Chapter: 4

Neural Substrates of NREM Sleep

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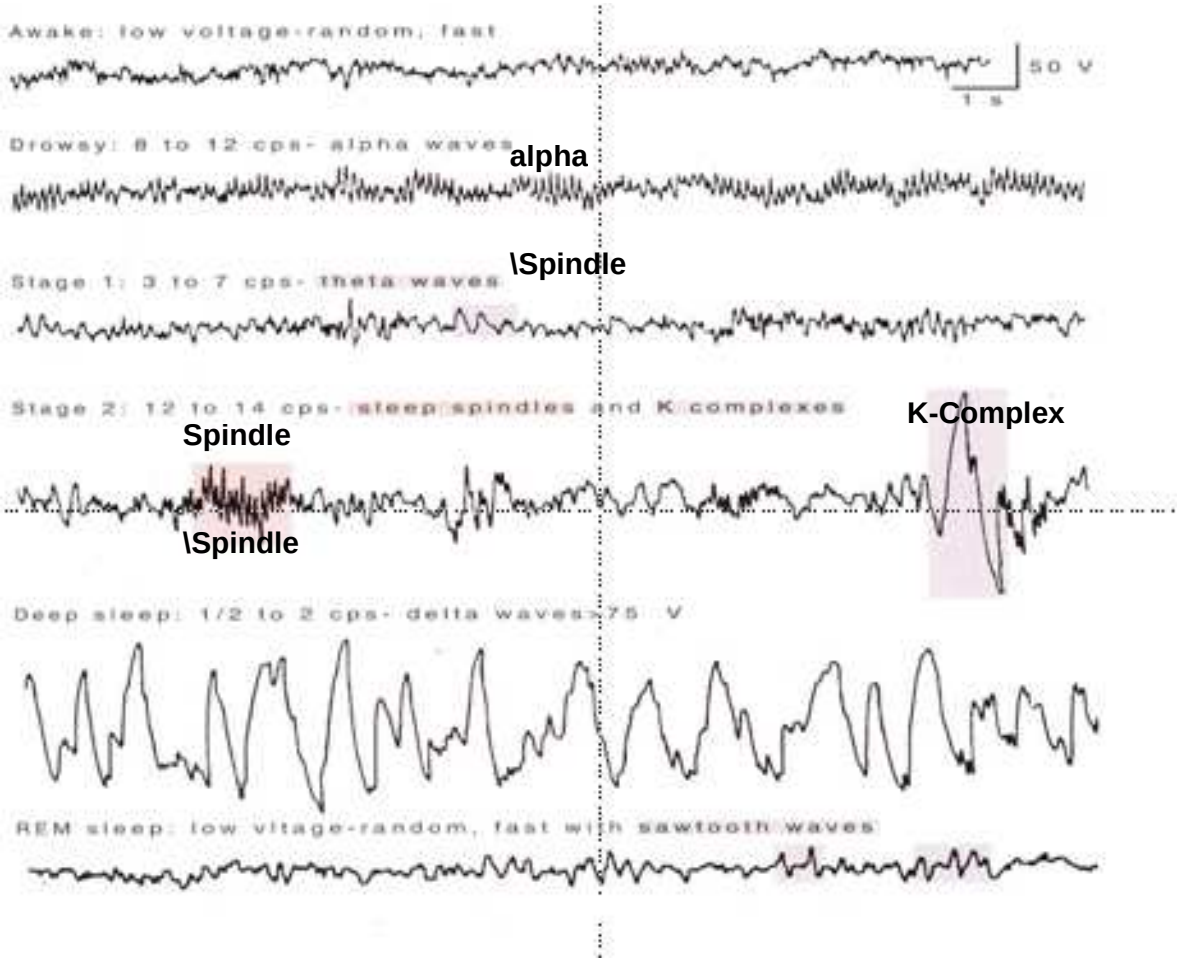
Sleep is a unique behavioral state initiated and maintained by specific neural mechanisms. The mammalian sleep consists of two different states, the rapid eye movement (REM) and non-rapid eye movement (Non-REM). The NREM sleep makes upto 75- 80 % (Linas and Pare 1991, Steriade et al 1993 b) and REM upto 20 -25 % of the total sleep (Mendelson 1987). The NREM is further classified into four stages according to the EEG synchronization (Rechtshaffen and Kales 1968). The NREM –S1 sleep state constitutes about 10-15 % of the total sleep and is characterized by eye ball rolling without much decrease in muscle activity. The NREM S2 is characterized by the appearance of sleep spindles and K-complex wave forms with < 1Hz oscillations in EEG. The Sleep spindle marks the beginning of EEG synchronization. The NREM-S2 sleep states constitute about 45- 50 % the total sleep time. The deeper sleep states of NREM , the S3 and S4 states together constitute the slow wave sleep (SWS) and EEG is highly synchronized with theta waves (4-7 Hz) and delta waves (0-4 Hz) waves representing the NREM S3 and S4 states respectively. Together, the slow wave sleep states constitutes about 10-15 % of the total sleep time. In a whole night's sleep , the NREM and REM sleep states alternate with 4 to 5 sleep cycles (a complete sleep cycle constitute one NREM and REM phase) . In human, the first sleep cycle occurs by 90 minutes with a very short REM episode. The NREM slow wave sleep predominates in the

