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Sleep in brain development

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ABSTRACT

With the discovery of rapid eye movement (REM) sleep, sleep was no longer considered a homogeneous state of passive rest for the brain. On the contrary, sleep, and especially REM sleep, appeared as an active condition of intense cerebral activity. The fact that we get large amounts of sleep in early life suggested that sleep may play a role in brain maturation. This idea has been investigated for many years through a large number of animal and human studies, but evidence remains fragmented. The hypothesis proposed was that REM sleep would provide an endogenous source of activation, possibly critical for structural maturation of the central nervous system. This proposal led to a series of experiments looking at the role of REM sleep in brain development. In particular, the influence of sleep in developing the visual system has been highlighted. More recently, non-REM (NREM) sleep state has become a major focus of attention. The current data underscore the importance of both REM sleep and NREM sleep states in normal synaptic development and lend support to their functional roles in brain maturation. Both sleep states appear to be important for neuronal development, but the corresponding contribution is likely to be different.

Key terms: sleep development, brain development, brain plasticity, NREM sleep, REM sleep,

Introducing sleep

Sleep is usually considered a resting state. In reality, this conception does not necessarily agree with some of the physiological processes during sleep. Neurons in most parts of the brain remain active during sleep and the brain expends much energy with this neural activity during sleep. It is easy to conceive that neurons responsible for autonomic functions such as respiration remain active in both sleep and waking, but neurons in other parts of the brain also remain active, often in a highly synchronous and rhythmic manner (Steriade, 2006).

Studies in humans half a century ago first demonstrated that sleep occurs in two distinct states: rapid eye movement (REM) sleep and non-REM (NREM) sleep (Aserinski and Kleitman, 1953). These sleep states exist in human fetuses and newborns, although their earliest age of appearance is controversial (Curzi-Dascalova et al., 1988; Curzi-Dascalova and Challamel, 2000; Mirmiran et al., 2003a; Peirano et al., 2003). Studies using chronically catheterized fetal animals and imaging of the human fetus have emphasized the similarities between fetal and postnatal sleep states (Richardson et al., 1994; Morrison et al., 1997; Czikk et al., 2001; Czikk et al., 2002; Morrison et al., 2005). The current concept regarding REM sleep is that there is a controlling network composed of several areas of the forebrain and that brainstem structures may be responsible for its final expression (Pace-Schott and Hobson, 2002; McCarley, 2007). With respect to the development of NREM sleep, it also requires the establishment of a specific network of excitatory and inhibitory neural components, that includes the formation of thalamocortical and intracortical patterns of innervation (Curzi-Dascalova and Challamel, 2000; Pace-Schott and Hobson, 2002; McCarley, 2007).

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Based on data from animals with prenatal brain development (sheep, for instance), there is evidence for prenatal sleep states development (Richardson et al., 1994; Morrison et al., 1997; Czikk et al., 2001; Czikk et al., 2002; Morrison et al., 2005). Of note, (i) regional blood flow within the brain increases during REM sleep, especially in areas thought to be involved with the generation of this sleep state (Czikk et al., 2001), (ii) cerebral leucine metabolism correlates to sleep states (Czikk et al., 2002), suggesting that protein synthesis and degradation processes within the brain are modified by them, and (iii) cerebral blood flow and oxygen delivery are higher during spontaneous and carbachol-induced REM sleep relative to spontaneous and scopolamine-induced NREM sleep (Morrison et al., 2005), indicating that pharmacologic manipulation induced fetal sleep states behaviorally, electrophysiologically and metabolically. In addition, in newborn lambs, the cerebral metabolic rate of oxygen consumption is as high during REM sleep as during wakefulness (Silvani et al., 2006). As a whole, these studies emphasize that comparisons of fetal and adult sleep states in developmental profile and pharmacological responses may be species specific (Morrison et al., 1997).

Regarding human sleep ontogeny, physiological and behavioral parameters that characterize REM sleep are present well before the normal term age (Curzi-Dascalova et al., 1988; Curzi-Dascalova and Challamel, 2000). There is also evidence showing that REM sleep may be more accurately described as having phasic and tonic stages (Shimohira et al., 2002); furthermore, these REM sleep patterns demonstrate consistent results on a night-by-night basis (Kimura et al., 2001). This distinction within REM sleep may contribute to the more appropriate interpretation of sleep differences between species with prenatal and postnatal brain development (Peirano et al., 2003).

The above mentioned considerations could be particularly relevant while considering that the last decades have witnessed a renewed interest in the study of the role of sleep in two main manifestations of brain plasticity: brain development on the one hand, and learning and memory, on the other hand (see Maquet et al., 2003; Frank and Heller, 2006).

