The stuff dreams are made of: anatomical substrates of REM sleep

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Exactly how animals switch between different sleep states remains unknown. A new study in *Nature* provides a glimpse into the mechanisms and anatomy of the brain regions that trigger rapid eye movement sleep.

Where do dreams come from? Why do we dream? A recent paper[1] brings us closer to answering the first question, although the answer to the second question remains elusive.

Rapid eye movement (REM) sleep was discovered in 1953. Its hallmarks are periods of rapid eye movements, low-voltage electroencephalogram (EEG) and muscle tone suppression that recur throughout the night in a 90-minute rhythm (in humans) and are accompanied by dreams. A physiologically identical state is present in most mammals[2]. Less elaborate dreams can occur in non-REM sleep as well.

In the new paper, Lu *et al.*[1] combine studies of neuronal activation, staining for the protein encoded by the immediate-early gene *c-fos*, identification of the neurotransmitters of activated cells and brain lesions to determine the dynamics of the regulation of the REM sleep–generating system in the rat. Work in the cat[3,4] has defined the location of 'REM sleep–on' neurons, cells selectively active during REM sleep and believed to trigger this state. These cells are concentrated in the brainstem ventral to the locus coeruleus, in a region known as the subcoeruleus. Damage to this area reduces or disrupts REM sleep. The new paper[1] and previous work[5] in the rat show that REM-on cells are found in the sublaterodorsal (SLD) nucleus (analogous to the subcoeruleus region in the cat) and also in a region just rostral to the locus coeruleus[1]. These findings suggest a universal localization of the REM-on region in mammals (**Fig. 1**). The brainstem location of the REM sleep–generating mechanism[3] indicates that REM sleep may have evolved primarily in service to the brainstem, with any forebrain functions having developed relatively recently.

Injection of glutamate agonists or GABA antagonists into the rat SLD can trigger elements of REM sleep, but not the rapid eye movements and erections that normally accompany this state[5]. Lu *et al.*[1] show that damage to the SLD decreased daily REM sleep amounts. They also report that damage to the putative REM sleep–off region in the lateral pontine tegmentum and ventral periaqueductal gray doubled the daily amount of REM sleep.

On the other hand, lesions of the noradrenergic, serotonergic and pontine cholinergic cell groups did not affect daily REM sleep time in this study, contrary to some previous work. Starting in 1970, researchers had proposed that an inhibitory interaction between cholinergic and monoaminergic cell groups was responsible for the generation of REM sleep[6]. The recent papers[1,5] largely abandon both the monoaminergic and cholinergic cell groups in their models of REM sleep control. Although previous lesion work in the cat had also suggested that monoaminergic cells were not essential for the generation of REM sleep, it may be too early to dismiss the possibility of a role for monoaminergic cells in the modulation of REM sleep[3]. Before relegating acetylcholine to a minor role in REM sleep control in the rat, it would be useful to determine whether acetylcholine is selectively released in the SLD and caudal medulla regions during natural REM sleep in the rat, as it is in the cat[7].

Substituting for acetylcholine and norepinephrine in the model proposed by Lu *et al.*[1] is a mutually inhibitory interaction between GABAergic and glutamatergic cells in both the REM-on SLD and REM-off lateral pontine and ventral periaqueductal gray regions. This is posited to create a bistable switch that causes a rapid transition into REM sleep by activating REM-on cell groups and inactivating REM-off cell groups. This switch maintains the stability of this state until it is somehow turned off. However, in the rat, the transition of monoaminergic, cholinergic and other neuronal activity and EEG from the non-REM to REM sleep pattern typically takes 30 seconds[8]. In the cat, this transition lasts approximately 5 minutes[9]. It remains to be determined how the hypothesized flip-flop of activity in cell groups separated by only millisecond conduction delays can account for this slow transition.

Although it is well known that the forebrain is not required for REM sleep generation, these results do not exclude a role for the forebrain in

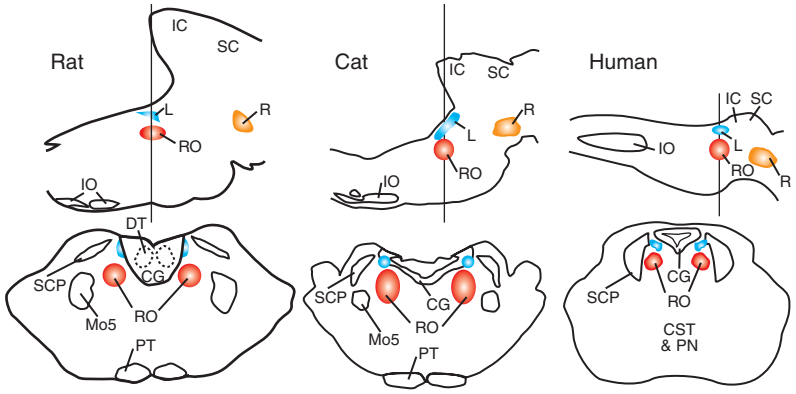

Figure 1 Location of the "REM sleep-on" (in red) regions in the rat and cat, and speculation on the likely location of the same region in humans. The top panel shows a sagittal view, and the bottom panel a coronal view. Regions containing these REM sleep-on neurons are located ventral to the locus coeruleus (in blue), and are thought to project rostrally to induce the EEG changes and alterations of consciousness, and caudally to produce the suppression of muscle tone and autonomic changes characteristic of REM sleep. CST, corticospinal tract; DT, dorsal tegmental nucleus; CG, central gray; IC, inferior colliculus; IO, inferior olive; L, locus coeruleus (blue); Mo5, motor nucleus of the trigeminal; PN, pontine nuclei; PT, pyramidal tract; R, red nucleus; RO, REM-on cell region (red); SC, superior colliculus; SCP, superior cerebellar peduncle. Note that differences in the size of the LC and RO in the figure may reflect differences in techniques used and relative size of other structures, rather than species differences.