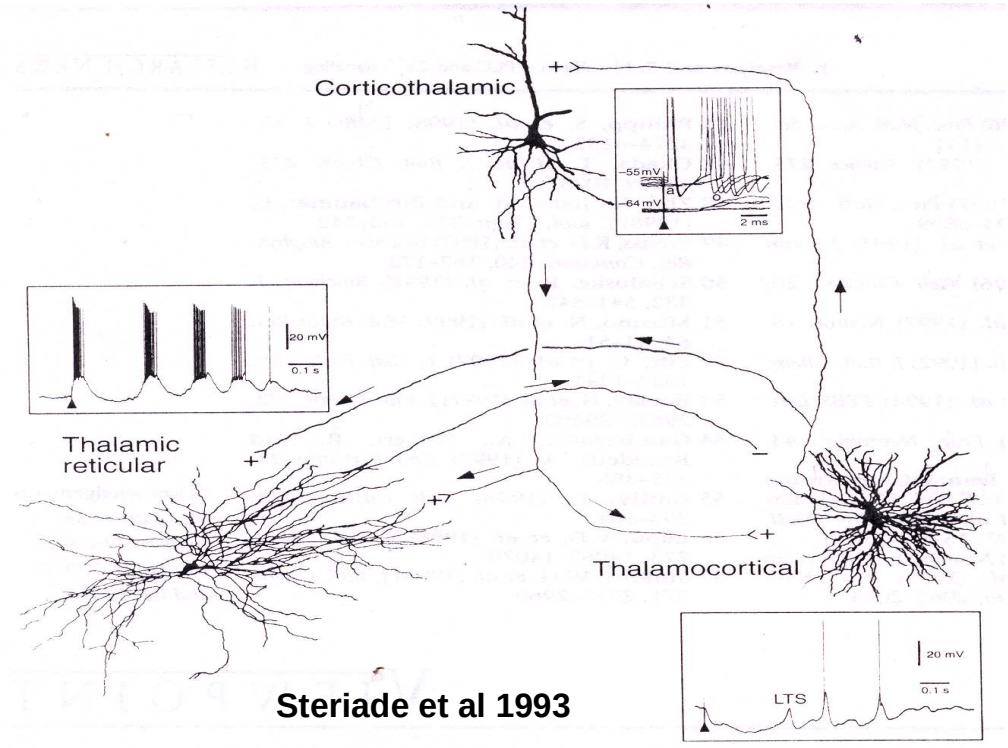
initial first half of the nights sleep where as the REM sleep predominates in the second half of the night's sleep. The cyclic appearance of various sleep states indicate that it is timed by interaction of various factors (neurotransmitters and their receptors , intracellular second messengers to endocrine and other factors including gene transcription) and an ultradian oscillator in the mesopontine area that controls the regular alternation of NREM and REM sleep.



