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PERSPECTIVES

Cholinergic involvement in control of REM sleep paralysis

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REM sleep, also known as dreaming sleep, is marked by intense cortical activation and absence of skeletal muscle tone, so-called REM sleep paralysis (atonia). It is commonly believed that REM sleep paralysis functions to prevent movement during vivid dreams. Indeed, REM sleep behaviour disorder – a neurological condition marked by violent dream enactment – results from loss of REM sleep paralysis. For the last 50 years, biologists have focused on the identification of brain mechanisms responsible for REM sleep. A majority of evidence suggests that a brainstem region known as the sublaterodorsal nucleus (SLD), also called the subcoeruleus, is important for REM sleep generation (Jouvet 1962). However, there is uncertainty concerning the chemical mechanisms by which the SLD triggers REM sleep phenomena. For example, some data suggest that cholinergic modulation of SLD cells underlies REM sleep generation, whereas, other data suggest that GABAergic disinhibition and glutamatergic excitation of SLD cells are critical for REM sleep control (Boissard *et al.* 2002; Lu *et al.* 2006). The recent study by Weng *et al.* (2014) provides a potentially new framework for understanding REM sleep control by showing that both cholinergic and glutamatergic processes operating within the SLD could be important for triggering REM sleep paralysis.

The SLD contains cells that are crucial for generating REM sleep paralysis. Pharmacological and electrical activation of SLD neurons produces a REM-like sleep state that is characterized by muscle paralysis and cortical activation. In contrast, SLD lesions produce REM sleep without atonia in animals, and neurodegeneration of the SLD region is associated with REM sleep behaviour disorder in humans. REM sleep-active SLD neurons are glutamatergic and are thought to induce REM paralysis by activating GABA and glycine-containing neurons in the ventromedial medulla and spinal cord, which in turn trigger motor atonia by inhibiting skeletal motoneurons (Boissard *et al.* 2002). During REM sleep, acetylcholine is thought to participate in the activation of these descending atonia pathways. For example, application of cholinergic agonists into the SLD can induce long-lasting periods of cortical activation and muscle paralysis (Steriade & McCarley, 2005). Nevertheless, not all experimental interventions produce this same effect. In fact, cholinergic stimulation of the SLD can also induce prolonged bouts of wakefulness (George *et al.* 1964). Taking these contradictions to heart, Weng and co-workers set out to understand better how cholinergic mechanisms regulate REM sleep paralysis at the level of the SLD.

Because the SLD contains a heterogeneous pool of neurons that mediate a range of behaviours, Weng and co-workers developed a new approach for studying how cholinergic mechanisms affect the function of spinally projecting SLD neurons specifically. They did this by retrogradely labelling SLD neurons from the spinal cord and then used *in vitro* electrophysiology (i.e. patch clamp recordings) to characterize how cholinergic drugs (e.g. carbachol) influence their activity. This approach provides a powerful tool for determining how (or if) cholinergic mechanisms contribute to the control of REM sleep paralysis.

The authors made several important observations that will probably affect the way sleep biologists understand REM sleep control. First, they found that spinally projecting SLD cells are excited by carbachol *in vitro* (a cholinergic receptor agonist) (Fig. 1). This observation is important because it indicates that acetylcholine could trigger REM paralysis by directly activating SLD neurons *in vivo*. Next, they found that carbachol increases the frequency of glutamatergic EPSCs on to SLD neurons. Although they did not identify the source of these glutamatergic inputs, this finding is none the less important because it suggests cholinergic mechanisms regulate REM sleep paralysis by controlling the glutamatergic drive at the SLD (Fig. 1). Lastly, Weng *et al.* (2014) demonstrate that both the pre- and postsynaptic effects of carbachol are mediated by co-activation of M1 and M3 muscarinic receptors. Together, these results are important because they suggest that REM sleep paralysis may be driven by a cholinergic mechanism that acts at both the level of SLD neurons themselves, and at the glutamatergic inputs terminating on SLD cells (Fig. 1).

In summary, the study by Weng *et al.* (2014) establishes proof-of-principle of a cholinergic mechanism mediating sleep paralysis whereby acetylcholine activates spinally projecting SLD neurons directly as well as indirectly through amplification of glutamatergic drives. Validation of this mechanism as well as determination of the necessary involvement of acetylcholine in other aspects of REM sleep generation will require *in vivo* studies. Existing *in vivo* evidence neither confirms nor refutes the

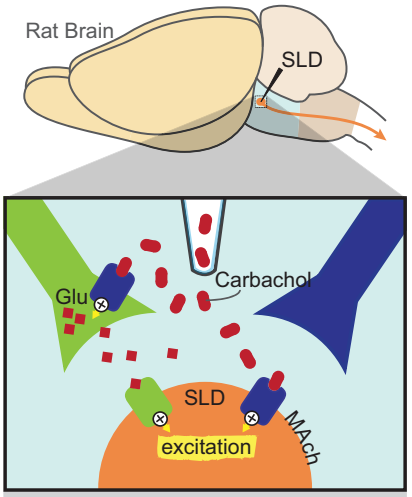

Figure 1. Involvement of cholinergic neurotransmission in REM sleep paralysis
Pathways mediating excitation of SLD neurons by exogenous cholinergic stimulation as identified by Weng *et al.* Glu, glutamate; MAch, muscarinic acetylcholine receptor; SLD, sublaterodorsal nucleus.

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involvement of SLD cholinergic neurotransmission in producing REM sleep or its component phenomena. Future studies should aim to block cholinergic neurotransmission in the SLD and/or selectively inactivate REM sleep-active cholinergic inputs to the SLD (e.g. pedunculopontine and laterodorsal tegmental nuclei). Furthermore, combining these interventions with simultaneous modulation of other neurotransmitter systems could be used to reveal neuromodulatory interactions that are important for REM sleep control. Ultimately, developing an inclusive theory of REM sleep generation requires that sleep biologists identify how complex interactions between multiple neurotransmitter systems, including GABAergic, glutamatergic and cholinergic circuitry give rise to REM sleep. Therefore, by characterizing the stimulatory effects of acetylcholine on neural activity and glutamatergic neurotransmission in the SLD, the study by Weng *et al.* (2014) stands as a significant contribution to the field of sleep neurobiology.

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Additional information

Competing interests

None declared.