Although frazzled new parents may beg to differ, infants do sleep more than adults. This sleep pattern is seen in a wide variety of mammalian species, with some obvious selective advantages. Sleep is a time of reduced body and brain metabolic rate [1,2], allowing energy conservation, particularly if a warm place is available, as can be provided by a compliant parent or sibling. The sleeping, quiescent infant is also less likely to attract predators and is easier to transport. At the earliest ages, infants who have not yet opened their eyes and whose cortex is not yet developed have limited learning opportunities from interactions with the outside world: another reason for reduced waking.

But sleep comes in many forms. Evolutionary arguments may make sense for slow-wave sleep. Sleep patterns at birth that are associated with a general shutdown of the brain, but may not provide such an obvious explanation for the relative predominance of rapid eye movement (REM) sleep. For example, in human neonates REM sleep constitutes approximately eight hours per day, or 50% of the total sleep time, whereas human adults devote less than two hours per day, or 20% of their seven to eight hours of sleep time, to REM sleep [3]. REM sleep is characterized by high brain metabolic and neuronal activity rates [4], reduced muscle tone, irregular and relatively automatic respiration uncoupled from its usual regulatory mechanisms [5], and diminished thermoregulation [6]. These properties seem maladaptive, which suggests that there must be some compensatory survival benefit for REM sleep to have persisted. Could REM sleep play a particularly important role in development?

Interesting evidence for this hypothesis has come from studying the effects of REM sleep deprivation on the development of the visual system. It is known that the occlusion of one eye during the maturation of visual connections that occurs after birth causes the open eye to acquire more central connections than the closed eye. This disproportionate representation seems to result from a difference of activity in the optic nerve between the open eye and closed eye [7]. Although early ideas that REM sleep was necessary for brain plasticity might suggest that REM sleep deprivation would prevent this reorganization, just the reverse occurs. REM sleep deprivation accelerates the shift of connections to favor the open eye [8,9]. Rather than facilitating change [10], REM sleep may therefore be a source of endogenous activity that tends to prevent altered sensory stimulation from causing abnormal connections to form. REM sleep may prevent the programmed cell death and the pruning of connections that occurs when critical synapses are not stimulated.

Another possible role for neonatal REM sleep might be in thermoregulation of the growing brain. It is known that nonREM sleep tends to cool the brain, reducing its thermoregulatory set point [11]. In contrast, REM sleep tends to heat certain brain regions [12]. The nonREM–REM alternation comprises a thermoregulatory oscillation.

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Abbreviation: REM, rapid eye movement

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It is often assumed that the amount of time spent in different sleep states is determined by processes controlled by the cerebral cortex. The emphasis on the cortical role in sleep may result more from the technical ease of recording electroencephalograms from the cortex than from persuasive functional evidence. At birth, cortical metabolism and neuronal firing are minimal [13], yet this is the time of greatest sleep. In adults, damage to the cortex produces little or no change in sleep, indicating that the signal for sleep does not originate in or at least does not require the cortex [14]. Animals with proportionally larger cortices do not have more REM or nonREM sleep time than animals with relatively little cortex [15]. The effects of long-term sleep deprivation have been shown to be largely autonomic in nature, including elevated body temperature, skin lesions, and increased food intake [16]. Such effects cannot be duplicated by any cortical lesions. However, many of these symptoms appear to be consistent with hypothalamic dysfunction [17,18].

Evolutionary evidence also suggests that the cortex may be a relatively recent participant in REM sleep. Plesiomorphic (primitive) mammals such as the egg-laying echidna and platypus have large amounts of REM-sleep-like activity in brainstem structures at birth [19,20]. The brainstem is the key region for REM sleep generation, being both necessary and sufficient for its occurrence [4]. However, the cortex of these animals scarcely changes activity during these states, showing slow-wave patterns during the REM sleep state. In this respect the sleep of placental mammals may represent ontogeny recapitulating phylogeny, since a reduction in electroencephalogram power is a late-developing component of REM sleep.

A prominent feature of REM sleep is the rapid eye movements and associated twitches that define the state. These are particularly marked and vigorous in neonates. It has been shown that twitches with some resemblance to REM sleep activity are present in the isolated spinal cord of neonates and diminish in the transected cord of older animals [13]. This has suggested to some that a primate phasic activity of the central nervous system transforms postnatally over an extended time period into the very different brainstem-generated pattern seen in adults. But in this issue of PLoS Biology, Karlsson et al. [21] show that this is not the case. In a set of technically demanding experiments, they demonstrate a remarkable similarity between sleep control mechanisms in the one-week-old rat and those in the adult cat, and by implication throughout the mammalian line.

