10

Brain Restoration: A Function of Sleep

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1. Introduction

Several hypotheses have been suggested in order to answer the question about the biological function of sleep, and although this question is still in discussion, all theories share the proposal that sleep plays a transcendental role for both physical and brain development.

It is well known that sleep deprivation impairs cognitive processes (Drummond & Brown, 2001; Nilsson et al., 2005; Smith et al., 2002), total time of rapid eye movements sleep (REM sleep) is increased after stress condition (Rampin et al., 1991), a brief nap during the day improves mood, memory consolidation and alertness during wakefulness (Backhaus & Junghanns, 2006; Hayashi et al., 1999), and also sleep promotes motor recovery following cerebral stroke (Gómez Beldarrain et al., 2008; Siengsukon & Boyd, 2008, 2009a, 2009b). For these reasons, it has been suggested that sleep preserves the brain in optimal conditions to support the damage occurred in different situations throughout the day. Although the exact way by which this occurs in the brain remains unknown, it is possible that sleep could do it by improving the functioning of antioxidant systems, the maintenance of cellular integrity through the synthesis of molecules involved in cellular structure or regulation of cell cycle, as well as improving synaptic efficiency. The purpose of this chapter is to summarize the main studies that demonstrate the role of sleep in brain restoration and, as a result, in body functioning.

2. Biology of sleep-wake cycle

Sleep is a biological phenomenon of reversible nature, which is generated and regulated by several complex systems of neuronal networks and neurotransmitters (García-García & Corona-Morales, 2008; Markov & Goldman, 2006; Stenberg, 2007). Behaviorally, sleep is described as a state of rest characterized by a reduction in mobility and low response to sensory stimuli (Stenberg, 2007). However, the detailed study of sleep involves recording of electrographic parameters, such as: electroencephalogram (EEG), electrooculogram (EOG) and electromyogram (EMG).

During the wakefulness period reactivity to sensorial stimuli is high, beta waves (frequency > 13 Hz) are present during all EEG recording (figure 1). Nevertheless, when a subject begins to fall asleep, the brain electrical activity is reduced and alpha waves (8-13 Hz) appear (figure 1) (Dobato-Ayuso et al., 2002). At this point the transition from wakefulness to sleep begins. According to behavioral and polysomnographic parameters,

sleep is divided in two main stages: slow wave sleep (SWS) (sometimes denominated non-REM sleep) and REM sleep.

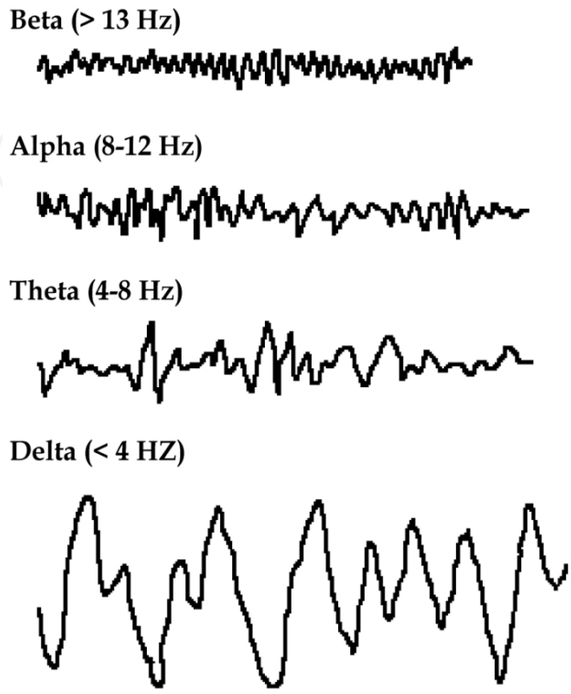

Fig. 1. Schematic representation of main different cerebral waves observed in EEG.
Four wave types are organized according to brain activity, from fast to slow. Frequency (Hz) is directly related to brain activation whereas wave amplitude is opposite to this. During wakefulness beta waves prevail in EEG recordings. Alpha and delta waves are present in slow wave sleep (N1-N3 stages) and theta activity is characteristic of REM sleep.