EEG showing the electrical activity of human brain during different stages of sleeps (Courtesy – Neuroscience by Dale Purvis)

The NREM sleep complexity is a function of thalamocortical systems which form the major pacemaker of EEG synchronization. The synchronized oscillations that characterize SWS include: spindles (7-15 Hz), delta waves (1–4 Hz), and slow

oscillation (0.5–1Hz). The EEG spindles are the epitome of brain electrical synchronization at the onset of sleep. These oscillations are generated in the thalamus as the result of synaptic interactions in a network in which the main players are the inhibitory GABA containing neurons of the reticular thalamic nucleus (RE) and the excitatory thalamocortical cells (TC), and cortical pyramidal neurons.



Steriade et al 1993

Recent experimental (Fuentealba et al., 2004) and modeling (Traub et al., 2005) studies support the notions that RE neurons are pacemakers of spindles. During the depolarizing phase of the slow oscillation, the synchronous firing of neocortical neurons impinges upon thalamic RE pace making neurons, thus creating conditions for formation of spindles. In these reticular cells, rhythmic (7-15 Hz) bursts in the form of spindles are generated by low- threshold Ca^{2+} spikes. The bursts of reticular cells inhibit large numbers of TC cells through their GABA

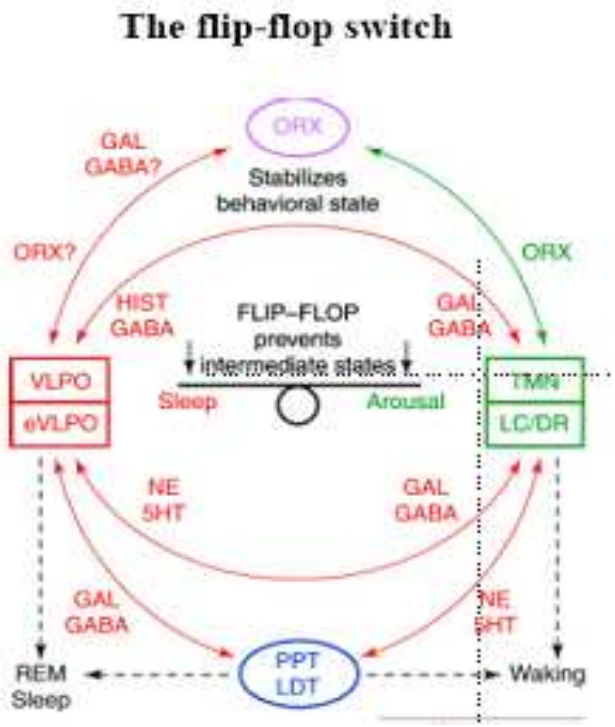
containing axons, which leads to the appearance of rhythmic IPSPs in TC neurons. Some of these IPSPs result in the removal of inactivation of the low threshold Ca^{2+} current to be followed by a rebound Ca^{2+} spike (H. Jahnsen et al., 1984) and associated burst of action potentials. The bursts are also transferred to the cortex, where they induce EPSPs in cortical pyramidal cells, thereby generating the EEG spindle waves. (See Box)

Spindle oscillations are progressively reduced and replaced by thalamocortical oscillations with slower frequencies during the late stages of NREM sleep, the SWS (slow wave sleep). Delta oscillations occur when the TC cells are more hyperpolarized than they are during spindle oscillations (Steriade 2006). Thus TC cells undergo a progressive hyper polarization from drowsiness and the early stages of sleep, when spindles prevail in the EEG, to the late sleep stages, when delta waves are predominant. In contrast to the origin of spindle oscillations in synaptic networks, a delta frequency rhythm can be generated in single cells by the interplay of two intrinsic currents of TC neurons- the hyperpolarization activated cation current I_h (Steriade 2006) and transient low threshold Ca^{2+} current I_t (Llinas, 1998). The hyperpolarization of TC cells is a critical factor for the interplay between I_h and $I_{t\ that}$ generates delta oscillation (Sejnowski and Destexhe 2000). The slow wave sleep is thus a specific state in which information is consolidated by activating the Ca^{2+} mediated intracellular cascade in the pyramidal neurons. Such network events associated with massive Ca^{2+} entry needs more time and thus preferred to occur only during sleep in which the normal processing of sensory information is absent and precisely the reason why we need to sleep.