Development of sleep

Fetal movements are interspersed with periods of quiescence and this cycling pattern increases in duration and becomes more regular with advancing gestation. This basic rest/activity cycle evolves into recognizable distinct behavioral states only after the neural mechanisms that underlie the patterning of each variable reach the corresponding developmental stage that allow them to cycle in concert. In all mammals studied to date (i) the amount of REM sleep is initially much higher early in development than it is in later adult life; conversely, the amount of NREM sleep (and wakefulness if ever present) is lower early in development than it is in later on; (ii) patterns of REM sleep and NREM sleep brain activity continue to change postnatally, although some precocious species, humans in particular, clearly begin this process *in utero;* (iii) ultradian, circadian, and homeostatic sleep regulatory mechanisms undergo important modifications in the neonatal period and thereafter (see Peirano et al., 2003).

Sleep is more than the absence of wakefulness, since them both are regulated and active processes that occur at particular times within the 24-hour period. The timing of sleep and waking is regulated by two processes: (i) a circadian pacemaker located in the suprachiasmatic nuclei of the anterior hypothalamus, which is entrained to the light-dark cycle and promotes wake during an active phase of the cycle and permits sleep during a rest phase of the cycle, and (ii) a homeostatic process in which a need for sleep accumulates during waking and is dissipated or satisfied during sleep (Borbély, 1982). Since these two processes do not necessarily run during the same time period, they need a strong signal to synchronize them. The first process is affected by light, and the second one appears more like a buildup and decay of an

unknown chemical that gets used up during the day and then is replenished when we sleep. Although these regulatory processes can operate independently, growing evidence indicates an intimate relationship between them. Finally, a third mechanism controls the ultradian alternance between NREM sleep and REM sleep, which appears to be controlled by a permanent interacting balance between brainstem aminergic and cholinergic neuronal discharges (Pace-Schott and Hobson, 2002; McCarley 2007). However, a recently described model (Lu et al., 2006) postulates that the main switching mechanisms for REM sleep involve reciprocal inhibitory interactions between mesopontine tegmentum GABA-ergic REM-off and REM-on populations (in this model the role for cholinergic and monoaminergic populations is to modulate the components of the main REM switch, but are not a part of it). These three mechanisms, in concert, produce organized sleep-wake patterns.

Several findings in adult mammals suggest that sleep is homeostatically regulated. Periods of forced waking lead to increased sleep drive, or sleepiness, with compensatory increases in the amount of sleep states in subsequent sleep (Borbély, 1982). Sleep homeostatic mechanisms undergo several important modifications during the neonatal period. The amount of waking is very low and neonates are unable to maintain consolidated bouts of waking. Short periods of sleep deprivation lead to a rapid rise in sleep pressure and produce compensatory increases in sleep time and/or intensity during recovery (Alfoldi et al., 1990; Anders and Roffwarg, 1973; Canet et al 1989; Thomas et al., 1996). Human neonates respond to selective (Anders and Roffwarg, 1973) or total sleep (Canet et al 1989; Thomas et al., 1996) deprivation with compensatory increases only in NREM sleep time.

Neonates show no evidence of circadian variations in sleep or waking states; it begins to emerge by about 5-6 weeks of age. In addition, the consolidation of sleep-waking states and their synchronization with a 24-hour day appear to be independent processes. Recent findings further support the notion that episodes of sleep and wakefulness are regulated independently, and suggest that their developmental changes can be attributed in part to increasing forebrain influences (Blumberg et al., 2005). Changes in the circadian distribution of sleep and waking episodes are also accompanied by changes within the sleep cycle itself. Young infants, unlike adults, typically begin a sleep episode in REM sleep and spend approximately equal amounts of time in each sleep state with episodes of REM sleep and NREM sleep alternating with a period of 50-60 minutes (Bes et al., 1994). Within the first weeks of life there is a rapid decrease in REM sleep during the day, accompanied by a large increase in NREM sleep at night (Coons and Guilleminault, 1982; Fagioli and Salzarulo, 1982; Navelet et al., 1982). Time spent in REM sleep declined inversely with increased wakefulness during daytime but remains fairly constant during the night (Coons and Guilleminault, 1982; Fagioli and Salzarulo, 1982; Navelet et al., 1982). Finally, changes in the nightly distribution of sleep stabilized by 3-4 months of age with a clear predominance of NREM sleep during the first third of the night and a predominance of REM in the last third (Hoppenbrouwers et al., 1982). The establishment of this adult-like distribution is marked by the changeover from REM sleep onset to the pattern of NREM sleep onset.

