaptic basis by which SLD REM neurons are regulated and in turn produce REM sleep atonia. Elucidating the anatomical, cellular and synaptic basis of REM sleep atonia control is a critical step for treating many sleep-related disorders including obstructive sleep apnoea (apnea), REM sleep behaviour disorder (RBD) and narcolepsy with cataplexy.

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Abstract figure legend Representative images of electroencephalographic (EEG) and electromyographic (EMG) changes during the transition from slow-wave sleep (SWS) or non-REM (NREM) sleep. During this time, the electroencephalogram transitions from a low frequency, high amplitude, slow-wave enriched pattern to a theta-enriched, high frequency, low amplitude pattern. At the same time, the electromyogram amplitude declines, reaching a minimal level (atonia). This electromyographic change is driven by projections from the REM sleep atonia circuit in the brainstem that inhibits motor neurons in the spinal cord or brainstem.

Abbreviations BLA, basolateral nucleus of the amygdala; CeA, central nucleus of the amygdala; DpMe, deep mesencephalic reticular nucleus; DRN, dorsal raphe nucleus; EEG, electroencephalogram; EMG, electromyogram; GAD, glutamic acid decarboxylase; GG, genioglossus nucleus; GiA, α gigantocellular reticular nucleus; GiV, ventral gigantocellular reticular nucleus; IPSP, inhibitory postsynaptic potential; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; LH, lateral hypothalamus; LPGi, lateral paragigantocellular nucleus; LPT, lateral pontine tegmentum nucleus; MCH, melanin-concentrating hormone; mPFC, medial prefrontal cortex; OSA, obstructive sleep apnoea; OxR1 and OxR2, orexin receptors 1 and 2; PB, parabrachial nucleus; PC, precoeruleus nucleus; PD, Parkinson's disease; peri-LCα, peri-locus coeruleus alpha nucleus; PnO, oralis pontine nucleus; PPT, pedunculopontine tegmental nucleus; REM, rapid eye movement; RBD, REM sleep behaviour disorder; SLD, sublaterodorsal nucleus; subLC, subcoeruleus nucleus; SWS, slow-wave sleep; vGat, vesicular GABA transporter; vGlut2, vesicular glutamate transporter 2; vlPAG, ventrolateral periaqueductal grey matter; VMM, ventromedial medulla.

The behavioural state of rapid eye movement (REM) sleep itself is characterized by the appearance of fast, desynchronized rhythms in the cortical electroencephalogram (EEG), hippocampal theta activity, autonomic activation, muscle atonia and its eponymous hallmark feature, bursts of rapid eye movements. REM sleep is also associated with dream content, although the extent to which dream content, REM sleep and rapid eye movements are correlated remains unclear. Given the striking resemblance of the REM cortical EEG to that of the waking state, some investigators have instead preferred the term 'paradoxical sleep' or 'active sleep' to describe this behavioural state.

There is near consensus among sleep neuroscientists that REM sleep is important, if not necessary, for normal neurobehavioural and physiological function. In large part this consensus derives from the ubiquitous and recurring nature of REM sleep, its strong 'rebound' after deprivation (Beersma *et al.* 1990), and the finding that REM deprivation, over the course of several weeks, is lethal in rodents (Kushida *et al.* 1989). And while the latter finding is credited with inspiring greater interest in REM sleep function, it remains to date unclear whether the reported lethal outcomes associated with REM sleep deprivation were in fact due to REM deprivation *per se*, or were rather secondary to the stress of the deprivation intervention itself. In general support of a contributing stress covariate is the finding that chronic, e.g. pharmacological, suppression of REM sleep does not appear to have deleterious effects on the body or mind, including in humans. Hence a unified explanation for REM sleep remains elusive.

As indicated, REM sleep is characterized, in part, by changes in muscle activity, including a complete loss of muscle tone in axial postural muscles, phasic muscle twitches in distal limb and orofacial muscles and, of course, phasic bursting of oculomotor muscles. Respiratory-related muscles are also tonically suppressed during REM sleep, but to a variable degree, ranging from nearly unaffected (diaphragm) to complete suppression (genioglossus muscle). The importance of postural atonia, in particular, during REM sleep is profoundly illustrated in human patients with REM sleep behaviour disorder (RBD). RBD is a parasomnia in which patients have excessive tonic and phasic electromyogram (EMG) activity during REM sleep, which can manifest

behaviourally as involuntary movements including kicking, punching, shouting and screaming (Schenck *et al.* 1986, 2013). These unconscious movements can be violent, often resulting in injury to both the individual and bed partner alike, occasionally with life-threatening outcomes. Emerging clinical data have also established an intriguing link between RBD and several degenerative neurological disorders including Parkinson's disease (PD) and other synucleinopathies, such as Lewy body dementia, multiple systems atrophy and pure autonomic failure (Boeve, 2013; Peever *et al.* 2014). Perhaps the most important aspect of this link is that RBD may appear decades prior to the motoric and cognitive symptoms of these neurodegenerative disorders. Hence the diagnosis of RBD may provide an early clinical predictor for some degenerative neurological disorders, including PD, (Boeve *et al.* 2007) and an early therapeutic window for delaying their full development.

Cataplexy, which affects approximately 70% of people with narcolepsy and is characterized by a bilateral loss of muscle tone during wake, is another example of pathological postural atonia control. Loss of muscle tone in cataplexy is triggered by strong, typically positive emotions (e.g. laughter, surprise) and can last from seconds to minutes (Overeem *et al.* 2011). While cataplexy can be partial, involving only individual muscle groups (often of the face or neck), it more typically includes postural muscle groups, resulting in patient collapse (Khoury & Doghramji, 2015). Respiratory muscles, on the other hand, are not affected. Interestingly, cataplexy occurs almost exclusively in narcolepsy, a neurological condition linked to low levels of orexin (also called hypocretin) peptides in the cerebrospinal fluid (Nishino *et al.* 2000; Peyron *et al.* 2000; Mignot *et al.* 2002), secondary to loss of orexin/hypocretin neurons in the lateral hypothalamus (Thannickal *et al.* 2000; Blouin *et al.* 2005; Crocker *et al.* 2005). Because of the shared, albeit directionally opposite, feature of dysregulated postural atonia control between cataplexy and REM sleep, it has been hypothesized that the failure of waking postural motor tone in cataplexy involves state-inappropriate activation of the same circuitry controlling postural muscle atonia during REM sleep (Siegel, 2011; Burgess & Scammell, 2012).

Given the foregoing, defining the anatomical, cellular and synaptic control mechanisms of motor atonia is critical not only for elucidating the neural mechanisms of sleep movement disorders (RBD and other parasomnias and cataplexy) but also for aiding the identification of early stage loci for a host of neurodegenerative diseases. In this review, we highlight work leading to the identification of pontine and medullary circuitry controlling REM sleep and REM sleep muscle atonia. We next explore the synaptic inputs that modulate the 'executive' elements of the REM sleep atonia control circuit and conclude by detailing the synaptic output mechanisms that contribute to postural, orofacial and respiratory motor neuron suppression during REM sleep.

REM circuitry: the pontine REM atonia generator

Pioneering experimental work in the 1960s (Jouvet & Michel, 1960; Mouret *et al.* 1967) and mid (Henley & Morrison, 1974) and late (Sakai *et al.* 1979) 1970s identified a region of the dorsal rostral pons crucial for the generation of muscle atonia during REM sleep in cats. The specific pontine neurons that linked most strongly to the generation of REM atonia were found in the ventral and medial locus coeruleus (LC), termed the peri-locus coeruleus α (peri-LCα) in cats (Sakai *et al.* 1979, 1981, 2001). The pontine homologue of the cat peri-LCα was subsequently identified in rats and mice and comprised a small region of the pontine tegmentum, just ventral to the caudal laterodorsal tegmental nucleus (LDT) and the LC. This region was termed the subcoeruleus (subLC; Pollock & Mistlberger, 2003; Brown *et al.* 2006) or sublaterodorsal nucleus (SLD; Boissard *et al.* 2002; Lu *et al.* 2006; Clement *et al.* 2011; Figs 1 and 2).

A large number of experimental studies in rats and mice have established that SLD neurons play a critical role in both the initiation and the maintenance of postural atonia during REM sleep. As examples, electrical stimulation of the SLD region produces bilateral loss of postural muscle tone (Hajnik *et al.* 2000), lesions of the SLD produce REM without atonia (Mouret *et al.* 1967; Hendricks *et al.* 1982; Morrison, 1988; Sanford *et al.* 2001; Lu *et al.* 2006), and rats killed during REM sleep exhibit dense c-Fos immunolabelling in SLD neurons, with the number of c-Fos-labelled cells positively correlated with the percentage of time spent in REM sleep (Maloney *et al.* 1999, 2000; Verret *et al.* 2005; Lu *et al.* 2006; Sapin *et al.* 2009), the latter marking SLD neurons as 'REM-On'. Unit recording studies have provided additional evidence that REM-On SLD neurons satisfy the criteria for REM-generating neurons: SLD neurons increase firing rate in anticipation of the onset of REM sleep, fire maximally during REM sleep and maintain sustained tonic discharge throughout REM sleep, and become silent during the transitions from REM to slow-wave sleep (SWS) or wakefulness (Sakai & Koyama, 1996; Sakai *et al.* 2001; Karlsson & Blumberg, 2005). Pharmacological activation of SLD neurons via microinjections of glutamate, glutamate agonists or bicuculline (the latter of which blocks GABAergic afferent inputs) produces, with short-latency, a long-lasting REM-like state characterized by low voltage EEG and continuous muscle atonia (Lai & Siegel, 1991; Onoe & Sakai, 1995; Xi *et al.* 1999*a*; Hajnik *et al.* 2000; Boissard *et al.* 2002; Pollock & Mistlberger, 2003; Sanford *et al.* 2003).