Studies have showed the importance of the pre-optic area in promoting NREM sleep. The medial pre-optic area is previously shown to involve in thermoregulation and sleep. It appears that slow wave sleep helps to lower the body temperature set point and an increase in heat dissipation with transition from waking to SWS (V.Mohankumar 2003). Sherin et al 1996 have described the role of VLPO (ventro lateral preoptic area) in sleep maintenance. Approximately 80 % of the neurons of VLPO are of GABA ergic and Galaninergic and precise lesioning of VLPO region would disturb the NREM sleep and delta power but not REM sleep (Saper et al 2001, Jun Lu et al 2000) and lesions of the extended VLPO (the dorso medial extension) are seem to be associated with regulation of REM sleep . The neurons of VLPO cluster project extensively to the TMN of posterior hypothalamus (Sherin et al 1998) and the extended VLPO seem to project to the dorsal and medial raphae system (Bjorkum et al 1999) . Whereas that of ventral and medial pre-optic area is involved in thermoregulation *per se*. Thus discrete regions of hypothalamus are associated with various aspects of sleep wake behavior and sleep and body temperature regulation. Though they interact extensively, are functionally and anatomically distinct (Szymusiak et al 1991, Jun Lu et al 2000).

The sleep positive neurons of VLPO are shown to have reciprocal interaction with wake promoting neurons of basal forebrain (cholinergic) , brain stem and posterior hypothalamic (TMN) neurons (Lin et al 1988, Steininger 1999) . Saper et al (2001) have proposed a Flip-Flop model to explain the reciprocal inhibitory interaction between the sleep and wake promoting brain regions. According to this model , the wake and sleep promoting regions inhibit each other thus reinforce the

firing pattern of the flip –flop switch and hence reassure the stability of sleep - wakefulness behavior. Additionally, orexin / hypocretin system of lateral hypothalamus also plays a major role in modulating the sleep-wake behaviour. These neurons give excitatory inputs to wake promoting aminergic groups (LC, DR, TMN, VTA and PPT, LDT) bringing about stable wake state and prevents untimely transition of wake –sleep cycle. Further, orexin also excites cholinergic neurons of basal forebrain thus augmenting wake state. During wake state GABA neurons of basal forebrain inhibits sleep promoting VLPO. During NREM orexinergic and aminergic neurons are inhibited by VLPO whereas during REM aminergic neurons are GABAergically inhibited by Peri acquiductal Grey (PAG). Thus during REM wake promoting aminergic neurons are deprived of orexinergic excitation whereas the excitation of brain stem cholinergic system is intact to drive the cortex into an operational mode. Surely, this bi-stable hypothalamic sleep – wake switch model has proposed a specific functional role for orexin in maintaining the normal sleep wake cycle and accordingly in maintaining REM-NREM mechanisms.



Saper et al 2001

In addition, the circadian pacemaker and homeostatic control of sleep are also responsible for initiating the NREM sleep . VLPO is under constant inhibitory control of the supra chiasmatic neurons (SCN cells transmits the synchronized light dark rhythm information to areas concerned with sleep –wake cycle) and cholinergic neurons of basal forebrain (homeostatic control) during wake period . However, by the end of wakefulness, this inhibitory controls of SCN and cholinergic cells wane away thereby allowing the excitation (dis inhibition) of VLPO neurons to initiate the slow wave sleep. In addition , the hypothalamic integrator system (Medial pre optic area and dorsal hypothalamic Area) help to integrate the homeostatic increase in sleep pressure during prolonged wakefulness with the circadian propensity to initiate sleep . Once the NREM sleep has been initiated by the integrated influence of homeostatic and circadian factors on hypothalamic structures , prominent thalamo -cortical oscillatory rhythms begin to appear on

EEG. Additionally , the integrator regulates the wake promoting systems of brainstem, forebrain and posterior hypothalamus to favor the sleep onset. Once sleep is initiated , an ultradian oscillator in the mesopontine area regulates the alternation of NREM and REM sleep . It appears that the circadian and homeostatic mechanisms together with hypothalamic integrator system ensure the orchestrated signaling among the wake promoting and sleep promoting neurons to wards a proper sleep –wakefulness behavior.

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