Sleep and brain development

A key factor in the maturation of central sensory pathways is stimulus-induced neuronal activity (Hubel and Wiesel, 1979). Depriving kittens of normal visual experience during the critical period for visual development permanently alters the physiologic response of the brain to visual stimulation. During this developmental period, synaptic connectivity in the cortex exhibits a high level of plasticity as synapses are formed and retracted, a process strongly driven by sensory activity. Brain plasticity, therefore, refers to the ability of the brain to persistently change its

structure and function according to genetic information in response to environmental changes or to comply with the interaction between these two factors (Chen and Tonegawa, 1997). By facilitating brain plasticity, sleep would allow the organism to adapt its behaviour to the circumstances, within the constraints set by species-specific genetic material (Maquet et al., 2003).

The neonatal brain has brief periods of waking in which to interact and learn in the adult sense of the word. The gradual reduction in REM sleep amount with advancing age is offset by an increase in waking amount. It is clear that the waking state favors cognitive processes during early life. Transient periods of alertness can be induced or prolonged by changes in body posture and articulated visual or auditory stimuli during the first weeks of life; in both circumstances waking extension depends on a social partner. However, the essential changes in alertness that occur at 2 months of age are "the infant's ability to construct its own context of wakefulness by initiating goal-directed actions and inventing new combinations among coordinated movements" (Wolff, 1984). The timing for these changes coincides with major transitions in various aspects of the infant's neural and sensory repertoire, and the infant becomes better adapted to the extra-uterine environment.

It seems paradoxical that CNS maturational processes in the late prenatal and neonatal periods are highly active at the time that extrinsic sensory stimulation is quite limited. During these periods, a large percentage of time is spent in REM sleep, characterized by endogenous, intense, generalized neuronal firing in most areas of the brain, "it is the intensity of phasic neuronal activity during REM sleep which is high in early development and diminishes as rapid brain maturation is completed" (Mirmiran and Ariagno, 2003b). Roffwarg and coworkers were the first to propose that the primary purpose of REM sleep was to act as an inducer of CNS development in the fetus and the neonate (Roffwarg et al., 1966). Based on the early myelination of the sensory processing areas in the CNS, they further proposed that REM sleep provided endogenous stimulation to these areas. Fetal movements that are anticipatory in nature (breathing, sucking, swallowing, yawns, stretches and eye movements) occur during REM sleep.

Studies of REM sleep deprivation have provided consistent support to the role of REM sleep in brain maturation and especially on subsequent visual development (Marks et al., 1995; Oksenberg et al., 1996; Shaffery et al., 1998; Shaffery et al., 1999; Hogan et al., 2001; Shaffery et al., 2002). Kittens with normal binocular vision subjected to REM sleep deprivation during the second week of a 2-week monocular deprivation (MD) period, had further anatomically and functionally deleterious effects on the lateral geniculate nucleus (LGN) relative to MD alone (Marks et al., 1995). The effect of REM sleep deprivation in unoccluded kittens resulted in a higher magnitude impact than the one provoked by MD, suggesting that deprivation of REM sleep during CNS development amplifies the plasticity processes generated when normal visual afferentation to central visual areas is interrupted (Oksenberg et al., 1996). Further, they demonstrated that (a) the elimination of ponto-geniculo-occipital-wave phasic activity during REM sleep (a method that preserves sleep and wake proportions as well as other REM features) similarly yielded enhanced plasticity effects in the LGN (Shaffery et al., 1999), and (b) REM sleep deprivation delayed the development of synaptic plasticity in the LGN (Hogan et al., 2001), and retarded the maturational reduction of long-term potentiation (LTP) in visual cortex of immature rats (Shaffery et al., 2002), as was the case for rats reared in darkness (Kirkwood et al., 1995).

These results emphasize that REM sleep is also an important part of visual development after birth, stimulating neurons in a fundamentally different way from that derived from visual experience (Marks et al., 1999). Moreover, since REM sleep excites neural components elsewhere in the brain –not just in the visual system–

it also might help other areas of the brain develop. Recent studies indicate that mechanisms of synaptic plasticity, which participate in brain development and perhaps also in learning and memory processes, remain susceptible to the effects of REM sleep deprivation in the adolescent rat (Shaffery et al., 2006a; Shaffery et al., 2006b).