Human clinical reports have also revealed a strong correlation between structural damage to the dorsal pons

and the development of RBD. For example, Mathis *et al.* (2007) reported a case of human RBD following an encephalitis-induced lesion that was restricted to the dorsal pontine tegmentum (presumably involving the human SLD bilaterally). Development of RBD was also reported in a patient following a unilateral stroke affecting the right SLD region (Xi & Luning, 2009) and in another patient following a discrete dorsomedial pontine lesion due to vasculitis (St Louis *et al.* 2014). Taken together, the foregoing experimental and clinical data provide evidence that SLD neurons are both necessary and sufficient for generating postural atonia during REM sleep.

A theoretical model of REM sleep control

In 1975 Hobson and McCarley introduced a 'reciprocal-interaction' model of behavioural state control. In this influential model, which was informed by the work of Jouvet (1972), these scientists proposed that reciprocal interactions between mesopontine cholinergic REM-On neurons and aminergic REM-Off neurons were responsible for the alternation of wakefulness, SWS and REM sleep (Hobson *et al.* 1975; McCarley & Hobson, 1975). The model predicted that, during wakefulness, activity of the aminergic system would inhibit the laterodorsal and pedunculopontine tegmental nuclei (LDT/PPT) cholinergic system. With the onset of SWS, aminergic inhibition would wane and cholinergic excitation would wax, reaching a reciprocal trough and peak during REM sleep. Consistent with this model, monoaminergic neurons project to and inhibit cholinergic LDT/PPT neurons (Kubota *et al.* 1992; Luebke *et al.* 1992; Semba & Fibiger, 1992; Williams & Reiner, 1993; Honda & Semba, 1994; Fig. 2, Pathway 3, REM-Off),

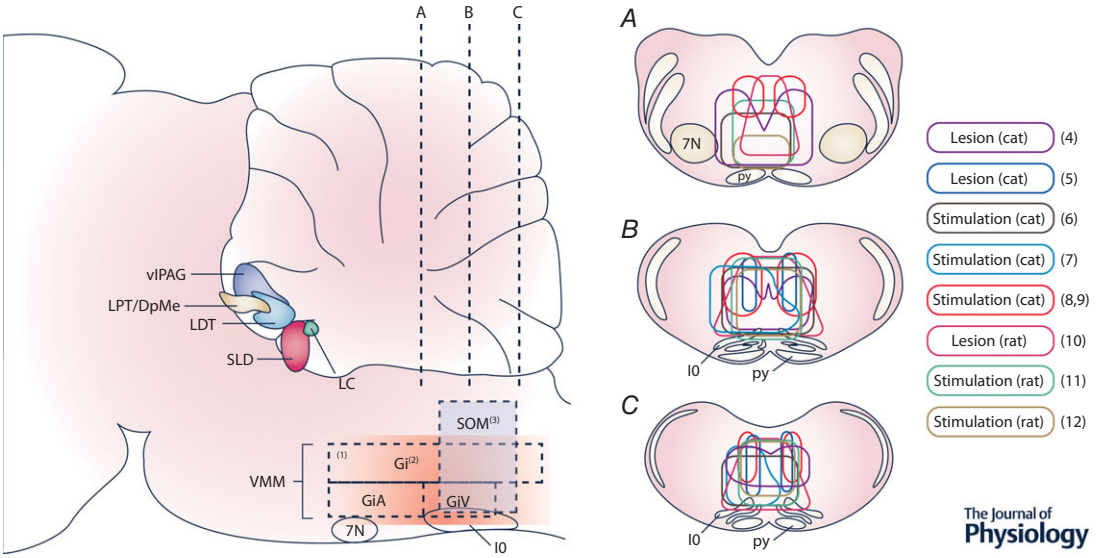

Figure 1. Anatomic representation of brain regions involved in the regulation of REM sleep and REM sleep atonia
Sagittal representation of a rodent brain (left), with coronal views at three rostral–caudal levels (right, *A*–*C*). A zone within the medulla, specifically in the ventromedial medulla (VMM), is thought to play a key role in REM sleep atonia control. (1) The most rostral part of the VMM does not have a significant role in REM sleep atonia (Sastre *et al.* 1981; Lu *et al.* 2006). (2) The VMM near the inferior olive, near Magoun's inhibitory section, is the key zone for REM sleep atonia control (Magoun & Rhines, 1946; Kanamori *et al.* 1980; Chase *et al.* 1984; Schenkel & Siegel, 1989; Holmes & Jones, 1994; Lai & Siegel, 1997; Hajnik *et al.* 2000; Boissard *et al.* 2002; Morales *et al.* 2006; Sapin *et al.* 2009). (3) Caudal to the inhibitory zone, glutamatergic neurons regulate REM sleep atonia (Vetrivelan *et al.* 2009). Coronal views (*A*–*C*) show the zones of stimulation (continuous outlines) or lesion (dashed outlines) that either induce muscle atonia (stimulation) or decrease muscle atonia (lesion). (4) Lesions in the cat have targeted the VMM near the inferior olive (Holmes & Jones, 1994), while stimulation studies (6, 7) have also targeted the VMM as an atonia zone (Magoun & Rhines, 1946). Other studies, both lesion (5) studies (Schenkel & Siegel, 1989) and stimulation (8, 9) experiments (Takakusaki *et al.* 2001; Habaguchi *et al.* 2002) have targeted a more dorsal region just lateral to the midline, the caudal and dorsal extent of the nucleus gigantocellularis and nucleus magnocellularis or dorsal paragigantocellular region. In rats, both lesion (10) studies (Vetrivelan *et al.* 2009) and studies with electrical stimulation (11, 12) have targeted the ventromedial medulla as a key atonia zone (Lai and Siegel, 1988; Hajnik *et al.* 2000). Overall, despite the use of different methods and species, there is a significant overlap in the regions implicating the ventromedial medulla in atonia. Abbreviations: DpMe, deep mesencephalic reticular nucleus; Gi, gigantocellular nucleus; GiA, α gigantocellular nucleus; GiV, ventral gigantocellular nucleus; IO, inferior olive; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; LPT, lateral pontine tegmentum; py, pyramids; SLD, sublaterodorsal nucleus; SOM, supraolivary medulla; vlPAG, ventrolateral periaqueductal grey matter; VMM, ventromedial medulla; 7N, facial nucleus.

and LDT/PPT cholinergic neurons project back to and excite noradrenergic LC and serotoninergic dorsal raphe nucleus (DRN; Svensson & Engberg, 1980; Egan & North, 1985; Satoh & Fibiger, 1986; Jones, 1990; Semba & Fibiger, 1992; Luppi *et al.* 1995; Fig. 2, Pathway 4, REM-On).

Over the years, however, it became apparent that the reciprocal inhibition model could not fully account for the complexity of behavioural state transitions. And to this end, more recent experimental work has informed several modifications and additions to the model (Pace-Schott & Hobson, 2002; Luppi *et al.* 2006; McCarley, 2007). The first of these modifications to the model was the introduction of non-cholinergic, possibly glutamatergic, neurons as REM-generators (Sakai *et al.* 2001; Boissard *et al.* 2002; Lu *et al.* 2006; Luppi *et al.* 2006). In this conceptualization cholinergic inputs would directly activate putative glutamatergic REM-generator neurons (Fig. 2, Pathway 1, REM-On) and the strength of REM-generator output would remain under the control of the aminergic-cholinergic interplay (Fig. 2, Pathway 3, REM-Off and Pathway 4, REM-On). The second modification to the model was the addition of GABAergic synaptic inputs that, during wakefulness and SWS, and in addition to monoaminergic inputs (Fig. 2, Pathway 2, REM-Off), would inhibit the glutamatergic REM-generator (Fig. 2, Pathway 7, REM-Off; Boissard *et al.* 2003; Lu *et al.* 2006).