2.1 Slow Wave Sleep

During this period, brain waves recorded in the EEG are synchronous due to reduction of frequency and increase in amplitude, until become very slow waves (figure 1) (Dobato-Ayuso et al., 2002). During this sleep stage vital functions (including respiratory and heart rates) are at the minimum and muscle tone in the EMG is very relaxed (Carskadon & Dement, 2005). At the beginning of this stage only a few slow ocular movements can be observed in the EOG, once that sleep depth is increased these movements disappear (Carskadon & Dement, 2005). In humans SWS is usually subdivided in three phases (NI-N3), in which the depth of the slow waves is gradually increased (Silber et al., 2007).

Cerebral activity recorded during SWS is the result of a decrease in firing frequency of cortical neurons, which were active during wakefulness, by action of GABA-ergic neurons in preoptical ventrolateral area (Steriade, 2001). Therefore; slow waves registered during SWS are result of the prolonged hyperpolarization of cortical neurons (Steriade, 2001).

2.2 REM sleep

During REM sleep brain activity is characterized by waves of low amplitude and high frequency (figure 1). Markedly rhythmical theta waves and series of beta waves less than 10 s of duration appear in the EEG recording (Carskadon & Dement, 2005; Dobato-Ayuso et al., 2002; Fuller et al., 2006). The muscle tone is at the minimum or absent (except in eyes and respiratory muscles) (Chase & Morales, 1990). Fast ocular movements in both horizontal and vertical direction are recorded by the EOG (Aserinsky & Kleitman, 2003); the presence of these ocular movements gives the name to this sleep stage.

Neuronal groups mainly in the peduncle pontine (PPT) and laterodorsal tegmental (LDT) nucleus increase their firing frequency producing cortical desincronization. Particularly, these neurons fire exclusively during REM sleep period and are therefore called REM-on cells. In addition, these neurons are also responsible for the loss of muscle tone characteristic of this sleep stage, due to the inhibition of motoneurons in the spinal cord (Aloe et al., 2005; Sakai et al., 2001; Sakai & Koyama, 1996). An additional component of REM sleep is the occurrence of ponto-geniculate-occipital waves (PGO); which are transitory waves that have their origin in the pons and they later propagate towards the lateral geniculate nucleus into the thalamus and towards the occipital cortex (Datta & Siwek, 2002).

During the course of one night, all different stages of sleep and wakefulness alternate between them generating the called sleep-wake cycle, with a frequency of 4 to 6 cycles per night (≈90-120 minutes each) (figure 2) (Carskadon & Dement, 2005). The sleep pattern every night can also be changed by experiences that occur during the previous day (Drucker-Colín, 1995; García-García et al., 1998).

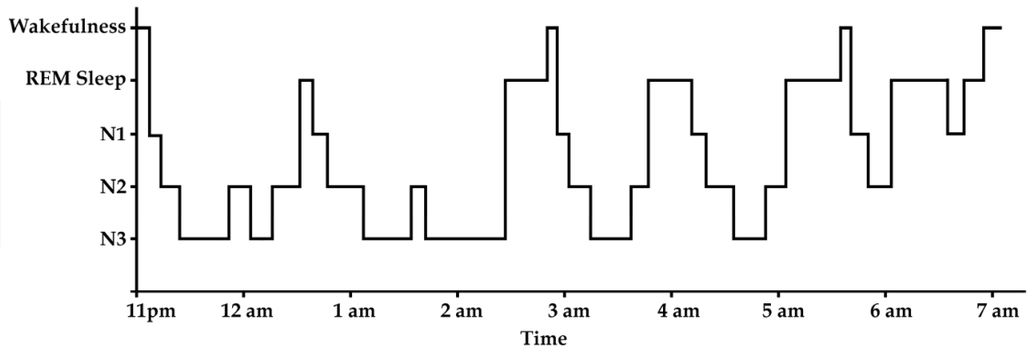

Fig. 2. Hypnogram of normal sleep-wake cycle of a human adult during a sleep night. First sleep cycle generally starts in wakefulness, followed by slow wave sleep (N1-N3) and REM sleep; in subsequent cycles, sleep stages could be randomly distributed. Overnight, 4-6 sleep cycles from 90-120 minutes of duration each can be recorded. There is a N2 and N3 predominance on the first part of night whereas N1 and REM sleep appear most frequently towards dawn. Commonly, some brief wakefulness periods may appear throughout night; however, they do not affect the sleep quality.

