PHYSIOLOGY IN SLEEP

What physiological changes occur in sleep? It is mandatory to know the effects of sleep on respiration, circulation, autonomic functions, temperature regulation and other systems.

Respiration

It is known that generation and maintenance of respiration occur due to respiratory centres in medulla and pons containing complex network of respiratory neurons, which respond to various inputs including CSF pH. Respiratory neurons consist of dorsal respiratory group (ventro-lateral nucleus of the solitary tract). Ventral group, neurons located in ventral medulla, is a column of cells extending from the retrofacial nucleus of the first cervical segment and consisting of nucleus ambiguous and nucleus retroambigualis. Third respiratory neuron group is Pontine.

Dorsal respiratory group neurons show respiratory activity that begins early and increases during respiration. Ia and Ib cells project predominantly to the spinal cord and activate respiratory neurons. Pulmonary stretch receptor afferents (Vagal) projects to dorsal respiratory group and synapse directly on Ib and pump cells. Ventral respiratory group neurons contain variety of cells that are premotor in function. On expiratory cells of the BOTZINGER complex and post inspiratory neurons, Botzinger cells have widespread inhibitory connection of both the brain stem and spinal cord levels.

Pontine respiratory group, pneumotaxic centre of Lumsden is located in the rostraldorsolateral pons and comprises two sub nuclei of the parabrachial nuclei-nucleus parabrachial medialis and kolliker Fuse nucleus. These neurons exhibit inspiratory – expiratory and phase spanning activity. There is interaction between pontine respiratory group and vagal afferents in determining the duration of inspiratory and expiratory phase but pontine group is not necessary for the generation of respiration because breathing remains rhythmic even after separation of the pontine respiratory group from medulla.

The ventral medullary surface has three chemosensitive zones. Topical anaesthetic or cold blockade of zones eliminate respiratory cycle. Given coincident, how important is the respiratory component relative to the non-respiratory component of the cells activity? These are the questions about the size of the respiratory effect. Orem and Dick (11) applied a standard effect size statistics, eta-squared (n2) to solve this problem.

n2 is the proportion of the total variance (a2) of the neuronal activity over a series of breaths that is made up by the variance across fractions of the respiratory cycle (am2).

$$n2 = \frac{am2}{a2} = \frac{am2}{am2 + a2}$$

Where a2 is the variance within fraction of the respiratory cycles and am2 is the variance of means across fractions.

It seems unacceptable to consider both an inspiratory cell with an n2 value of 0.9 and inspiratory cell with and n2 value of 0.1 as simply inspiratory cells. The consistency and signal strength of respiratory signals of these cells differ dramatically the message delivered to their respective synaptic terminals contain different respiratory contents, and different n2 value of different respiratory neurons must reflect either endogenous differences among cells or differences in the afference to them.

There are on one hand cells that are quintessentially respiratory. These high n2 valued cells seem to be protected from non-respiratory distortions, perhaps because of rigid sequence of excitatory and inhibitory postsynaptic potentials that preclude activity that is not strictly respiratory. There are on the other hand, respiratory cells whose activity is, to a varying degree, non-respiratory. The activity of these low n2 valued cells is the apparent result of mixture of input that has respiratory and non-respiratory forms.

In NREM sleep, respiration is controlled by an automatic system driven by chemical stimuli,. There is a class of respiratory neurons in the medulla that seems to be a automatic system. These neurons are quintessentially respiratory, and they are affected little by NREM sleep. These cells (high n2-valued cells) produce large and consistent respiratory signals and seem protected from non-respiratory influences. A multitude of influences purportedly affect the respiratory system, and yet there are remarkably, in the conscious, alert animal, that shows no evidence of non-respiratory contamination. Nested with them are other respiratory signals, and they are affected greatly by NREM sleep. Their activity seems to reflect non-respiratory influence.

This diversity of brainstem respiratory neurons has led to the principle that the effect of sleep on brainstem respiratory activity is proportional to the amount of non-

respiratory activity in that activity. The corollary is that the wakefulness stimulus for breathing is non-respiratory forms and affects some respiratory neurons more than others. Many structures may send non-respiratory information to medullary respiratory neurons, the reticular formation and the complex of central nervous system structures involved in behavioural control. However, there are other possibilities about which little is known, for example. cerebellum and other motor structures may provide input to the respiratory system in wakefulness as part of a bracing of the muscular system for movement.

It has been proposed that breathing in REM sleep is controlled by both the metabolic and behavioural control systems. There are few data at the cellular level relevant to this idea. In particular, it is not known how low n2-valued cells, putatively behavioural elements, behave in REM sleep, but regardless of this, it is clear that some cats can perform a learned respiratory response in REM sleep, which indicates that behavioural control is possible in that state.

Medullar respiratory neurons have extremely variable behaviour in REM sleep-behaviour that can account in part for the irregular breathing of that state. Thus, whatever the source of the variability, it is integrated within the respiratory system at levels as high as the medulla. It is also known that medullar respiratory activity in REM sleep is correlated with elemental phasic REM activity (pontine-geniculate-occipital waves), a finding clearly indicating non-respiratory and state-specific influences on the respiratory system in REM sleep.

