Sleep physiology
• Sleep is a state of unconsciousness from which person can be aroused by sensory stimuli.
• A normal adult person sleeps 7-8 hr/day. A newly-born infant sleeps (16-18 hi/day), An old person sleeps less (5-6 hr/day).

What is the difference between sleep & coma???
WAKING / SLEEPING RHYTHM

• Waking and sleeping periods follow each other in a circadian rhythm (i.e. 24 hr. rhythm) which is synchronized with daily light-dark cycle.

• This synchronization is function of suprachiasmatic nucleus of hypothalamus that receives collateral from visual pathway.

• Physical & psychological factors affect onset & duration of sleep. E.g. cold & fear prevent onset of sleep, whilst fatigue & boredom facilitate its onset.
TYPES OF SLEEP
There are two types of sleep which follow each other in a cyclic manner during the sleep period; these types are:

- Non REM Sleep.
- REM Sleep

(REM = Rapid Eye Movement).
NON-REM SLEEP (slow wave sleep),

- It is a quiet sleep during which there is no REM.
- There are no dreams, but other signs of mental activity may show up; as sleep-talking or sleep walking & night terror of children.
- Muscles are relaxed.
- There are four stages of it, identified by EEG recording as follows. **STAGE I** (very light steep): If a person is awakened during this stage, he asserts that he was not asleep, but just closing his eyes. This stage occurs only at the onset & at the waking up from sleep. **STAGE II** (light sleep): **STAGE III** (intermediate sleep): Breathing is slow & HR is about 65 beats/min, temperature & arterial BP continue to decline. **STAGE IV** (deep sleep): only in the early sleep cycles. There is maximum slowing of breathing & HR (about 60 beats/min).
REM SLEEP

- there is rapid roving movement of the eye.
- Dreams occur during this type of sleep.
- Although EEG pattern is indicative of an activated brain, the awakening threshold is as high as in deep sleep. That is why REM sleep is also called "paradoxical sleep".
- There is marked decrease in muscle tone except for occasional twitches of facial & finger muscles.
<table>
<thead>
<tr>
<th>Criteria</th>
<th>NREM sleep</th>
<th>REM sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Incidence</td>
<td>Before REM sleep</td>
<td>After NREM sleep</td>
</tr>
<tr>
<td>2. Duration (per cycle)</td>
<td>Longer (80 min)</td>
<td>Shorter (20 min)</td>
</tr>
<tr>
<td>3. Depth of sleep</td>
<td>Variable</td>
<td>Very light</td>
</tr>
<tr>
<td>4. Threshold of awakening stimulus</td>
<td>Variable</td>
<td>High</td>
</tr>
<tr>
<td>5. Rapid eye movement</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>6. Dreams</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>7. Muscle tone</td>
<td>Low</td>
<td>Very Low</td>
</tr>
<tr>
<td>8. Sleep talking &amp; sleep walking</td>
<td>May occur</td>
<td>Do not occur</td>
</tr>
<tr>
<td>9. Penile erection</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>10. EEG</td>
<td>8- &amp; δ-waves</td>
<td>β-waves</td>
</tr>
<tr>
<td>11. Controlling center</td>
<td>Raphe nuclei</td>
<td>Nucleus ceruleus</td>
</tr>
</tbody>
</table>
SLEEP CYCLES

• Normal sleep starts by non-REM sleep for about 80 min (70-100) followed by REM sleep for about 20 min (10-40).

• The cycle is then repeated but with shorter NREM & longer REM periods.

• In the later cycles, sleep becomes lighter with no NREM stage IV phases.

• 4-5 sleep cycles occur in a normal one night sleep.

• The duration of deep sleep periods shortens with the advance of age.
MECHANISM OF SLEEP

(Three theories to explain how sleep is induced)
1. THE METABOLIC THEORY

- During wakefulness, brain cells produce a sleep-inducing factor (factor-S – a glucopeptide) which accumulates in CSF. When it reaches a certain level it induces NREM sleep.
- This factor was isolated from CSF & urine of persons after a period of sleep deprivation.
- A REM sleep factor also exists.
- Serotonin is considered as a "sleep hormone" because it stimulates production of these sleep-inducing substances.
- Concentration of factor-S in brain declines steadily during sleep → termination of sleep & start of wakefulness.
2. THE PASSIVE THEORY
(DEAFFERENTATION THEORY)

- Ascending reticular activating system (ARAS) sends facilitatory signals to cerebral cortex to ↑ its excitability & maintain wakeful, alert state.

- According to this theory, sleep is induced when facilitatory signals from ARAS to cortex are withdrawn, which occurs when activity of ARAS is depressed either by fatigue or by lack of sensory input signals or corticofugal signals.

- This theory explains how sleep is rapidly induced by physical and mental relaxation in a comfortable bed in a quiet, dark room at comfortable temperature. Under these conditions, all sensory signals are reduced to minimal (functional sensory deafferentation) & ARAS activity is markedly reduced. After a long period of wakefulness ARAS activity is depressed by fatigue. This reduces excitability of cortical neurons → sleep.
3. THE ACTIVE THEORY (SLEEP CENTERS)

- According to this theory there are specific centers which induce NREM sleep, others which induce REM sleep.
- There is awaking/sleeping oscillator which regulates activity of these sleep centers.