3. Biological function of sleep

In physiology, to know and study the function of some particular organ, this one is removed from the organism (generally in animal models) and changes produced due to its absence are observed. Sleep is not the exception since most methods used for the study of its function consists in suppressing it, manipulation known as sleep deprivation (SD).

Total sleep deprivation (TSD) in rats, by a period of three weeks, produces a significant physical deterioration: ulcerations in skin, tail and legs as well as an increase in food intake accompanied by excessive loss of weight that finally causes the death of the animal (Everson et al., 1989). In addition to physical deterioration, cognitive processes are severely affected by sleep deprivation; TSD or prolonged sleep fragmentation produces a decrease in cellular proliferation (Guzmán-Marín et al., 2003) and neurogenesis (García-García et al., 2011; Guzmán-Marín et al., 2007; Guzmán-Marín et al., 2005) in the hippocampus of adult rats. Furthermore, differentiation and survival of new cells in this region are affected by SD (García-García et al., 2011; Roman et al., 2005). In humans, insomnia or chronic loss of sleep is associated with excessive diurnal sleepiness and a decrease in psychomotor performance; being also affected the mood and functions of immune system (Malik & Kaplan, 2005). In this same way, in both animals and humans, it has been demonstrated that sleep, subsequent to a training period, improves execution of test (Stickgold et al., 2000) as well as memory consolidation (Fischer et al., 2002; Rauchs et al., 2004) whereas TSD or selective REM sleep deprivation (REMSD) impairs it considerably (Drummond & Brown, 2001; Nilsson et al., 2005; Smith et al., 2002). Although the exact way by which loss of sleep produces these negative cerebral effects is still unknown; it has been suggested that neuronal activity generated during prolonged periods of wakefulness can damage nervous cells and even induce cellular death (Inoué et al., 1995; Mamelak, 1997; Reimund, 1994).

4. Brain restoration as a sleep function

During high neuronal activity periods, glucose oxidation and oxygen requirements are increased due to high cost involved in the maintenance of bipotentials (Attwell & Laughlin, 2001), consequently, there is an increase in the intracellular production of reactive oxygen species (ROS), such as superoxide anions, hydroxyl radicals and hydrogen peroxide (Finkel & Holbrook, 2000). Usually, ROS levels in nervous system are regulated by several antioxidant mechanisms among which are glutathione, glutathione peroxidase and superoxide dismutase (SOD) (Attwell & Laughlin, 2001; Young & Woodside, 2001). Nevertheless, when intracellular amount of ROS is increased to the level that antioxidant systems are unable to maintain the cellular homeostasis, occurs a phenomenon known as oxidative stress (Finkel & Holbrook, 2000). It has been demonstrated that oxidative stress can damage cellular structure inducing destruction of different cellular components, including lipids, proteins and nucleic acids (Kannan & Jain, 2000).

One of the suggested functions of sleep is the role that it has on regulation of oxidative stress into the brain (Reimund, 1994). For example, it has been demonstrated that the induction of brain oxidation (through the injection of an organic hydroperoxide that promotes ROS production without cause cellular damage) during wakefulness promotes sleep (Ikeda et al., 2005). In addition, TSD or REMSD induces oxidative stress in different cerebral regions,

mainly in the thalamus, hypothalamus and hippocampus, by increasing the concentration of oxidized glutathione forms (Komoda et al., 1990), reducing levels of reduced glutathione (D'Almeida et al., 1998; Singh et al., 2008), increasing lipid peroxidation (Komoda et al., 1990) as well as the decline of SOD activity (Ikeda et al., 2005; Ramanathan et al., 2002) (figure 3). However, some studies have reported that both TSD (8 hours or 14 days) and 96 hours of REMSD do not induced significant changes in the morphology and number of neurons in the brain of adult rats (Cirelli et al., 1999; Hipolide et al., 2002). In contrast, TSD > 45 hours reduces the cellular membrane integrity in neurons on supraoptic nucleus (Eiland et al., 2002). Furthermore, 6 days of REMSD affect both size and shape of neurons present in locus ceruleus (LC) and PPT/LDT nucleus, regions involved in REM sleep regulation (Majumdar & Mallick, 2005), there is also an increase in neuronal expression of pro-apoptotic genes (i.e. Bax) and a decrease in actin and tubulin levels (Biswas et al., 2006).