By severing the connections to and from the forebrain (cerebral cortex and associated structures), Karlsson et al. were able to study sleep-related activity in the midbrain and brainstem. They described the rat homologs of the medullary neurons that induce the atonia seen in sleeping adult cats and narcoleptic dogs [22,23,24] (Figure 1). More rostrally, they identified neural activity in the region of the locus coeruleus that facilitates movement and report contrasting inhibitory activity in the adjacent subcoeruleus region, again paralleling studies in the cat [25,26,27]. They also found cells that appear to generate or at least contribute to the twitches of REM sleep.

The similarities to the adult cat’s REM sleep control mechanisms are so striking that what becomes interesting are the small differences that are reported. The locus coeruleus REM “sleep-off cells,” which are active in waking, reduce activity in nonREM sleep, and cease activity in REM sleep, appear to not have long-duration waveforms in the neonatal animals examined by Karlsson et al., unlike the case of the adult rat and cat [28,29]. Another difference is the apparent absence of the cessation of dorsal raphe (serotonin) unit discharge in REM sleep. Although the authors speculate that this is due to the absence of forebrain connections in their experimental preparation, it has been shown that forebrain mechanisms are not necessary for this cessation of raphe activity in adult cats [30]. However, identification of the narrow dorsal raphe nucleus is difficult even in adult cats, and it is certainly possible that these neurons were overlooked in the neonatal rat.

The upshot of these findings is a picture of a largely mature REM sleep generator mechanism at birth. The developmental progression of REM sleep signs, particularly the reduction in sleep duration and the development of the characteristic reduction in electroencephalogram voltage to a waking-like pattern in REM sleep, may result from the maturation of the targets of these brainstem systems, the modulation of these generator mechanisms by developing systems, or a relatively subtle maturing of connections within the REM sleep generator systems. This work pushes the probable organization of the REM sleep generator system in rats back to before one week of age, possibly to an in utero stage.

What does all this say about the function of REM sleep? Although we are left with the same initial speculations, the neonatal model provides a different perspective for approaching these functions. It is particularly useful to know that key elements of the REM sleep system are present in neonatal rats, since these animals are ideal subjects for in vitro studies of tissue slices [31,32]. It is not practical to perform in vitro experiments on the adult brainstem. However, there has always been some question as to whether studies of neonatal brainstems would be applicable to the question of adult REM sleep mechanisms. One can now imagine examining the metabolism and membrane characteristics of these critical cell groups as a means of gaining better insight into REM sleep function. However, as Karlsson et al.’s work demonstrates [21], most of the neurons of interest are not homogeneously concentrated in any easily targeted region. Identifying the individual neurons of interest in vitro remains a challenge. This challenge will have to be surmounted in order to identify the control mechanism and better understand the function of REM sleep.