During sleep, physiological changes occur in most of the systems of the body in one or other forms. Autonomic nervous system is affected most. Cardiovascular system, respiration, upper airway muscles, cerebral blood flow and thermoregulation are important systems, which show significant physiological changes, many of them may be unfavourable and undesirable. It makes one think that all physiological changes occurring are thus against nature of law. It is worth exploring.

Sleep alters both breathing pattern and the respiratory responses to many external stimuli. These changes allow the development of sleep related hypoxemia in patients with respiratory disease and may contribute to the pathogenesis of apnoea in patients with sleep apnoea syndromes. There may be many factors affecting control of breathing during sleep. Respiratory muscle does not have a built in pacemaker, as does the heart.

Respiratory muscle act only after getting impulses from respiratory centres who in turn dependent on input from chemo receptors located in the carotid body, mechanical receptors located in the lungs and behavioural information from higher cortical centres during functions like singing, laughing, crying and speaking. These non-respiratory functions are quite important during awake period, which is lost during sleep. The ventilatory response to hypoxia falls during sleep in adult humans. This response is much more pronounced during REM sleep than during NREM sleep in both the sexes however during NREM sleep women were affected less, reasons for the sex difference is not well understood. The Hypercapnic ventilatory response is again depressed but during NREM sleep women are spared (12). During REM sleep response was lowest and there was no sex difference. Response to increase airway resistance during sleep was increased respiratory effort during NREM sleep and rapid and shallow breathing during REM sleep.

Isocapnic hypoxia in normal subject is a poor stimulus to arousal with many subjects remaining asleep with SaO_2 as low as 70% and no difference between NREM and REM sleep. Conversely, the arousal sensitivity to hypoxia is decreased in REM sleep in patients having obstructive sleep apnoea with asphyxial hypoxia (13). Hypercapnia wakens most of the subjects before the end tidal CO_2 has risen by 15 mm Hg above the level in wakefulness. Arousal from REM sleep after airway occlusion is far more rapid than arousal from NREM sleep whereas patients with obstructive sleep apnoea have longer apnoeas during REM sleep. Why this happens is not clear? During REM sleep irregular breathing is common and neither isocapnic hypoxia nor hypercapnia will regularize it. Irregular breathing during NREM sleep is seen usually at the onset of sleep but may lead to occlusive apnoea if respiratory resistance is added. The activity of upper dilator muscles decreases during sleep, which is more marked during REM sleep.

It is not possible with our current knowledge to apportion causes for the decreases in ventilatory responses during sleep. It seems likely that major causes for the decease in ventilatory responses during NREM sleep is loss of wakefulness drive to breathe coupled with the decrease in metabolic rate and increased airflow resistance. The further reduction during REM sleep is likely to result from altered central nervous system functions during REM sleep.

The impaired ventilatory response permits the development of hypoventilation during sleep and of sleep related hypoxaemia in patients with chronic bronchitis and emphysema and other respiratory diseases that cause hypoxia. In all these conditions the hypoxia is most marked in REM sleep when the ventilatory responses are the lowest. The impaired ventilatory responses during sleep may be accompanied by a decrease in response of the upper airway opening muscles to chemo stimulation during, although it has not been tested, and both factors may be important in the initiation and continuation of apnoea. The remarkable insensitivity to external stimuli during sleep allows patients with all these conditions to develop clinically significant hypoxia and hypercapnia before arousal occurs.

Autonomic Nervous System in Sleep

The global involvement of autonomic regulation in the phenomena of sleep, one of the most important facts emerging so far from the analysis of the experimental evidence suggest that behavioural states are the expression of systemic changes in the functional organization of the whole encephalon. In all species, the autonomic phenomenon of NREM sleep suggest the presence of closed loop operation that maintain homeostasis at lower level of energy expenditure, compared with wakefulness. In contrast the autonomic activity during REM sleep is characterized in all species by the homeostatic (open loop) operations.

In humans, direct experimental evidence of changes in autonomic outflow during sleep is lacking. Indirect evidence shows that sympathetic activity decreases during stage I of NREM of sleep and remains almost constant throughout the following NREM stages with insignificant increase in REM sleep. The penile erection during REM sleep in men also reflects a change in automatic flow.

A complex pattern of sequential changes in both sympathetic and parasympathetic outflow to the heart has been identified. The decreases in heart rate from wakefulness to NREM sleep are mainly caused by tonic increases in parasympathetic influences because it persists after sympathectomy. A further decrease in heart rate during REM is mainly brought about by a topically reduced sympathetic discharge. Short lasting changes in both sympathetic and parasympathetic activity probably also involving baroreceptor reflexes underlie phasic changes in heart rate

(tachycardia followed by bradycardia) associated with the burst of rapid eye movements and myoclonic twitches.

In mammals, thermoregulatory responses to changes in body or ambient temperatures are controlled by hypothalamic pre optic integrative mechanism that drive subordinate brain stem and somatic and autonomic mechanism. The state dependent thermoregulatory phenomena may be enhanced or depressed according to the thermal load influencing the central thermostat during NREM sleep. Thermoregulation is practically suspended during REM sleep. The central sympathetic depression in REM sleep also underlies the thermal sweating in humans. REM sleep entails what may be called an intrinsic and species-specific physiological risk. The changes in motor and secretory activities of the gastro intestinal tract including gastro oesophageal reflux occur during sleep.