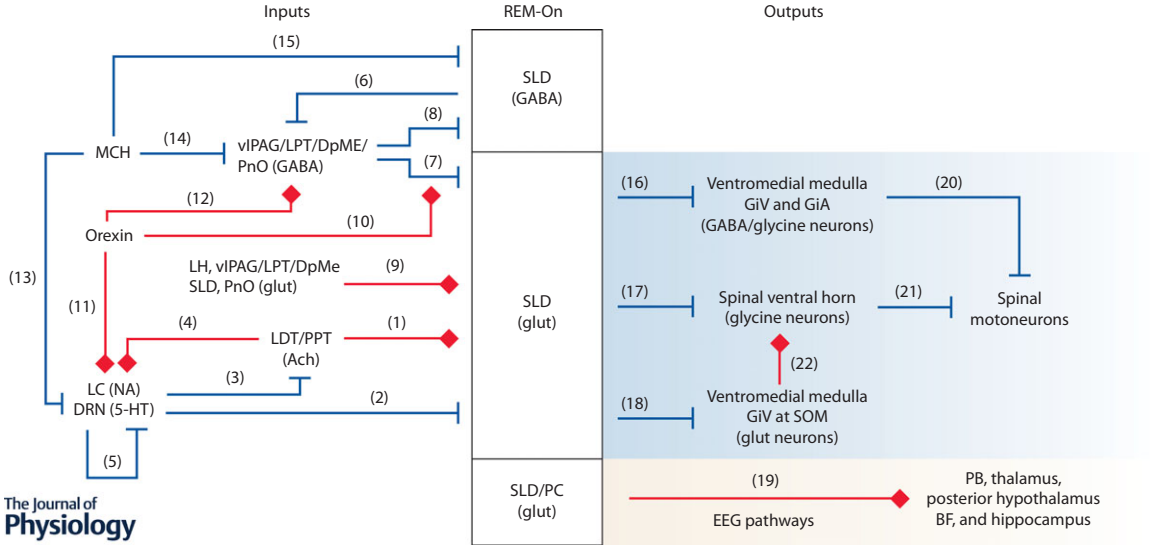

Figure 2. Schematic summary showing synaptic regulation of SLD REM-atonia neurons
The activity of SLD neurons is likely to be controlled by coordinated cholinergic, monoaminergic, GABAergic, glutamatergic and peptidergic inputs. Key references for the represented pathways include (1) REM-On pathway (Baghdoyan *et al.* 1987; Semba, 1993; Kubin, 2001; Weng *et al.* 2014); (2) REM-Off pathway (Semba, 1993; Williams *et al.* 2012); (3) REM-Off pathway (Hobson *et al.* 1975; McCarley & Hobson, 1975; Luebke *et al.* 1992; Semba & Fibiger, 1992; Williams & Reiner, 1993); (4) REM-On pathway (Hobson *et al.* 1975; McCarley & Hobson, 1975; Svensson & Engberg, 1980; Egan & North, 1985; Satoh & Fibiger, 1986; Jones, 1990; Semba & Fibiger, 1992; Luppi *et al.* 1995); (5) REM-Off pathway (Hobson *et al.* 1975; McCarley & Hobson, 1975); (6) REM-On pathway (Lu *et al.* 2006; Fuller *et al.* 2007); (7) REM-Off pathway (Boissard *et al.* 2003; Lu *et al.* 2006; Sapin *et al.* 2009); (8) REM-Off pathway (Lu *et al.* 2006; Fuller *et al.* 2007); (9) REM-On pathway (Shammah-Lagnado *et al.* 1987; Lai *et al.* 1993; Semba, 1993; Boissard *et al.* 2003); (10) REM-Off pathway (Peyron *et al.* 1998; Mileykovskiy *et al.* 2002; Zhang *et al.* 2004; Xi & Chase, 2010; Torterolo *et al.* 2013); (11) REM-Off pathway (Peyron *et al.* 1998; Date *et al.* 1999; Ivanov & Aston-Jones, 2000; Brown *et al.* 2002; Liu *et al.* 2002; Sakurai *et al.* 2005); (12) REM-Off pathway (Boissard *et al.* 2003; Lu *et al.* 2006); (13) REM-On pathway (Bittencourt *et al.* 1992; Del Cid-Pellitero & Jones, 2012; Monti *et al.* 2013; Yoon & Lee, 2013; Devera *et al.* 2015); (14) REM-On pathway (Luppi *et al.* 2013*a*); (15) REM-On pathway (Torterolo *et al.* 2009, 2013); (16) REM-On pathway (Boissard *et al.* 2002; Morales *et al.* 2006; Sapin *et al.* 2009); (17) REM-On pathway (Lu *et al.* 2006); (18) REM-On pathway (Vetrivelan *et al.* 2009); (19) REM-On pathway (Lu *et al.* 2006; Fuller *et al.* 2007); (20) REM-On pathway (Chase *et al.* 1984, 1986; Soja *et al.* 1987*b*; Lai & Siegel, 1988; Castillo *et al.* 1991*a*,*b*; Holstege & Bongers, 1991; Kodama *et al.* 2003; Kato *et al.* 2006; Lai *et al.* 2010); (21) REM-On pathway (Taal & Holstege, 1994; Alvarez *et al.* 2005); (22) REM-On pathway (Takakusaki *et al.* 2001, 2003). Abbreviations: ACh, acetylcholine; BF, basal forebrain; DpMe, deep mesencephalic reticular nucleus; DRN, dorsal raphe nucleus; GiA, α gigantocellular nucleus; GiV, ventral gigantocellular nucleus; glut, glutamate; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; LH, lateral hypothalamus; LPT, lateral pontine tegmentum; MCH, melanin-concentrating hormone; NA, noradrenaline; PB, parabrachial nucleus; PC, precoeruleus; PnO, oralis pontine; PPT, pedunculopontine tegmental nucleus; SLD, sublaterodorsal nucleus; SOM, supraolivary medulla; vlPAG, ventrolateral periaqueductal grey matter; 5-HT, serotonin.

More recent experimental work has resulted in further refinements to the original model, including the identification of two functionally segregated, but anatomically opposed sets of glutamatergic REM-generating neurons. The first of these cell groups spans the SLD, caudal LDT and adjacent precoeruleus (PC) and promotes cortical activation through ascending inputs to the parabrachial nucleus and forebrain (Fig. 2, Pathway 19, REM-On; Fuller *et al.* 2011; Krenzer *et al.* 2011), whereas the second cell group, which includes SLD REM-atonia neurons, generates postural muscle atonia through descending projections to the medulla and spinal ventral horn (Figs 1 and 2, Pathway 16, 17, 20 and 21, all REM-On; Boissard *et al.* 2002; Lu *et al.* 2006; Morales *et al.* 2006). The existence of separate pathways mediating the cortical and motoric components of REM sleep in fact provides a possible basis for the occasional dissociation of cortical activation and muscle atonia during pathological states such as cataplexy, sleep paralysis and RBD (Fuller *et al.* 2007; Vetrivelan *et al.* 2009; Luppi *et al.* 2011).

Taken together, work over the past two decades has identified glutamatergic SLD neurons as REM generators and further shown that these neurons are regulated by many neurotransmitter systems including not only acetylcholine and monoamines – as predicted by the original 1975 reciprocal-interaction model – but also GABA, glutamate and peptides. In fact, contemporary models of REM circuit control now consider the cholinergic and aminergic components as modulatory, not central, elements of the REM sleep regulatory circuit network. We next discuss the synaptic regulation of SLD REM-On atonia neurons by these systems.

Inputs: the cellular and synaptic SLD

Cholinergic regulation. The cholinergic hypothesis of REM sleep induction derives from the observations that systemic administration of the cholinergic antagonists atropine or cholinesterase inhibitor physostigmine block or enhance, respectively, REM sleep (Jouvet & Michel, 1960) and that microinjections of carbachol (a cholinergic agonist) into the pontine tegmentum produce a long-lasting REM-like state in cats and rodents (Baghdoyan *et al.* 1987; Hobson *et al.* 1993; Kubin, 2001). Although the amount and onset delay of REM sleep generated by carbachol in the pons varies by location and dose of injection, species and the type of preparation (Kubin, 2001; Grace & Horner, 2015), the hypothesis that pontine cholinergic neurons participate in REM genesis is still widely accepted. In support of this view, acetylcholine levels in the dorsal pons are high during REM sleep (Leonard & Lydic, 1997), depletion of acetylcholine inhibits REM sleep and blocking acetylcholine degradation promotes REM sleep (reviewed in Jones, 1991*a*,*b*). In addition, LDT/PPT cholinergic neurons are active during REM sleep and wakefulness but silent during SWS (Boucetta *et al.* 2014), and when LDT/PPT cholinergic neurons are optogenetically activated during SWS they promote the transition from SWS to REM sleep (Van Dort *et al.* 2015). LDT/PPT cholinergic neurons also project to the SLD (Quattrochi *et al.* 1989; Jones, 1990; Semba, 1993), and carbachol excites spinally projecting SLD neurons (Fig. 2, Pathway 1, REM-On; Weng *et al.* 2014). It is also the case that the medulla (see below) contains cholinergic neurons that may be REM-On (Holmes & Jones, 1994); however, these neurons do not project to the SLD (Semba, 1993; Holmes *et al.* 1994). Taken as a whole these findings strongly support a role for LDT/PPT cholinergic neurons in not only activating monoaminergic REM-Off neurons (Fig. 2, Pathway 4, REM-On; Svensson & Engberg, 1980; Egan & North, 1985; Satoh & Fibiger, 1986; Jones, 1990; Semba & Fibiger, 1992), but also in activating the pontine REM generator(s) (Fig. 2, Pathway 1, REM-On; Jones, 1993; Steriade, 2004).

Importantly, a recent paper has cast doubt over the necessity of cholinergic input to the SLD for generating REM sleep (Grace *et al.* 2014). In this study the authors specifically showed that microinjection of scopolamine – a competitive antagonist at muscarinic acetylcholine receptors – in the SLD region was without effect on the frequency or duration of REM bouts and REM muscle atonia. Scopolamine administration was, however, found to increase both REM duration and the failure rate of transitions from SWS to REM. Therefore, while the results from Grace and colleagues convincingly show that acetylcholine is dispensable for the induction of REM sleep and muscle atonia, cholinergic inputs may reinforce REM sleep once initiated. To this end, the authors proposed that cholinergic inputs to the REM-generator(s) including the SLD REM-atonia neurons could help ensure rapid transitions into REM sleep that are less likely to fail (Grace & Horner, 2015). For the interested reader, Grace and Horner recently published an elegant historical overview of the cholinergic system in REM control (Grace & Horner, 2015).