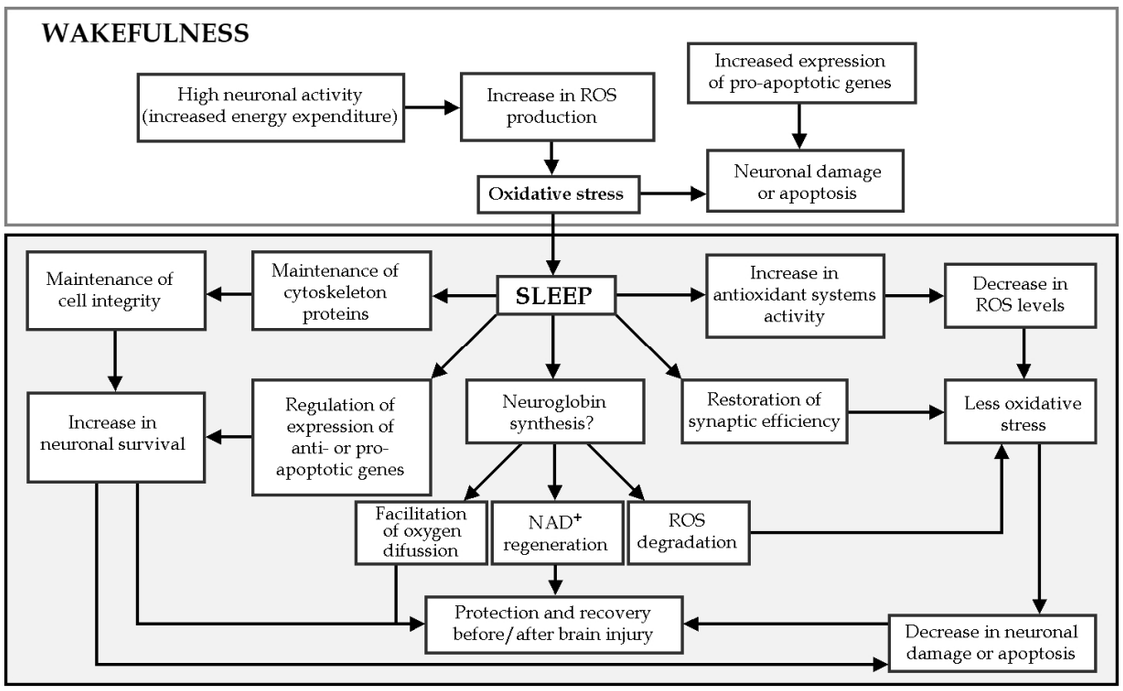

Fig. 3. Possible ways involved in brain restoration during sleep.
High neuronal activity and increased energy expenditure generated during wakefulness (and sleep deprivation, not shown) produce an excess of reactive oxygen species (ROS) becoming oxidative stress, which is able to produce neuronal damage, apoptosis and induce sleep (upper panel); the final aim of this sleep induction (lower panel) could be protect or recover the brain from different kinds of cerebral injuries. This sleep function is probably carried out by increasing antioxidant systems activity and restoration of synaptic efficiency, which decrease oxidative stress and neuronal damage. Another way is probably through maintenance and regulation of cell structure genes and proteins that allow increase neuronal survival. Finally, an extra but unknown (?) way for brain recovery during sleep could be through neuroglobin synthesis; these proteins could help to improve neuronal survival by ROS degradation, oxygen transport facilitation and NAD+ regeneration under hypoxia conditions.

Interestingly, 3 days of sleep recovery after REMSD are sufficient to counteract these cellular changes (Biswas et al., 2006; Majumdar & Mallick, 2005). These results suggest that sleep could prevent neuronal damage through the maintenance of cell integrity and neuronal survival by preservation of cytoskeleton proteins (Biswas et al., 2006), regulation of anti- and pro-apoptotic protein expression (Biswas et al., 2006; Montes-Rodriguez et al., 2009) or through the expression of genes involved in the maintenance of different cellular processes; such as cholesterol and protein synthesis, synaptic vesicle formation, antioxidant enzymes synthesis, etc. (Cirelli et al., 2004; Mackiewicz et al., 2007) (figure 3).

