Sleep (continued)

**Neural control of arousal**

- Neuro modulators

- **ACh** from the pons and basal forebrain, behavioral activity levels correlate with ACh levels. Desynchronize the EEG. Controls neural excitability. ACh high in REM sleep.

- **NE** from the locus coeruleus: vigilance, attention, amphetamines, produces arousal

- **5HT** from the Raphe nuclei (in pons)” correlates with sleep stages. Active during transitions out of REM sleep

- **Histamines** (tuberomammilary, nucleus, and hypothalamus): activate the cortex directly and indirectly (through basal forebrain ACh) **Anti-Histamines** promote drowsiness

- **Orexin**: excitatory projections to cortex and many neuromodulatory centers. Wakefulness promoting. Indirect arousal effects, narcolepsy when damaged

**Neural control of sleep**

*What makes us go to sleep?*

- Adenosine hypothesis: adenosine accumulation during the awake period. Adenosine as a sleep promoting substance

**Awake state**

Astrocytes-(Glycogen fuel) -> Neurons

Astrocytes-(Adenosine) -> Neurons

Glycogen depletion-> Increase in adenosine-> progressive increase in general inhibition-> increase in sleep tendency

**Sleep state**

Glycogen-> Astrocytes
Neural bases of sleep: SWS

**Ventral lateral Preoptic Area (vLPOA)**

Destruction->No sleep-> death

Stimulation-> drowsiness and delayed sleep

Mutual inhibition: vLPOA sends inhibitory projections in histamine, Ne, 5HT, ACh systems, and these systems in turn inhibit the vLPOA

Flip flop circuitry

On: Inhibited: Sleep promoting region in vLPOA-> activated: brain stem and forebrain arousal (alert waking state)

Off: Activated: Sleep promoting region in vLPOA-> inhibited: brain stem and forebrain arousal system(slow wave sleep

**Turning the flip-flop on:** orexin neurons

-orexin neurons active during awake state and project to the arousal system

ON: motivation to remain awake, stimulus driven, mediated by external signals, biological clocks, hunger signals

**Neural control of sleep:** SWS

**Turning the flip-flop off:** the adenosine hypothesis

-active state: glucose consumption from blood

-when blood glucose not sufficient, use glycogen

-glycogen-> (locally) glucose adenosine (nucleoside transmitter)

-Adenosine accumulate in those parts of the brain that were the most active

-Adenosine is inhibitory-> decrease brain stem activity-> increase vLPOA-> SWS

Off: also related to food consumption: satiety signals inhibit orexin neurons

**Therapeutic manipulations of SWS**

Prolonged total sleep deprivation leads to loss of body weight, temperature deregulation and eventually death

However 1 night sleep deprivation (total or 2nd half of the night) has antidepressant effect
Neural control of sleep: REM

dreams=windows to the psyche, 65% sad, angry 20% happy excitement 1% sexual

Executive mechanism (switch, flip-flop)

-ACh levels are high during REM(and awake) from pons

REM Flip flop

-mutual inhibition: sublaterodorsal nucleus(SLD): ventrolateral PAG (vPAG)

SLD projections can explain the normal features of REM

-Cortical Activation: Thalamus (dream content), Medical Pontine Reticular Formation (dream intensity)

-REM: Tectum (superior colliculi)

-Genital Activity: lateral Preoptic area (sexual preparedness)

-Atonia: medulla, prevents the acting out of dreams

-Lesion of paralysis neurons (in medulla) yield REM without atonia

When orexin neurons are damaged: emotional stimuli take over (cataplexy)

Amygdala and Hypothalamus

Biological rhythms

-internal clocks

-Infadian (less than 1 day)

-circadian (one day): sleep/wake cycle- 25 hours free running

-supradian (more than one day): menstrual cycle

-Circannual(one year): hibernation

-Suprachiasmatic Nucleus: Circadian/Supradian

-time scale day-> month
- Small (8600 cells) within the hypothalamus
- Reset by light (retina-hypothalamic tract)" melanospin in special retinal ganglion cells projecting to SCN. LIGHT IS A zeitgeber (giver of time)
- Intrinsic and network rhythmic phenomena: SCN neurons by themselves or as a group in a dish have a circadian rhythm
- Transplantation studies indicate the SCN uses chemical non-synaptic connection to affect its targets

SCN sends inputs to the SWS flip-flop. Inhibits vLPOA (decrease drowsiness), excite orexin neurons (promote wakefulness)

- SCN tickling= slow production of a self-inhibiting protein
- Normal sleep onset: 10-11pm, Average length 8 hours
- Advanced sleep phase syndrome: sleep onset 6-7pm, wake up 3-4am. Genetic mutation
- Delayed sleep phase syndrome: sleep onset 2-3am, wake up 10-11 am, genetic mutation
- Normal genetic variations may explain normal variations in sleep onset time and sleep duration

Pineal Gland: circadian/Circannual
- In the midbrain (near cerebellum) secretes melatonin (during night)
- Melatonin: highest levels just before bedtime
- Melatonin helps jet-lag (take before adjusted bed-time) side effects: depression, low sex drive, weight loss
- Melatonin helps blind people to sleep better