Monoaminergic regulation. Both noradrenergic and serotoninergic neurons of the LC and DRN, respectively, are silent during REM sleep, resume firing just before awakenings (McGinty & Harper, 1976; Trulson & Jacobs, 1979; Aston-Jones & Bloom, 1981) and, importantly, cease discharging during periods of cataplexy (Wu *et al.* 1999, 2004). Silencing of LC and DRN neurons during REM sleep has been attributed to both recurrent inhibition (Fig. 2, Pathway 5, REM-Off; Hobson *et al.* 1975; McCarley & Hobson, 1975) and GABAergic input from REM active neurons (Nitz & Siegel, 1997*a*,*b*; Gervasoni *et al.* 2000; Verret *et al.* 2006; Goutagny *et al.* 2008; Clement *et al.* 2014). Both the original and the modified reciprocal inhibitory interaction models (see above) argue that

this reduction of activity in brainstem monoaminergic neurons is permissive in the generation of REM sleep (Pace-Schott & Hobson, 2002; McCarley, 2007). In other words, the models predict that noradrenergic and serotoninergic synaptic inputs inhibit both LDT/PPT cholinergic neurons (Fig. 2, Pathway 3, REM-Off) and pontine REM-generating neurons, including REM-atonia neurons of the SLD (Fig. 2, Pathway 2, REM-Off; Pace-Schott & Hobson, 2002; McCarley, 2007).

To the foregoing, local application of noradrenaline or an α2-adrenoceptor agonist, but not serotonin, in the peri-LCα region in cats inhibits REM active neurons and induces REM sleep without atonia, robustly so when injections are placed in the caudal region of the peri-LCα (Tononi *et al.* 1991; Sakai & Koyama, 1996; Crochet & Sakai, 1999*a*,*b*). In agreement with the inhibitory response of noradrenaline on REM active peri-LCα neurons, spinally projecting neurons of the SLD are also directly inhibited by noradrenaline (Williams *et al.* 2012). These findings suggest that the activity of SLD REM-atonia neurons may be suppressed by noradrenaline released during wakefulness and, by extension, disinhibition of SLD neurons would permit the onset and maintenance of muscle atonia during REM (Fig. 2, Pathway 2, REM-Off). Interestingly, antidepressants that are noradrenaline reuptake inhibitors, and hence increase noradrenergic tone, have been shown to be effective in reducing the occurrence of cataplexy attacks (Schachter & Parkes, 1980; Nishino & Mignot, 1997). Selective serotonin reuptake inhibitors and tricyclic antidepressants have likewise been used, albeit less frequently, to successfully suppress cataplexy (Gowda & Lundt, 2014).

GABAergic regulation. During wakefulness and, to a lesser extent, SWS, REM-generator neurons in the pons are under strong GABAergic inhibitory tone, presumably to prevent them from firing (Xi *et al.* 1999*b*; Luppi *et al.* 2006). This hypothesis derives support from the observation that local application of $GABA_A$ antagonists in the peri-LCα of cats (Xi *et al.* 1999*a*, 2001) or in the SLD of rats (Boissard *et al.* 2002; Pollock & Mistlberger, 2003; Sanford *et al.* 2003; Fenik & Kubin, 2009) rapidly produces a long-lasting REM sleep-like state characterized by desynchronized EEG and postural muscle atonia. Hence disinhibition from GABAergic inputs could be an important synaptic 'mechanism' by which SLD REM-atonia neurons are activated on entry into REM sleep. But what is the synaptic source of SLD-projecting GABAergic REM-Off neurons? Studies combining retrograde tracers, immunolabelling for c-Fos and glutamic acid decarboxylase (GAD) or *in situ* hybridization for GAD67 or GAD65 mRNAs have identified three potential primary sources of this input, which include the ventrolateral periaqueductal grey matter (vlPAG), the lateral pontine tegmentum (LPT) – also known as deep mesencephalic reticular nucleus (DpMe) – and the oralis pontine (PnO) region, which includes the SLD itself (Fig. 2, Pathway 7, REM-Off; Boissard *et al.* 2003; Lu *et al.* 2006; Sapin *et al.* 2009).

With respect to these potential sources of GABAergic input, a dense projection from the vlPAG and LPT/DpMe to the SLD has been confirmed in different species (reviewed in Boissard *et al.* 2003) and, importantly, lesions of both the vlPAG and LPT/DpMe as well as pharmacological inactivation increase REM sleep and can generate a cataplexy-like state (Sastre *et al.* 1996; Crochet *et al.* 2006; Lu *et al.* 2006; Vanini *et al.* 2007; Kaur *et al.* 2009; Sapin *et al.* 2009). Taken together the foregoing findings strongly suggest that GABAergic projections from the tegmental area may provide critical inhibitory control over the REM generator, including REM-atonia neurons. Another potential source of SLD-projecting GABAergic REM-Off neurons is the PnO (Fig. 2, Pathway 7, REM-Off), which includes local SLD GABAergic neurons (not represented in Fig. 2). The rostral PnO not only projects to the SLD (Lai *et al.* 1993; Semba, 1993; Boissard *et al.* 2003) but contains GABAergic REM-Off neurons (Maloney *et al.* 2000). Moreover, antisense disruption of GABA synthesis within the SLD region of the PnO decreases wakefulness and increases REM sleep, suggesting the interesting possibility that local GABAergic SLD neurons may disinhibit glutamatergic SLD REM-atonia neurons during REM sleep, and inhibit their activity during wakefulness (Xi *et al.* 1999*a*).

In addition to their projections to glutamatergic SLD REM-atonia neurons (Fig. 2, Pathway 7, REM-Off), GABAergic REM-Off neurons of the vlPAG and LPT/DpMe are reciprocally connected with GABAergic REM-On neurons in the SLD region (Fig. 2, Pathway 6, REM-On and Pathway 8, REM-Off). This mutual inhibition has been proposed to form a 'flip–flop' switch that would sharpen state transitions, which are typical of the rapid switching from SWS to REM and *vice versa* (Lu *et al.* 2006; Fuller *et al.* 2007). This model has been challenged by the recent finding that disruption of the GABA/glycine transmission in the vlPAG and LPT/DpMe did not produce the predicted increase in REM sleep (Krenzer *et al.* 2011). Yet a more recent optogenetic study found that inhibition of vlPAG GABA neurons did, in fact, potently promote REM sleep (Weber *et al.* 2015). Interestingly, Weber *et al.* used GAD2-cre mice, while Krenzer *et al.* used vGat-cre mice, potentially highlighting alternative mechanisms of GABA transport that differentiate key REM-inhibiting populations within the vlPAG. Another challenge to this model is the reported lack of REM-active GABAergic neurons in the SLD region (Sapin *et al.* 2009), which conflicts with reports from two other groups who found REM-On GABAergic neurons in the SLD (Maloney *et al.* 1999; Lu *et al.* 2006). If the former finding is correct, i.e. REM active GABAergic neurons locate to the vlPAG, not SLD, this might help

explain the absence of a REM effect following disruption of GABA/glycine transmission in the vlPAG in the study by Krenzer *et al.* (2011).

Collectively the available experimental evidence, with minor exceptions, continues to support the flip–flop switch model for REM sleep regulation. In this circuit arrangement, two descending arms of the circuit (from vlPAG and LPT/DpMe REM-Off GABAergic neurons) provides inhibitory control over SLD REM-atonia neurons (Fig. 2, Pathway 7, REM-Off) and SLD GABAergic REM-Off neurons (Fig. 2, Pathway 8, REM-Off) during wakefulness, whereas the ascending arm (from SLD GABAergic REM-On neurons) inhibits REM-Off vlPAG and LPT/DpMe neurons, and possibly the extra-SLD PnO, (Fig. 2, Pathway 6, REM-On) during REM sleep. By its design, this circuit would prevent the inappropriate activation of REM-atonia neurons during wakefulness, which of course would result in cataplexy, and at the same time ensure rapid reconstitution of muscle tone on awaking. Determining the precise source(s) of GABAergic REM-Off input to the SLD REM-atonia neurons remains a clear experimental priority.

Glutamatergic regulation. In addition to disinhibition from monoaminergic and GABAergic inputs, there is emerging experimental evidence that a glutamatergic REM-On input directly activates SLD REM-atonia neurons during REM sleep (Fig. 2, Pathway 9, REM-On; Luppi *et al.* 2012). For example, local injections of glutamate receptor agonists into the peri-LCα of cats or into the SLD region of rats induce a REM-like state with continuous muscle atonia (Lai & Siegel, 1991; Onoe & Sakai, 1995; Hajnik *et al.* 2000; Boissard *et al.* 2002). More importantly, local activation of glutamate receptor antagonists rapidly reverses muscle atonia induced by bicuculline application in rats, but does not alter the cortical REM-like state, suggesting that glutamatergic input to the SLD is required to generate atonia during REM sleep but perhaps is not necessary for REM EEG desynchronization (Boissard *et al.* 2002). Hence, it remains possible that SLD REM-atonia neurons are either tonically excited by glutamate during all sleep–waking states – but that this excitation increases further at the onset of REM sleep – or that there are glutamatergic REM-On neurons that activate the SLD during REM (Luppi *et al.* 2012, 2013*b*). Indeed data on the effects of glutamatergic antagonists in the SLD region across all sleep–wake states, and particularly during naturally occurring REM sleep, are eagerly awaited as they would shed considerable light on this important question.