Additionally, it has been proposed that during sleep a synaptic efficiency improvement is necessary in order to prevent the storage of unnecessary information (Tononi & Cirelli, 2003, 2006), which requires high energy expenditure for cells (Attwell & Laughlin, 2001) because, as already mentioned, an overwork of the cell produces an increase in oxidative stress that finally affects the cerebral integrity which is necessary not only for well functioning of cognitive processes, such as memory (Born et al., 2006; Stickgold & Walker, 2007; Tononi & Cirelli, 2001), but also for maintenance of neuronal ways involved in adaptive processes (Shank & Margoliash, 2009). Related to this, in people with acquired brain injury, sleep seems to play a special role in recovery of motor damage, independently of the cerebral region that is affected (Gómez Beldarrain et al., 2008; Siengsukon & Boyd, 2008, 2009a, 2009b) (figure 3). In addition, it is possible to say that neurotrophins (molecules that improve neuronal development and facilitate the synaptic efficiency) are involved in brain restoration occurred during sleep. However, according to its sleep-inducing factor characteristics, i.e. higher level in wakefulness than in sleep, neurotrophins are maybe actively involved in brain restoration along wakefulness but not in sleep and therefore, it is difficult that neuronal restoration during sleep occurs completely by this way. In this sense, an interaction between wakefulness and sleep is necessary to promote cerebral restoration (Montes-Rodriguez et al., 2006).

On the other hand, recent studies have demonstrated that neuronal hypoxia or cerebral ischemia induces an increase in neuroglobin (Ngb) expression (Schmidt-Kastner et al., 2006; Sun et al., 2001); Ngb is a protein belong to the globin family, mainly synthesized and located in neurons from thalamus, hypothalamus, LC and PPT/LDT nucleus (Burmester et al., 2000; Hankeln et al., 2004; Hundahl et al., 2008; Wystub et al., 2003), brain regions involved in sleep generation and regulation. It has been suggested that Ngb plays a neuroprotector role through oxygen transport into neurons, NAD^+ regeneration under anaerobic conditions (to maintain glycolysis) or by ROS degradation (Burmester & Hankeln, 2004; Sun et al., 2003; Wang et al., 2008). The fact that Ngb plays an important role in the recovery of the injured brain, being synthesized in cerebral regions involved in sleep regulation (Hundahl et al., 2008) and, that patients with cerebral damage display a high amount of sleep (Masel et al., 2001; Watson et al., 2007), altogether, let us think that the synthesis of these proteins could be a way by which sleep promotes brain restoration (figure 3); nevertheless, this is a topic that needs to be highly investigated.

5. Conclusion

The biological function of sleep is a topic that has widely been studied; nevertheless, in spite of the great amount of information that already exists, there is not a consensus about why we sleep. At cellular level, little is known about the role that sleep plays in the conservation

of cellular integrity in conditions of health and neuronal damage (García-García & Drucker-Colín, 2008). Therefore, it is necessary to continue with the search of detailed mechanisms involved in both physical and brain restoration that occurs total or partially during sleep, which as much as possible increases subjects survival.

6. Acknowledgements

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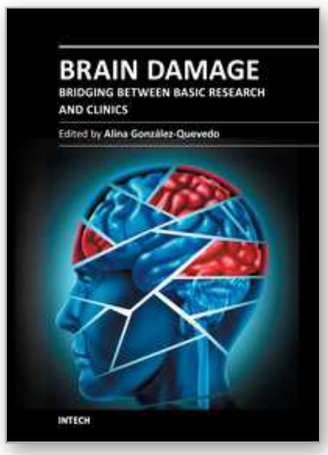

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"Brain Damage - Bridging Between Basic Research and Clinics" represents a collection of papers in an attempt to provide an up-to-date approach to the fascinating topic of brain damage in different pathological situations, combining the authors' personal experiences with current knowledge in this field. In general, the necessary link between basic and clinical neurosciences is highlighted, as it is through this interaction that the theoretical understanding of the pathophysiological mechanisms can be successfully translated into better ways to diagnose, treat and prevent the catastrophic events that occur when the brain suffers from external or internal noxious events. The book spans different aspects of brain injury, starting from damage occurring in the fetal and child brain, followed by different neurodegenerative processes. Attention is also focused on the negative effects of drug addictions and sleep deprivation on the brain, as well as on the early assessment of brain injury for preventive strategies employing sensitive biomarkers.

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