Title: Optogenetic dissection of the neurobiological mechanisms generating muscle atonia during REM sleep in mice

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Team Research: SLEEP
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Context: Basic sleep research and animal models of sleep pathologies

Abstract / objectives: Sleep encompasses two distinct entities, slow wave sleep and REM sleep (also coined paradoxical sleep). REM sleep is characterized by a generalized atonia of the skeletal musculature, associated to cortical activation and phasic rapid eye movements. A major disabling sleep disorder (REM sleep behavior disorder, RBD) is directly related to an abnormal maintenance of muscle tonus with violent motor behaviors during PS. While these symptoms are quite well described, the underlying neurobiological mechanisms remain to be elucidated. It is therefore of clinical relevance to understand in rodents the anatomical and functional organization of the neuronal network mediating the natural PS muscle atonia. In this scientific context, our team recently achieved a breakthrough in the anatomy / neurochemistry of networks responsible for PS-related atonia. Based on data collected in rats over the last decade, we now propose a new functional model assigning to brainstem glutamatergic and GABAergic neurons a central interactive role in basic mechanisms generating REM sleep. In particular, we identified REM sleep-
on (specifically active during REM sleep) glutamatergic neurons located in a dorsal pontine nucleus (sublaterodorsal tegmental nucleus, SLD). These neurons may generate muscle atonia through projections to another contingent of REM sleep-on neurons located in the ventro-medial medullary reticular formation (GiV) and expressing GABA/glycine inhibitory neurotransmitters. In our model, the later neurons mediate the well-demonstrated REM sleep-dependent hyperpolarization of all brainstem-spinal somatic motoneurons. However, direct functional demonstration is still lacking. The recent development of optogenetic tools, allowing the control of the firing activity of genetically-targeted neurons with unprecedented temporal and spatial resolutions, offers an exceptional opportunity to fill this gap. Our experimental strategy will consist to evaluate the effects on muscle tone and motor behaviors of the optogenetic manipulation during REM sleep of glutamatergic SLD neurons in transgenic mice. At the experimental level, archaerhodopsins (inhibitory when illuminated by green/yellow laser light) will be transfected in the SLD neurons of vGluT2-Cre transgenic mice by means of engineered adenoviral factors. These treated mice will be then prepared for polygraphic recordings combined to video and laser stimulation through optic fibers chronically implanted above either the transfected SLD cell bodies or their parent efferent axons within GiV. This technologically ambitious project is a crucial step for the understanding of basic mechanisms responsible for atonia during REM sleep. Besides, the optogenetic validation of a murine model for RBD would open up new paths for developing targeted pharmacological treatments or newly designed therapies.

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Main recent publications and chapters