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References

1. Nofzinger EA, Boyce D, Germain A, Price JC, Mieswald JM, et al. (2004) Functional neuroimaging evidence for hyperarousal in insomnia. Am J Psychiatry 161: 2126–2129.
2. Maquet P (1995) Sleep function(s) and cerebral metabolism. Behav Brain Res 69: 75–83.
3. Roffwarg HP, Muzio JN, Dement WC (1966) Ontogenetic development of the human sleep-dream cycle. Science 152: 604–619.
4. Siegel JM (2006) Brainstem mechanisms generating REM sleep. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. Philadelphia: W. B. Sanders. pp. 112–133.
5. Baker T, McGinty D (1977) Reversal of cardiopulmonary failure during active sleep in hypoxic kittens: Implications for sudden infant death. Science 199: 419–421.
6. Parmeggiani PL, Azzaroni A, Calasso M (2002) Systemic hemodynamic changes raising brain temperature in REM sleep. Brain Res 940: 55–60.
7. Wiesel TN (1999) Early explorations of the development and plasticity of the visual cortex: A personal view. J Neurobiol 41: 7–9.
8. Shaffery JP, Roffwarg HP, Speciale SG, Marks GA (1999) Ponto-geniculo-occipital-wave suppression amplifies lateral geniculate nucleus cell-size changes in monocularly deprived kittens. Brain Res Dev Brain Res 114: 109–119.
9. Shaffery JP, Oksenberg A, Marks GA, Speciale SG, Mihailoff G, et al. (1998) REM sleep deprivation in monocularly occluded kittens reduces the size of cells in LGN monocular segment. Sleep 21: 837–845.
10. Siegel JM (2001) The REM sleep-memory consolidation hypothesis. Science 294: 1058–1060.
11. McGinty D, Szymusiak R (1990) Keeping cool: A hypothesis about the mechanisms and functions of slow-wave sleep. Trends Neurosci 13: 480–487.
12. Wehr TA (1992) A brain-warming function for REM sleep. Neurosci Biobehav Rev 16: 379–397.
13. Corner MA (1985) Ontogeny of brain sleep mechanisms. In: McGinty DJ, Drucker-Colin R, Morrison AR, Parmeggiani PL, editors. Brain mechanisms of sleep. New York: Raven Press. pp. 175–198.
14. Villablanca J, Marcus R (1972) Sleep-wakefulness, EEG and behavioral studies of chronic cats without neocortex and striatum: The ‘diencephalic’ cat. Arch Ital Biol 110: 348–382.
15. Zepelin H, Siegel JM, Tobler I (2005) Mammalian sleep. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. Philadelphia: Elsevier Saunders. pp. 91–100.
16. Rechtschaffen A, Bergmann BM (2002) Sleep deprivation in the rat: An update of the 1989 paper. Sleep 25:18–24.
17. Everson CA, Crowley WR (2004) Reductions in circulating anabolic hormones induced by sustained sleep deprivation in rats. Am J Physiol Endocrinol Metab 286: E1060–E1070.
18. Everson CA, Nowak TSJ (2002) Hypothalamic thyrotropin-releasing hormone mRNA responses to hypothyroxinemia induced by sleep deprivation. Am J Physiol Endocrinol Metab 283: E85–E93.
19. Siegel JM, Manger P, Niemhuis R, Fahringer HM, Pettigrew J (1996) The echidna Tachyglossus aculeatus combines REM and nonREM aspects in a single sleep state: Implications for the evolution of sleep. J Neurosci 16: 5500–5506.
20. Siegel JM, Manger PR, Niemhuis R, Fahringer HM, Shalita T, et al. (1999) Sleep in the platypus. Neuroscience 91: 391–400.
21. Karlsson KE, Gall AJ, Mohns EJ, Seelke AMH, Blumberg MS (2005) The neural substrates of infant sleep in rats. PLoS Biol 3: e143. DOI: 10.1371/journal.pbio.0030143
22. Sakai K (1985) Anatomical and physiological basis of paradoxical sleep. In: McGinty DJ, Drucker-Colin R, Morrison AR, Parmeggiani PL, editors. Brain mechanisms of sleep. New York: Raven Press. pp. 111–138.
23. Siegel JM, Wheeler RL, McGinty DJ (1979) Activity of medullary reticular formation neurons in the unrestrained cat during waking and sleep. Brain Res 179: 49–60.
24. Siegel JM, Niemhuis R, Fahringer H, Paul R, Shiromani P, et al. (1991) Neuronal activity in narcolepsy: Identification of cataplexy related cells in the medial medulla. Science 262: 1315–1318.
25. Kodama T, Nai Y, Siegel JM (2003) Changes in inhibitory amino acid release linked to pontine-induced atonia: An in vivo microdialysis study. J Neurosci 23: 1548–1554.
26. Lai Y, Kodama T, Siegel JM (2001) Changes in monoamine release in the ventral horn and hypoglossal nucleus linked to pontine inhibition of muscle tone: An in vivo microdialysis study. J Neurosci 21: 7384–7391.
27. Mileykovskiy BV, Kiyashchenko LI, Kodama T, Lai Y, Siegel JM (2000) Activation of pontine and medullary motor inhibitory regions reduces discharge in neurons located in the locus coeruleus and the anatomical equivalent of the midbrain locomotor region. J Neurosci 20: 8551–8558.
28. Aston-Jones G, Bloom FE (1981) Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. J Neurosci 1: 876–886.
29. Hoshino K, Pompeiano O (1976) Selective discharge of pontine neurons during the postural atonia produced by an anticholinesterase in the decerebrate cat. Arch Ital Biol 144: 244–277.
30. van den Pol AN, Ghosh PK, Liu RJ, Li Y, Aghajanian GK, et al. (2002) Hypocretin (orexin) enhances neuron activity and cell synchrony in developing mouse GFP-expressing locus coeruleus. J Physiol 541: 169–185.
31. Greene RW, Gerber U, McCarley RW (1989) Cholinergic activation of medial pontine reticular formation neurons in vitro. Brain Res 476: 154–159.