Although further research is needed to show the significance of these findings in humans, based on our own results showing increased retinal activity during REM sleep relative to NREM sleep in humans during early infancy (Peña et al., 1999), we suggested that greater retinal activity during this sleep state may represent a biological condition that favors the maturation of the retina (and probably other structures within the visual system). The association between retinal activity and sleep states was markedly attenuated at 4 months of post term age (Peña et al., 1999), when the quantity of wakefulness has increased (Curzi-Dascalova and Challamel, 2000; Coons and Guilleminault, 1982; Fagioli and Salzarulo, 1982; Peirano et al., 2003) and its quality improved (Wolff, 1984), paralleling the daytime decrease in the amount of REM sleep (Curzi-Dascalova and Challamel, 2000; Coons and Guilleminault, 1982; Fagioli and Salzarulo, 1982; Fagioli et al., 1989; Peirano et al., 2003).

The role of REM sleep on CNS development is further illustrated by studies indicating long-lasting behavioral changes resulting from pharmacologic REM sleep deprivation in early life (Mirmiran et al., 1983; Mirmiran, 1986; Mirmiran and Van Someran, 1993; Mirmiran, 1995). REM sleep deprived animals have a reduced brain size, hyperactivity, anxiety, attention and learning difficulties, increased voluntary alcohol consumption and reduced masculine sexual behavior. Moreover, while environmental enrichment has been shown to enhance cortical maturation, this was no longer possible in the REM sleep deprived rats (Mirmiran et al., 1983). These findings, however, should be interpreted cautiously because (i) drugs have multiple effects on the developing brain, and (ii) neonatal REM sleep suppression may not be the causal factor in adult deficits in sleep behavior (Frank and Heller, 1997). In the earlier pharmacological manipulation for REM sleep suppression more than a single neurotransmitter system was modified (Mirmiran et al., 1983; Mirmiran, 1986), while later studies used more selective pharmacologic agents that enabled the suppression of REM by changing individual neurotransmitter systems (Frank and Heller, 1997). Therefore, to what extent the outcome of the pharmacological suppression of REM in these studies is the result of interference with neurotransmitter systems rather than the loss of REM sleep *per se,* or even the balance between NREM sleep and wakefulness is still controversial (Mirmiran and Van Someran, 1993; Frank and Heller, 1997; Vogel et al., 1990; Vogel et al., 2000; Feng et al., 2001; Feng and Ma, 2002).

The presence of NREM sleep regulation in both neonatal rats (Alfoldi et al., 1990) and humans (Anders and Roffwarg, 1973; Thomas et al., 1996) suggests that NREM sleep may also be important for developing animals. The maturation of NREM sleep not only coincides with the formation of thalamocortical and intracortical patterns of innervation and periods of heightened synaptogenesis, but it is also associated with important processes in synaptic remodeling (Bear and Malenka, 1994; Cramer and Sur, 1995).

During NREM sleep, waking patterns of neuronal activity are reactivated, suggesting that information acquired during wakefulness is further processed during this sleep state. Buzsaki have suggested that sharp wave bursts initiated in the hippocampus during slow-wave sleep (SWS) and associated with theta and gamma oscillations may provide the mechanism by which "quanta" of information may be relayed back to the neocortex during memory consolidation (Buzsaki, 1996). His group further demonstrated a correlation between neocortical and hippocampal activity during SWS, which suggests that these hippocampal patterns are coupled selectively to the neocortical cell groups

that participated in the triggering of the bursts (Sirota et al., 2003). It is therefore possible that NREM sleep contributes to synaptic remodeling by providing an endogenous source of repetitive, synchronized activity within specific neuronal pathways (Kavanau, 1994). Frank and coworkers have shown plasticity in the developing visual cortex induced during NREM sleep immediately following a novel experience of MD (Frank et al., 2001). Sleep, following MD, facilitated cortical changes in ocular dominance. The magnitude of plasticity was similar to that observed after continued MD, and larger than that seen after sleep deprivation in darkness, suggesting that sleep independently enables mechanisms of cortical plasticity. Since there was a positive correlation between the amount of NREM sleep and enhancement of cortical plasticity, they suggested that this sleep state, at least during the first hours after MD, plays an important role in the rapid cortical synaptic remodeling elicited by MD. This study provides support to results showing that recent experiences are strongly replayed (sleep reactivation) during SWS (Kudrimoti et al., 1999; Ji and Wilson, 2007).

CONCLUDING REMARKS

The large amounts of sleep during periods of rapid brain growth, connectivity and synaptic plasticity suggest a role for sleep in brain development. The evidence indicates that sleep states may be important for neuronal development, although the contribution of each state is likely to be different. In addition, the possible importance role of the succession of NREM sleep and REM sleep has recently been emphasized. Finally, since both sleep states also appear to promote processes dependent on synaptic remodeling, such as learning and memory (Maquet et al., 2003; Walker and Stickgold, 2006; Yoo et al., 2007; Stickgold and Walker 2007), they might influence periods of heightened synaptic plasticity and development in the maturing brain.

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