An important technical consideration for the foregoing is that the methods to definitively identify glutamatergic neurons *vis a vis* vesicular transporters are relatively new. Previous studies on glutamatergic inputs to the SLD used glutamate antibodies, which lacked both sensitivity and specificity. Hence, the source of glutamatergic input to the SLD remains unknown. For example, the lateral hypothalamus, vlPAG and LPT/DpMe, and ventrolateral medulla all contain glutamatergic neurons and project to the SLD (Fig. 2, Pathway 9, REM-On; Shammah-Lagnado *et al.* 1987; Lai *et al.* 1993; Semba, 1993; Boissard *et al.* 2003), but whether or not the projections to the SLD from these regions are glutamatergic remains unknown. In addition, a small number of cells in the contralateral SLD region, and a larger number of cells in the ipsi- and contralateral pontine reticular formation, project to the SLD (Lai *et al.* 1993; Boissard *et al.* 2003), but their neurochemical phenotype, too, remains unknown. Defining which of these inputs to the SLD are both *bona fide* glutamatergic and contribute to the development of atonia should be achievable using newer technical approaches, including optogenetics and conditional retrograde tracing systems.

Orexin regulation. Orexin (or hypocretin) neurons are a discrete cluster of neurons in the posterior lateral hypothalamus (de Lecea *et al.* 1998; Sakurai *et al.* 1998). Orexin neurons have widespread projections (Peyron *et al.* 1998) and their receptors (Ox1R and Ox2R) are expressed in virtually all of the brain's major arousal centres, suggesting an important contribution of orexin signalling to the generation and maintenance of wakefulness (Sakurai *et al.* 2010). Indeed, optogenetic activation of orexin neurons triggers awakening from sleep (Adamantidis *et al.* 2007), although this effect is attributed to secondary activation of other arousal centres (Carter *et al.* 2010). Loss of orexin neurons, which is the neuropathological basis of narcolepsy, produces excessive daytime sleepiness, fragmented sleep and cataplexy (Peyron *et al.* 2000; Thannickal *et al.* 2000; Crocker *et al.* 2005; Burgess & Scammell, 2012). Narcoleptic patients also have REM sleep abnormalities including shortened REM sleep onset latency, vivid dreaming and a greater than expected occurrence of RBD, although the mechanism of the motor disturbances during REM sleep remains to be clarified (Frauscher *et al.* 2011).

There are now several animal models (naturally occurring mutations or genetically engineered) that reproduce human narcolepsy symptoms (sleepiness and cataplexy). All of these models exhibit disruptions in orexin signalling (Chen *et al.* 2009; Scammell *et al.* 2009). Disruption of Ox2Rs in dogs results in a phenotype characterized by sleepiness and severe cataplexy (Lin *et al.* 1999). Yet, interestingly, these dogs have normal cerebrospinal fluid orexin levels (John *et al.* 2004*b*), suggesting that disruption of Ox2Rs is sufficient, at least in this species, to produce severe narcolepsy. In mice, however, fragmented wakefulness and cataplexy are only observed following disruption of the orexin peptide (Chemelli *et al.* 1999; Mochizuki *et al.* 2004), the orexin neurons themselves (Hara *et al.* 2001) or when both Ox1Rs

and Ox2Rs are knocked out (Sakurai, 2007; Hasegawa *et al.* 2014). Mice lacking Ox1Rs or Ox2Rs, but not both concurrently, have milder sleep phenotypes and cataplexy (Willie *et al.* 2003; Mieda *et al.* 2011; Mochizuki *et al.* 2011 and reviewed in Sakurai, 2007).

Physiologically, orexin neurons are active during wakefulness and fire in association with movement. A decrease in firing is observed during quiet waking and these neurons fall silent during SWS and REM sleep, although transient bursts of action potentials do occur during REM sleep (Lee *et al.* 2005; Mileykovskiy *et al.* 2005). Of note, extracellular orexin levels in the basal forebrain and lateral hypothalamus are high during wakefulness, low during SWS sleep, and rise again during REM sleep (Kiyashchenko *et al.* 2002), which is an apparent paradox given that orexin neurons are generally quiescent during REM sleep.

With respect to the regulation of REM sleep, orexin neurons innervate REM sleep nodes in the pons, including the SLD (Fig. 2, Pathway 10, REM-Off; Zhang *et al.* 2004; Torterolo *et al.* 2013). More specifically, orexin neurons innervate noradrenergic and serotonergic REM-Off neurons of the LC and DRN (Fig. 2, Pathway 11, REM-Off; Peyron *et al.* 1998; Date *et al.* 1999; Sakurai *et al.* 2005) as well as REM-Off vlPAG and LPT/DpMe neurons (Fig. 2, Pathway 12, REM-Off; Peyron *et al.* 1998; Boissard *et al.* 2003; Lu *et al.* 2006). Electrophysiological data further reveal that orexin directly activates LC and DRN neurons (Ivanov & Aston-Jones, 2000; Brown *et al.* 2002; Liu *et al.* 2002; Murai & Akaike, 2005; Kohlmeier *et al.* 2008, 2013). It has been proposed that orexin might promote REM sleep by directly activating SLD REM-On neurons (Xi *et al.* 2002, 2003). This conclusion is, however, not fully supported by experimental findings; for example, orexin neurons fire only occasionally during REM sleep and direct evidence for orexin release in the pons during REM sleep is lacking. On the other hand, orexin injected directly into the dorsal pons – encompassing the SLD region – prolongs waking in animals that are already awake whereas a prolonged state of REM sleep is induced if orexin is applied during SWS (Xi & Chase, 2010).

To explain the foregoing results, the authors proposed that orexin might act on different components of the REM circuit, and thereby bias wakefulness or REM sleep, depending on the state of activation or inhibition of the different nodes (Xi & Chase, 2010). While an intriguing hypothesis, confirmation will require additional experimental work to elucidate a functional circuit framework, which is currently lacking. An alternative hypothesis is that orexin is released in the pons during wakefulness and potentiates REM-Off GABAergic inhibition of SLD REM-atonia neurons (Luppi *et al.* 2006; Lu *et al.* 2006). Hence orexin projections to the vlPAG and LPT/DpMe (Boissard *et al.* 2003; Lu *et al.* 2006) and to the SLD (Zhang *et al.* 2004; Torterolo *et al.* 2013) may activate, respectively, vlPAG/LPT/DpMe REM-Off GABAergic neurons (Fig. 2, Pathway 12, REM-Off), as well as their presynaptic terminals to SLD REM-atonia neurons, to prevent cataplexy (Fig. 2, Pathway 10, REM-Off).

As indicated, positive emotions are the most common trigger for cataplexy in narcoleptic humans (joking, laughter, being tickled or a pleasant surprise; Anic-Labat *et al.* 1999; Overeem *et al.* 2011) and probably as well for dogs (palatable food or play; Mitler *et al.* 1974; Nishino & Mignot, 1997; Tonokura *et al.* 2007; Scammell *et al.* 2009) and mice (palatable food such as chocolate, running wheels, or group housing; Chemelli *et al.* 1999; Espana *et al.* 2007; Clark *et al.* 2009; Scammell *et al.* 2009; Oishi *et al.* 2013). In humans anger is also a trigger (Anic-Labat *et al.* 1999; Overeem *et al.* 2011), whereas aversive situations do not trigger cataplexy in dogs (Blouin *et al.* 2013), but do in narcoleptic cattle and sheep (Strain *et al.* 1984; White & de Lahunta, 2001). Strong emotions as a 'trigger' thus appear to be a common denominator whereas the positive *vs.* negative valence of the trigger seems to be species-specific. The circuit mediating emotion-driven cataplexy is also incompletely understood. It has been proposed, for example, that strong emotions might activate the central and basolateral nucleus of the amygdala (CeA and BLA; Garavan *et al.* 2001, Straube *et al.* 2008), possibly following initial activation of the medial prefrontal cortex (mPFC; Damasio *et al.* 2000, Sabatinelli *et al.* 2007, Ponz *et al.* 2010, Etkin *et al.* 2011, Oishi *et al.* 2013). Interestingly both the CeA and BLA contain neurons that are active during cataplexy (Gulyani *et al.* 2002), and inhibitory (vesicular GABA transporter, vGat positive) neurons of the CEA heavily innervate neurons of the vlPAG/LPT/DpMe (Rizvi *et al.* 1991, Oka *et al.* 2008, Burgess *et al.* 2013), which are possibly GABAergic REM-Off. Under non-pathological conditions, inhibitory inputs to the vlPAG/LPT/DpMe are opposed by excitatory orexin inputs (Peyron *et al.* 1998, Boissard *et al.* 2003, Lu *et al.* 2006) and maintain inhibitory tone of vlPAG/LPT/DpMe to the SLD REM-atonia neurons during strong emotions. In narcoleptic patients, however, loss of orexin inputs may 'disfacilitate' vlPAG/LPT/DpMe REM-Off neurons, which could in turn trigger the inappropriate activation of SLD neurons during wake and ultimately lead to loss of postural muscle tone (Lu *et al.* 2006; Luppi *et al.* 2006; Burgess & Scammell, 2012). Additional circuit mapping experiments will be required to confirm this model of emotion-driven cataplexy, and are eagerly awaited.