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REM sleep control in the intact animal. When the connections between the pons and forebrain are severed, the pons and medulla alone can generate a REM sleep state, whereas no REM sleep is seen in the forebrain. Conversely, when the pons is connected to the forebrain and all connections between it and the medulla are severed, a REM sleep state is observed in the forebrain, but no such state is found in the medulla[3]. Lu *et al.*[1] identify the extended part of the ventrolateral preoptic nucleus in the hypothalamus[10] as a region that can inactivate the lateral pontine and ventral periaqueductal gray REM-off regions, thereby releasing the SLD REM-on region from inhibition and triggering REM sleep. In opposition to this inhibition of REM-off cells, they propose that the hypocretin neurons of the hypothalamus, which are active during certain waking behaviors but inactive in REM sleep[11], project to the same REM-off neurons, but because hypocretin is excitatory, block REM sleep.

An understanding of REM sleep control is central to an understanding of sleep disorders, particularly the pathological signs seen in narcolepsy. Narcolepsy is characterized by excessive daytime sleepiness and sudden losses of muscle tone in alert waking (cataplexy), caused, in at least most cases, by a loss of hypocretin cells[12]. Lu *et al.*[1] explain aspects of this syndrome, particularly the relatively rapid onset of REM sleep in these patients during sleep periods, in terms of the instability of the flip-flop switch. However, this does not completely explain cataplexy. In the normal individual, all noradrenergic locus coeruleus and histaminergic cells are active in waking and inactive in sleep, particularly in REM sleep. In cataplexy, the loss of the excitatory hypocretin input that maintains noradrenergic activity during certain emotions allows noradrenergic activity to cease in waking, while histaminergic activity persists[13]. The disfacilitation of motoneurons resulting from the loss of noradrenergic input contributes to the loss of muscle tone, whereas the maintained discharge of histamine cells allows maintenance of consciousness, the defining criteria of cataplexy.

Neuronal recording studies in the cat and dog have identified a population of neurons in the medial medulla of the cat and dog that are active only during periods of muscle tone suppression[14], that is, REM sleep and cataplexy. Stimulation of these cells suppresses muscle tone by release of GABA and glycine, and lesioning this region reduces the normal muscle tone suppression of REM sleep[3]. Activity in this inhibitory cell group is synaptically linked to inactivity in locus coeruleus cells, which when active help maintain muscle tone[3,13,14]. Lu *et al.* find that large medullary lesions do not prevent muscle tone suppression in the rat, so they hypothesize that direct connections from the pons to glycinergic interneurons in the ventral horn are responsible for muscle tone suppression in the rat. This could represent a species difference between dogs, cats and rats. However, previous work[5] identified projections in the rat from the SLD to the same medial medullary regions identified in the cat and dog. The lesion placement by Lu *et al.* (see Fig. 4d in their paper) is rostral to the region that other studies have identified as the medullary relay for muscle tone suppression[15]. Therefore, it remains possible that the medullary inhibitory region is similar in the rat, cat and dog.

Finally, there is the question of "why do we dream," or the physiological correlate of the question, "why do we have REM sleep?" Although physiologists have made considerable progress in localizing the cells critical for REM sleep control, we have not yet been able to use this knowledge to answer the fundamental question of why this state exists. The search for the control of REM sleep can become an infinite regression; if REM-on cells trigger REM sleep, then what triggers or disinhibits the REM-on cells? What then controls this latter cell population? One would like to see evidence that REM sleep is initiated to accomplish some task and terminated when that task is completed. Many ideas for the nature of this task have been offered, from brain warming, to the upregulation of certain classes of receptors, to arousal to allow surveillance of the environment[2]. The discovery of the ultimate driving mechanism(s) of REM sleep will undoubtedly be facilitated by studies in the rat using these pioneering techniques[1,5].

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More neurons may not make you smarter

The hippocampus continues to add new neurons even in adulthood. When animals are housed in 'enriched' or stimulating environments with opportunities for exercise and/or games, they show greater neurogenesis in the hippocampus. Animals exposed to these more complex cages also show improvements in several tasks of memory and anxiety.

A study by René Hen and colleagues on page 729 reports, however, that there is no link between the increased neurogenesis that comes with enriched environments and improvements in the memory tasks. The authors used a focused dose of radiation to prevent neurogenesis selectively in the hippocampus of mice before placing them in enriched cages. When tested six weeks later on an anxiety and spatial memory task, these animals still did better than animals housed in standard cages, suggesting that the lack of neurogenesis did not matter to their learning ability.

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