(a) NREM SLEEP CENTER
(b) REM SLEEP CENTER
(c) WAKING/SLEEPING OSCILLATOR CENTER
(a) NREM SLEEP CENTER

- Raphe magnus nuclei in brain stem are considered as a NREM sleeping center.
- Their stimulation induces NREM sleep.
- Their damage leads to prolonged insomnia.
- Inhibitory fibers from raphe nuclei project to ARAS & cerebral cortex. These fibers are serotonergic so drugs that block synthesis of serotonin, produce prolonged insomnia.
(b) REM SLEEP CENTER

- The nucleus ceruleus of pons is considered as a REM sleep center.
- Its stimulation converts NREM to REM sleep.
- It stimulates cerebral cortex & inhibits raphe nuclei.
- It inhibits facilitatory reticular formation leading to marked ↓ in skeletal muscle tone.
(c) WAKING/SLEEPING OSCILLATOR CENTER

• Suprachiasmatic nucleus of anterior hypothalamus is responsible for synchronizing waking/sleeping rhythm with 24-hr light/dark cycle.

• Suprachiasmatic nucleus acts by stimulating raphe nuclei which in turn induce sleep.

• Damage of this nucleus → intense wakefulness. This eventually leads to severe exhaustion which could be fatal.
PHYSIOLOGICAL CHANGES DURING SLEEP
NERVOUS SYSTEM

- Voluntary activity & sensory perception are abolished.
- Brain is still receptive & shows evoked potentials in response to sensory stimuli as clicking sounds although these sounds may fail to arouse the sleeper.
- Protective spinal withdrawal reflexes are depressed but can still be elicited.
- Sleeping synchronizes various nervous centers together.
- The synchronization of nervous centers is the main function of sleep; i.e. putting all the nervous centers back to the zero line.
- This synchronization is disturbed during long periods of wakefulness which leads to ↑ in rate of error in judgment & behavior.
CARDIOVASCULAR SYSTEM

• There is slowing of HR to 60 beats/min
• Drop in the arterial BP.
• General slowing of circulation with prolongation of circulation time.

RESPIRATORY SYSTEM

• There is ↓ in rate & depth of breathing which ↓ pulmonary ventilation.
• Airway resistance ↑ because of ↑ed vagal tone.
• BLOOD PCO2 rises up with a tendency to acidosis due to ↓ed pulmonary ventilation.
• Hematocrit value ↑ because of chloride shift.
DIGESTIVE SYSTEM

• There is enhanced secretory and motor activity.
• Splanchnic blood flow ↑ & absorption is enhanced.

METABOLISM

• Metabolic rate decreases by 10-30 %.
• Body temperature drops by 0.5- 1°C.
• Circadian metabolic & temperature cycles are synchronized with waking/sleeping cycles, but are not dependent on sleep; i.e. they occur even without sleep.
ENDOCRINE GLANDS

• *Secretion* of most hormones show a variable degree of circadian rhythmicity which is synchronized with the waking/sleeping rhythm but again it is mostly independent of sleep.

• *ACTH* and *Cortisol* secretion $\downarrow$ to a minimal level at midnight & reaches a maximum level at 8 AM.

• Secretion of *growth* hormone, however, is directly related to sleep. It is stimulated by NREM sleep and inhibited by REM sleep.
SKELETAL MUSCLE TONE
• ↓es during sleep, it ↓ during REM more than during NREM sleep. It occurs by inhibition of facilitatory reticular formation.

KIDNEYS
• rate of urine formation ↑es due to ↓ sympathetic tone & ↑ renal blood flow.

PUPILS:
• constricted despite lid closure.
• Oculomotor nucleus is released from cortical inhibition.
• Parasympathetic tone is higher during sleep.
(1) Measurement and Stages of Sleep

Three principle measures of sleep:

(i) Electro-encephalogram (Head)
(ii) Electro-oculogram (Eye)
(iii) Electro-myogram (Neck)
sleep deprivation - Humans

- Recuperation theories predict that with sleep deprivation:

  (1) Increases in physiological/behavioural disturbances ✓
  (2) After deprivation, missed sleep must be regained ✗

- But, people recover well after sleep deprivation:
  Randy Gardner – 260 hrs awake: 1st recovery night 14 hrs sleep
  Then back to normal
Chemical Substances That Function as Synaptic Transmitters
More than 50 chemical substances have been proved to function as synaptic transmitters.

1\textsuperscript{st} group: \textit{small-molecule, rapidly acting transmitters}. Rapidly acting transmitters that cause most acute responses of nervous system, such as transmission of sensory signals to brain & of motor signals back to muscles.