MCH regulation. Intermingled with orexin neurons is another cell population containing melanin-concentrating hormone (MCH) peptide. Orexin and MCH neurons have similar projections but their firing patterns across the sleep–wake cycle are roughly opposite, and they are thought to produce opposite effects on

their postsynaptic targets (Adamantidis & de Lecea, 2008; Espana & Scammell, 2011; Jones & Hassani, 2013). They are also reciprocally regulated (Gao, 2009): MCH inhibits orexin neurons by depressing the glutamatergic input to orexin neurons (Rao *et al.* 2008) whereas orexin neurons inhibit MCH neurons by an orexin-mediated feed-forward inhibition (Apergis-Schoute *et al.* 2015). While MCH neurons are best known for their regulatory role in energy homeostasis (Pissios *et al.* 2006), several recent studies have demonstrated that they are specifically active during REM sleep (Verret *et al.* 2003; Hanriot *et al.* 2007; Hassani *et al.* 2009). Even more recent experimental work employing optogenetic activation in behaving animal models has shown that acute activation of MCH neurons promotes REM sleep (Jego *et al.* 2013; Tsunematsu *et al.* 2014) or both REM and SWS sleep (Konadhode *et al.* 2013). Thus MCH neurons appear to be involved in both REM and SWS regulation, with the caveats that (1) their ability to drive SWS may be time of day dependent (Jones & Hassani, 2013; Konadhode *et al.* 2013) and (2) on the basis of silencing and ablation studies (Jego *et al.* 2013; Tsunematsu *et al.* 2014), their role in the induction or maintenance of REM sleep could be minor.

The postsynaptic targets and synaptic mechanisms through which MCH neurons promote REM and SWS remain unclear. MCH is an inhibitory peptide that acts through both presynaptic and postsynaptic mechanisms, although presynaptic action seems to be more common (Gao, 2009; van den Pol, 2012). MCH neurons have also been thought to produce and release GABA (Elias *et al.* 2001; Harthoorn *et al.* 2005; Del Cid-Pellitero & Jones, 2012) and optogenetic activation of MCH terminals elicits GABA release within the tuberomammillary nucleus (Jego *et al.* 2013). On the other hand, other recent studies have reported that MCH neurons do not contain the vesicular GABA transporter (vGat), and hence may not be capable of releasing synaptic GABA (Chee *et al.* 2015). If MCH neurons indeed release synaptic GABA, they must rely on another, as yet unidentified vesicle transporter, not vGat, to package GABA.

It has been proposed that MCH neurons may contribute to the suppression of the activity of REM-Off neurons (LC, DRN, and vlPAG and LPT/DpMe neurons) during REM sleep (Fig. 2, Pathways 13 and 14, REM-On; Monti *et al.* 2013; Luppi *et al.* 2013*a*) through the release of GABA and MCH. In general support of this model are the findings that MCH neurons send dense projections to all of these regions (Bittencourt *et al.* 1992; Clement *et al.* 2012; Del Cid-Pellitero & Jones, 2012; Yoon & Lee, 2013), that MCH microinjected in the LC or DRN increases the number of REM sleep episodes (Lagos *et al.* 2009; Monti *et al.* 2015), and that MCH inhibits the firing of DRN neurons (Devera *et al.* 2015). If MCH neurons do not indeed package and release synaptic GABA, they may alternatively inhibit REM-Off neurons directly through MCH release or indirectly through glutamate-mediated feedforward inhibition (Chee *et al.* 2015).

MCH neurons also project to REM-On neurons in the PnO region, which, again, is a pontine region that includes the SLD (Torterolo *et al.* 2013). Therefore MCH neurons might influence SLD control of muscle atonia during REM sleep via this input. Microinjections of MCH into PnO/SLD significantly increase REM sleep and decrease latency to REM sleep onset, supporting the hypothesis that the MCH system contributes to the generation of both EEG and EMG aspects of REM sleep through pontine circuits (Torterolo *et al.* 2009; Fig. 2, Pathway 15, REM-On). How MCH acts on SLD REM-On neurons is not fully understood, although it is possible that MCH neurons directly activate REM-On neurons in the region, including SLD REM-atonia neurons, *vis a vis* glutamate release. Confirmation of this intriguing possibility will require additional experimental work.

Outputs: descending SLD circuits

SLD REM-atonia neurons are largely, if not exclusively, glutamatergic. During both REM sleep and REM sleep rebound most c-Fos positive SLD neurons co-localize the vesicular glutamate transporter 2 (vGlut2), which is a specific marker for glutamatergic neurons (Lu *et al.* 2006; Clement *et al.* 2011). Focal disruption of glutamatergic transmission by SLD neurons in mice produces REM sleep without atonia, which is phenotypically very similar to that observed in human RBD cases (Krenzer *et al.* 2011). And while is it generally accepted as fact that glutamatergic SLD neurons play a key role in generating postural atonia during REM sleep, the descending pathway by which they do so remains a subject of debate. Specifically, the respective contributions of the direct (SLD→spinal ventral horn; Fig. 2, Pathways 17 and 21 REM-On) *versus* indirect (i.e. SLD→ventromedial medulla→spinal ventral horn; Fig. 2, Pathways 16 and 20, REM-On) projection systems in mediating REM atonia (Fuller *et al.* 2007; Brown *et al.* 2012; Chase, 2013; Luppi *et al.* 2013*b*) remain to be clarified, although these two synaptic pathways are likely to provide synergistic control of REM sleep atonia.

The first, 'direct' synaptic model proposes that SLD REM-atonia neurons send axons directly to the spinal cord (Fig. 2, Pathways 17 and 21, REM-On), forming appositions with parvalbumin-immunoreactive neurons in lamina VIII (Lu *et al.* 2006; Fuller *et al.* 2007), most of which belong to the class V1 interneurons that are known to project to spinal motor neurons of layer IX and to contain glycine, GABA or both (Taal & Holstege, 1994; Alvarez *et al.* 2005). Focal disruption of glycinergic/GABAergic transmission in the spinal ventral horn produces phasic movements during REM sleep

(Krenzer *et al.* 2011). One challenge to this model is the finding of a previous single unit recording study in cats that reported that spinally projecting neurons in the peri-LCα were inactive during REM sleep (Sakai *et al.* 1981). However, only a relatively small number of neurons were sampled and, moreover, many of the recording neurons may have been noradrenergic neurons, which are known to be silent during REM sleep (Aston-Jones & Bloom, 1981; Bruinstroop *et al.* 2012). And it is the case that in cats, which is the species used by Sakai *et al.*, glutamatergic SLD neurons intermingle with noradrenergic neurons of the LC complex. Additional studies are therefore required to clarify the circuitry through which SLD neurons directly generate the descending signal for REM muscle atonia.

The second 'indirect' synaptic model proposes that SLD glutamatergic REM-atonia neurons send projections to glycinergic neurons in the ventromedial medulla (VMM), including the ventral gigantocellular reticular nucleus (GiV) and α-gigantocellular reticular nuclei (GiA) and the adjacent lateral paragigantocellular (LPGi) group (Figs 1 and 2, Pathways 16 and 20, REM-On; Boissard *et al.* 2002; Morales *et al.* 2006; Sapin *et al.* 2009). Even before the discovery of REM sleep, the medulla was thought to play a key role in the regulation of the overall tone of an animal's spinal motor systems. In 1898, Sherrington described a chronic rigidity resulting from the removal of the cerebral cortex (Sherrington, 1898). Transections through the rostral pons, on the other hand, produced apparent atonia (Keller, 1945). These results seem conflicting: on the one hand, loss of cortical inputs produced hypertonia or rigidity while on the other hand, brainstem transections produced hypotonia/atonia. One potential explanation is the presence of inhibitory brainstem nodes that project to and actively suppress spinal motor function. And, in fact, these putative inhibitory neurons are the likely target of SLD glutamatergic REM-atonia neurons.

Medullary control of REM sleep and postural atonia

From a historical perspective, atonia was first thought to arise from a 'tonic tonus-inhibiting circuit' in the brainstem that normally receives an antagonistic input (Keller, 1945). In this model, rostral pontine transections released this antagonistic input, allowing the overriding tonus inhibition to win out and suppress spinal muscle tone. Magoun & Rhines (1946) provided critical evidence for the medulla's role in this tonus-inhibiting circuit. Using electrode stimulation of the medulla, they found inhibition of muscle reflexes and other forms of spinal motor excitation. The effective stimulation points were found to be along the VMM, spanning the rostral–caudal axis of the medulla and including neurons in the GiV and GiA nuclei. This inhibition was due to inhibitory postsynaptic potentials (IPSPs) on spinal motor neurons, which could be produced by stimulation of the medulla (Llinas & Terzuolo, 1964) in the same location of the medullary inhibiting region described by Magoun and colleagues (Jankowska *et al.* 1968). Given the similarities between this experimental inhibition and REM sleep atonia (Gassel *et al.* 1964, 1965; Morrison & Pompeiano, 1965; Kubota & Kidokoro, 1966), investigation focused on the VMM and its role in generating postural motor atonia (Pompeiano, 1967; Steriade & Hobson, 1976). It is the case that differences in experimental procedures (e.g. lesion *vs.* stimulation) and the brainstem anatomy of the experimental models (rats or mice *vs.* cats) has complicated the identification and characterization of the delimited medullary region mediating REM atonia (Fig. 1). Yet, despite these complications, common neuroanatomical features have emerged: a medullary REM sleep atonia zone near the rostral tip of the inferior olive, centred on the sagittal midline.

VMM neurons, including the more medial GiV and GiA groups and the lateral adjacent LPGi group, are maximally active during REM sleep (Siegel *et al.* 1979; Kanamori *et al.* 1980; Boissard *et al.* 2002; Morales *et al.* 2006; Sapin *et al.* 2009) and cataplexy (Siegel *et al.* 1991). Unit recording shows that these VMM neurons discharge tonically across the sleep–wake cycle, with a progressive increase in firing rate as the animal progresses from active wake to SWS, a dramatic increase in firing rate during the transition into REM, and an equally dramatic slowing of firing upon awaking (Kanamori *et al.* 1980; Chase *et al.* 1984). Medullary lesions also produce REM sleep without atonia or other abnormal behaviours during REM sleep (Schenkel & Siegel, 1989; Holmes & Jones, 1994; Lai & Siegel, 1997; Hajnik *et al.* 2000; Vetrivelan *et al.* 2009). These 'effective' lesions were focused on a specific rostral–caudal level of the medulla, near Magoun's inhibitory centre (Fig. 1). For example, large lesions of GiV and GiA neurons near the rostral pole of the medulla, i.e. near the pontomedullary junction, do not alter postural muscle tone during REM sleep (Sastre *et al.* 1981; Lu *et al.* 2006), whereas lesions at a more caudal level, i.e. at the level of the inferior olive, lead to exaggerated muscle twitches during REM sleep (Schenkel & Siegel, 1989; Holmes & Jones, 1994; Lai & Siegel, 1997; Hajnik *et al.* 2000; Vetrivelan *et al.* 2009). Both lesion (Schenkel & Siegel, 1989) and stimulation (Takakusaki *et al.* 2001; Habaguchi *et al.* 2002) studies indicated that the zone of atonia may extend dorsally above the area adjacent to the inferior olive, although the involvement of these regions may reflect the use of electrical stimulation/lesions that disrupt pontomedullary dialogue critical for REM sleep atonia. Lesion, recording and stimulation experiments suggest that this medullary inhibitory zone is present and functional at birth (Karlsson & Blumberg, 2005).

VMM neurons in the medullary inhibitory region are a mix of glutamatergic, GABA/glycinergic, cholinergic

and serotonergic neurons (Reichling & Basbaum, 1990; Jones *et al.* 1991; Holmes & Jones, 1994; Hossaini *et al.* 2012). More caudally and laterally, adrenergic REM-On neurons may play a role in sympathetic activity during REM sleep (Stettner *et al.* 2013). In generating the postural motor atonia of REM sleep, the indirect model posits that glutamatergic SLD neurons project to inhibitory medullary neurons, which are likely to be GABA/glycinergic. The GiV and GiA neurons of this relay project to spinal and brainstem motor neurons (Fig. 2, Pathway 20, REM-On; Chase *et al.* 1984, 1986; Holstege & Bongers, 1991; Castillo *et al.* 1991*a*; Kato *et al.* 2006) and when stimulated (electrically or pharmacologically; Chase *et al.* 1984, 1986; Soja *et al.* 1987*b*; Lai & Siegel, 1988; Castillo *et al.* 1991*a*,*b*; Holstege & Bongers, 1991; Kodama *et al.* 2003; Kato *et al.* 2006; Lai *et al.* 2010) produce short latency glycinergic IPSPs in postsynaptic motor neurons and evoke release of glycine – and possibly GABA – in the spinal ventral horn (Chase *et al.* 1986; Soja *et al.* 1987*b*; Lai & Siegel, 1988; Castillo *et al.* 1991*b*; Kodama *et al.* 2003; Lai *et al.* 2010). Consistent with this model, glutamate release within the ventromedial medulla increases as animals enter REM sleep (Kodama *et al.* 1998). In addition, endogenous blockade of glutamatergic signalling onto these neurons reverses spinal postural muscle atonia during carbachol-induced REM sleep (Lai & Siegel, 1988), suggesting that glutamatergic input, likely to be from the SLD, is required for the ventromedial medulla pathway to produce muscle atonia.

One challenge to this model is the finding that elimination of glutamate but not GABA/glycine transmission from medullary neurons at the level of the inferior olive or supraolivary medulla (see Fig. 2, Pathways 18 and 22, REM-On) results in muscle twitches during REM sleep atonia (Vetrivelan *et al.* 2009). These findings raise the possibility of an additional medullary relay, excitatory rather than inhibitory, which the authors hypothesized may project to inhibitory spinal interneurons (Takakusaki *et al.* 2001, 2003). These results also emphasize the importance of the need for greater anatomical precision in defining the rostral–caudal level of the medulla in REM sleep atonia control. For example, GABA/glycine neurons that project to the ventral spinal horn are relatively sparse at the caudal ventromedial medulla compared to levels rostral to the inferior olive (Hossaini *et al.* 2012). Hence the putative GABA/glycine REM sleep inhibitory region of the medulla is likely to be more rostral to the level that was previously studied (Vetrivelan *et al.* 2009), near the rostral inferior olive. This putative GABA/glycine population also receives SLD projections but may directly target and inhibit spinal motor neurons.

Taken together, transection, lesion and recording experiments indicate a medullary inhibitory zone within the VMM near the rostral inferior olive that includes GiA, GiV and LPGi cell groups (Fig. 2, Pathways 16 and 20, REM-On). This zone contains glycinergic and possibly GABAergic pre-motor neurons (Boissard *et al.* 2002; Morales *et al.* 2006; Sapin *et al.* 2009). During REM sleep SLD neurons activate these medullary neurons, which then directly inhibit spinal motor neurons to maintain muscle atonia (Siegel, 2011; Luppi *et al.* 2012; Chase, 2013). Cell groups rostral to this zone are likely to not be involved in REM sleep atonia (Sastre *et al.* 1981; Lu *et al.* 2006), as even large cell-body lesions do not significantly disrupt REM sleep atonia. In contrast, cells caudal to this zone may regulate twitching and other motor movements in REM sleep using glutamatergic signalling (Fig. 2, Pathways 18 and 22, REM-On; Vetrivelan *et al.* 2009).

In addition to its role as a relay within a feed-forward model of atonia, i.e. SLD→VMM→spinal ventral horn, the medulla may play an active role in shaping REM sleep generation and, ultimately, motor control. Moreover, the medulla's inhibitory influence may depend on reciprocal interaction between medullary and pontine REM sleep centres. For example, loss of rostral brainstem innervation of the medulla due to experimental transection prevents the motor suppression evoked from medial medulla stimulation (Siegel *et al.* 1983). Specifically, pontine inhibition reduces the medulla's ability to suppress muscle activity (Kohyama *et al.* 1998) and inactivation of the pons blocks medullary-induced muscle tone suppression in the decerebrate cat, suggesting that medulla activity alone is insufficient to generate REM sleep atonia. While medullary activity may normally depend on pontine activity, these studies raise the additional possibility that VMM control of muscle suppression or REM sleep altogether acts via ascending drive to the SLD and other rostral brainstem areas. In this model, REM sleep and atonia generation is initiated in the medulla, rather than the SLD, and atonia is achieved via ascending projections to the SLD. Several lines of evidence support this alternative model. First, large SLD lesions reduce, but do not eliminate, REM sleep, suggesting a supplementary or alternative circuit capable of generating REM sleep (Lu *et al.* 2006), perhaps in the medulla (Weber *et al.* 2015). Second, investigations into the projection from the medial medulla to the spinal cord motoneurons and interneurons have not revealed a robust mechanism for transmission of the inhibitory atonia signal (Takakusaki *et al.* 1989). Third, numerous imaging studies of humans with RBD have documented lesions mostly in the pontomedullary junction, rather than the ventral medulla (Scherfler *et al.* 2011; St Louis *et al.* 2014, McCarter *et al.* 2015). While none of these lines of evidence is conclusive, they raise the possibility of an alternative to the linear, feed-forward model. Further investigations that identify the critical neurons, their neurochemistry and their interactions with pontine REM sleep-promoting structures will help define the respective roles of the medulla and pons in REM sleep and atonia generation.