2\textsuperscript{nd} group: \textit{neuropeptides} of much larger molecular size that cause more prolonged actions, such as long-term changes in numbers of neuronal receptors, long-term opening or closure of certain ion channels, & possibly even long term changes in numbers or sizes of synapses.
Small-Molecule, Rapidly Acting Transmitters

Class I
  Acetylcholine

Class II: The Amines
  Norepinephrine
  Epinephrine
  Dopamine
  Serotonin
  Histamine

Class III: Amino Acids
  Gamma-aminobutyric acid (GABA)
  Glycine
  Glutamate
  Aspartate

Class IV
  Nitric oxide (NO)
Neuropeptide, Slowly Acting Transmitters or Growth Factors

Hypothalamic-releasing hormones
  Thyrotropin-releasing hormone
  Luteinizing hormone–releasing hormone
  Somatostatin (growth hormone inhibitory factor)

Pituitary peptides
  Adrenocorticotropic hormone (ACTH)
  β-Endorphin
  α-Melanocyte-stimulating hormone
  Prolactin
  Luteinizing hormone
  Thyrotropin
  Growth hormone
  Vasopressin
  Oxytocin

Peptides that act on gut and brain
  Leucine enkephalin
  Methionine enkephalin
  Substance P
  Gastrin
  Cholecystokinin
  Vasoactive intestinal polypeptide (VIP)
  Nerve growth factor
  Brain-derived neurotropic factor
  Neurotensin
  Insulin
  Glucagon

From other tissues
  Angiotensin II
  Bradykinin
  Carnosine
  Sleep peptides
  Calcitonin
Acetylcholine

- Secreted by
  1. Terminals of large pyramidal cells from motor cortex,
  2. Basal ganglia,
  3. Motor neurons that innervate skeletal muscles,
  4. Preganglionic neurons of ANS,
  5. Postganglionic neurons of parasympathetic NS,
  6. Some of postganglionic neurons of sympathetic NS.

- In most instances, Ach has an excitatory effect; however, it have inhibitory effects at some peripheral parasympathetic nerve endings, such as inhibition of heart by vagus n.
**Norepinephrine (NE):**

- **secreted by:**
  - Most postganglionic neurons of sympathetic NS, where it excites some organs but inhibits others.
  - Terminals of many neurons whose cell bodies are located in brain stem & hypothalamus.

- Specifically, NE secreting neurons located in pons send nerve fibers to widespread areas of brain to help control overall activity & mood of mind, such as ↑ level of wakefulness.

- In most of these areas, NE probably activates **excitatory** receptors, but in a few areas, it activates **inhibitory** receptors instead.
**Dopamine**

- Secreted by neurons that originate in substantia nigra. Its is usually inhibition.

**Glycine**

- Secreted mainly at synapses in spinal cord. It acts as an inhibitory transmitter.

**GABA** (*gamma-aminobutyric acid)*:

- Secreted by nerve terminals in spinal cord, cerebellum, basal ganglia, & many areas of cortex.
- It causes inhibition.
Glutamate:
• Secreted by presynaptic terminals in many of sensory pathways entering CNS, as well as in many areas of cerebral cortex. It always causes excitation.

Serotonin:
• Secreted by nuclei that originate in median raphe of brain stem & project to many brain & spinal cord, & to hypothalamus.
• It acts as an inhibitor of pain pathways in cord, and an inhibitor action in higher regions of NS is believed to help control mood of person, even to cause sleep.
Nitric oxide

- Secreted by nerve terminals in areas of brain responsible for long-term behavior & for memory.
- It is different from other small molecule transmitters in its mechanism of formation in presynaptic terminal & in its actions on postsynaptic neuron:
  1- It is not preformed & stored in vesicles in presynaptic terminal as are other transmitters. It is synthesized almost instantly as needed, and it then diffuses out of presynaptic terminals over a period of seconds.
  2- It diffuses into postsynaptic neurons nearby.
  3- In postsynaptic neuron, it usually does not greatly alter membrane potential but instead changes intracellular metabolic functions that modify neuronal excitability for seconds, minutes, or perhaps even longer.
Neuropeptides

• They are not synthesized in cytosol of presynaptic terminals. Instead, they are synthesized as integral parts of large-protein molecules by ribosomes in neuronal cell body.

• Protein molecules then enter inside ER of cell body & subsequently inside Golgi apparatus, where two changes occur:

  1- neuropeptide-forming protein is enzymatically split into either neuropeptide itself or its precursor.

  2- Golgi apparatus packages neuropeptide into minute transmitter vesicles that are released into cytoplasm. Then transmitter vesicles are transported to the tips of nerve fibers by *axonal streaming* of axon cytoplasm, traveling at the slow rate of only a few centimeters per day. Finally, these vesicles release their transmitter at the neuronal terminals in response to action potentials in the same manner as for small-molecule transmitters.
• Much smaller quantities of neuropeptides are usually released than of small-molecule transmitters.
• This is compensated for by fact that neuropeptides are generally a thousand or more times as potent as small-molecule transmitters.
• Another important characteristic of neuropeptides is that they often cause much more prolonged actions. Some of these actions include prolonged closure of calcium channels, prolonged changes in metabolic machinery of cells, prolonged changes in activation or deactivation of specific genes in cell nucleus, &/or prolonged alterations in numbers of excitatory or inhibitory receptors. Some of these effects last for days, but others perhaps for months or years.