REM atonia at the level of the motor neuron

A series of studies in the 1960s were the first to implicate inhibitory supraspinal inputs in spinal cord motor neuron inhibition (Giaquinto *et al.* 1964*b*; Gassel *et al.* 1965). Later in the 1970s and 1980s a series of seminal intracellular recording studies – which informed the development of the REM-On glycinergic pre-motor neuron model – were conducted that measured the membrane potential of motor neurons during naturally occurring REM sleep (Giaquinto *et al.* 1964*a*; Morales & Chase, 1978; Nakamura *et al.* 1978; Chase *et al.* 1980; Glenn & Dement, 1981*b*). These studies found that, at the onset of REM sleep, spinal postural and cranial orofacial motor neurons receive large-amplitude glycinergic IPSPs that hyperpolarize their membrane potential (~ -10 mV). This hyperpolarized state is maintained for the entirety of the REM periods whereas the membrane of the motor neurons repolarizes upon awakening (Fig. 2, Pathways 20 and 21, REM-On). Juxtacellular microiontophoretic application of strychnine, but not $GABA_A$ antagonists, blocks these large-amplitude REM-On IPSPs and prevents REM membrane hyperpolarization of spinal motor neurons (Glenn & Dement, 1981*a*; Morales & Chase, 1982; Morales *et al.* 1987; Chase *et al.* 1989; Soja *et al.* 1991). These same glycinergic IPSPs were also observed during pharmacologically induced REM sleep (i.e. injections of carbachol or bicucculine in the PnO/peri-LCα) as well as following electrical stimulation of the ventromedial medulla (Chase *et al.* 1986; Soja *et al.* 1987*b*, Kohlmeier *et al.* 1996; Xi *et al.* 2001). And, as indicated, focal disruption of spinal ventral horn glycinergic/GABAergic transmission results in aberrant phasic activity during REM sleep (Krenzer *et al.* 2011). Taken together, these findings provide strong support for a motor-inhibition model in which postsynaptic inhibitory drive to spinal postural and possibly brainstem motor neurons, be that during natural or pharmacologically induced REM sleep, is primarily mediated by glycine synaptic transmission. However an important consideration, which may link to technical limitations for the spinal postural system, is that direct evidence that these glycine-mediated IPSPs are responsible for motor atonia is lacking.

To the extent that the 'glycinergic' model has provided an important framework for understanding the pathophysiology of a wide range of REM-based disorders, there have been two notable challenges to this model (Soja *et al.* 1987*a*; Brooks & Peever, 2008*a*). Soja *et al.* found that strychnine applied onto the trigeminal motor nucleus has only a small effect in reactivating the masseteric reflex during REM sleep. In the case of Brooks and Peever, reverse microdialysis was used to apply glycinergic and $GABA_A$ antagonists onto trigeminal motor neurons during wakefulness, SWS and REM sleep, revealing a tonic glycinergic/GABAergic drive during wakefulness and SWS that was, surprisingly, absent during REM sleep. This finding was unexpected and essentially refuted two decades of results obtained with intracellular recordings of spinal and brainstem motor neurons (Chase, 2013). A lively and energetic discussion ensued (Berger, 2008; Chase, 2008, 2009; Funk, 2008; Kubin, 2008; Lydic, 2008; Soja, 2008; Brooks & Peever, 2008*b*). More recently Brooks and Peever revised their initial model to incorporate multiple receptors, including $GABA_A$, $GABA_B$, glycine, glutamate and noradrenaline, as being involved in the inhibition and disfacilitation of cranial orofacial motor neurons to trigger REM sleep muscle atonia (Brooks & Peever, 2012; Schwarz *et al.* 2014).

In addition to direct inhibition, a disfaciliation mechanism has been proposed to explain REM-related suppression of motor neuron activity. The disfacilitatory mechanism was first described in cranial respiratory muscles (Kubin *et al.* 1992, 1998), and invoked the silencing of brainstem noradrenergic and serotoninergic neurons during REM sleep in the reduction of excitatory drive to motor neurons. In 1993, Kubin *et al.* proposed that cranial respiratory and spinal postural motor activity may be differently regulated during REM sleep. More specifically, Kubin *et al.* postulated that inactivation of monoaminergic systems was responsible for the suppression of cranial respiratory muscles (disfacilitation) whereas activation of glycinergic input was responsible for suppression of spinal motor neurons (direct inhibition; Kubin *et al.* 1993). In 2001 this hypothesis was challenged by the finding that a significant and similar reduction of noradrenaline and serotonin release occurs in both the hypoglossal nucleus and spinal cord when motor atonia is induced, suggesting that disfacilitation contributes to muscle atonia in both systems (cranial respiratory and postural muscles; Lai *et al.* 2001). In general support of a contributing disfacilitatory mechanism for REM sleep atonia of spinal postural muscles, noradrenaline and serotonin excite spinal motor neurons through $\alpha 1$ and $5HT_2$ receptors (White *et al.* 1991, 1996). The observed silencing of LC neurons and reduction in firing of DRN neurons during cataplexy (Wu *et al.* 1999; John *et al.* 2004*a*) also suggests an important contribution of monoaminergic excitation of motor neurons for the maintenance of postural tone; however, monoaminergic involvement in preventing cataplexy may still be mediated through other nodes rather than through direct spinal control. For example, recent studies have shown that disfacilitation of brainstem motor neurons from excitatory noradrenergic drive is insufficient to trigger atonia in postural muscles during REM sleep (Schwarz *et al.* 2014).

Also, as indicated, the medullary brainstem contains cholinergic neurons (Armstrong *et al.* 1983) that may be REM-On (Holmes & Jones, 1994; Volgin *et al.* 2008; Grace *et al.* 2013). These neurons, in fact, directly innervate the facial, trigeminal and hypoglossal motor neurons (Fort

et al. 1989, 1990; Travers *et al.* 2005) and therefore they could inhibit the pharyngeal motor neurons directly (Liu *et al.* 2005; Grace *et al.* 2013), although this has not been definitely demonstrated. In summary, the action of multiple neurotransmitters (i.e. glycine, GABA, monoamines, acetylcholine) may be required for complete REM sleep atonia, with direct inhibition of motor neurons being the most important synaptic mechanism mediating REM atonia of the postural muscles.

Cranial respiratory muscles also undergo REM sleep suppression of activity, with the genioglossus (GG) muscle of the tongue arguably showing the most dramatic suppression of activity (Horner, 2009). Work by several groups employing drug delivery via microdialysis while measuring GG activity has concluded that, unlike postural muscles, suppression of glycinergic and $GABA_A$ transmission contributes minimally to suppression of GG activity during REM sleep (Kubin *et al.* 1993; Morrison *et al.* 2003*a*). And further upstream, the reduction of activity in hypoglossal neurons controlling GG, and perhaps all cranial respiratory motor neurons, is thought to be mediated by noradrenergic and glutamatergic disfacilitation (Lai *et al.* 2001; Fenik *et al.* 2005*a*; Steenland *et al.* 2008*b*). Yet, interestingly, application of an α1-adrenoceptor agonist onto the hypoglossal motor pool fails to reactivate GG activity (Chan *et al.* 2006) suggesting that, in addition to a disfacilitation mechanism, a powerful inhibitory mechanism is operative. A competing hypothesis is that hypoglossal motor neurons are directly inhibited during REM sleep by cholinergic, GABAergic and/or glycinergic signals (Brooks & Peever, 2010; Grace *et al.* 2013; Fung & Chase, 2015). Intracellular recordings have demonstrated that during the transition from SWS to REM, hypoglossal motor neurons start receiving large-amplitude IPSPs, likely to be mediated by glycine release, and that they become hyperpolarized, as is seen in spinal and brainstem motor neurons (Fung & Chase, 2015). These recording studies therefore suggest an active inhibition *vis a vis* glycinergic inputs. However, blocking GABAergic and glycinergic transmissions in the hypoglossal motor neurons only partially increases GG activity during REM sleep (Kubin *et al.* 1993; Morrison *et al.* 2003*a*,*b*). On the other hand, blocking cholinergic transmission fully restores GG activity to SWS levels (Grace *et al.* 2013), suggesting that cholinergically mediated inhibition of hypoglossal motor neurons is principally responsible for the suppression of GG activity during REM sleep. Taken together, experimental findings support a coordinated role for disfacilitation and direct inhibition by acetylcholine in the suppression of GG activity during REM sleep.

Across REM sleep, tonic muscle atonia is periodically interrupted by a volley of muscle twitches and jerks, i.e. phasic activity. This myoclonic activity is mediated by a glutamatergic input and by the activation of AMPA postsynaptic glutamate receptors in spinal postural and cranial orofacial motor neurons (Chase & Morales, 1982, 1983; Soja *et al.* 1995; Burgess *et al.* 2008). Importantly, blockade of glutamatergic transmission also reduces muscle tone during wakefulness to levels measured during SWS, and has no effect on tonic EEG activity during SWS and REM sleep, indicating that muscle tone is maintained by a glutamatergic drive only during wakefulness. Moreover, application of glutamatergic agonists during REM sleep does not reverse muscle atonia, confirming that REM atonia is not the result of disfacilitation from a glutamatergic excitatory input. The lack of response to glutamate agonists also strongly suggests that motor neurons are actively inhibited during REM sleep (Berger, 2008; Funk, 2008).

Conclusion

Elucidating the synaptic and cellular mechanisms mediating REM sleep atonia continues to be an important experimental pursuit and may have clinical implications reaching far beyond that of treating RBD, cataplexy and sleep disordered breathing. For example, in Parkinson's with RBD, restoration of normal motor control can occur during REM sleep (De Cock *et al.* 2007). Elucidating the 'circuit basis' for this intriguing if puzzling observation may therefore inform a novel therapeutic approach for treating the motoric dysfunction of PD. We moreover propose that newer genetically driven techniques (Adamantidis *et al.* 2007; Anaclet *et al.* 2014, 2015; Xu *et al.* 2015) can and should be employed to fill the existing knowledge gaps. For example, acute inhibition of genetically defined pontine or medullary cell groups or their terminal fields during REM sleep would facilitate a more complete understanding of the roles of specific cell groups in mediating motor atonia, as well as help clarify the synaptic mechanisms, e.g. disfacilitation *versus* inhibition, by which motor neurons, be they spinal postural, cranial orofacial or cranial respiratory, are themselves suppressed.

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Additional information

Competing interests

None declared.

Author contributions

All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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