Neural control of arousal – neuromodulators

- ACh from the pons and basal forebrain. Behavioral activity levels correlate with Ach levels. Desynchronize the EEG. Controls neural excitation. ACh high in REM sleep
- NE from the locus Coeruleus: vigilance, attention, Amphetamines (NE agonists) Produce arousal
- 5HT from the raphe nuclei (in the pons). Correlates with sleep stages. Active during the transitions out of REM sleep.
- Histamines (tuberomammillary nucleus, hypothalamus): activates the cortex directly, and indirectly (through basal forebrain ACh). Anti-histamines promote drowsiness.
- Orexin (a.k.a. Hypocretin, from lateral hypothalamus): Excitatory projections to cortex and many neurology centers. Wakefulness promoting. Indirect arousal effects. Narcolepsy when damaged

Neutral control of sleep: SWS

- Central question – what makes us go/transition to sleep?
- Adenosine Hypothesis: Adenosine accumulation during the awake period. Adenosine as a ‘sleep promoting substance’
- Glycogen depletion -> increase in adenosine -> progressive increase in general inhibition -> increase in sleep tendency

Neutral bases of sleep: SWS

- Ventrolateral Preoptic area (vLPOA)
  - Destruction -> no sleep -> death
- Stimulation -> drowsiness -> and delayed sleep.
- Mutual inhibition: vLPOA sends inhibitory projections to Histamine, NE 5HT, Ach systems. These systems in turn inhibit the vLPOA.
- Can be unstable -> narcolepsy, sleep attacks (low arousal state)
- Turning the flip-flop ON: orexin neurons
  - Orexin neurons active during awake state and project to the arousal systems
  - ON: ‘motivation to remain awake’, ‘stimulus driven’, medicated by external signals: biological clocks, hunger signals
- Turning the flip-flop OFF: the adenosine hypothesis
Active state: glucose consumption from blood
- When blood glucose not sufficient, used 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

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

**Neutral control of sleep: REM**

- Dreams – 65% sad/angry 20% happy/excitement, 1% sexual
  - ACh levels are high during REM (and awake). From Pons
- REM flip flop
  - Mutual inhibition: Sublaterodorsal nucleus (SLD) and Ventrolateral PAG (vLPAG)
  - Orexin neurons also influence rem flip flop. Cataplexy
- SLD projections explain the normal features of rem sleep:
  - Cortical Activation: thalamus (dream content), Medial 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

Putting it all together
- When Orexin Neurons are damaged: Emotional stimuli take over (cataplexy),
- What controls the SLD? Amygdala and hypothalamus

**Biological rhythms**

- Internal clocks
- Infradian – less than a day (hunger)
- Circadian – 1 day, sleep/wake cycle 25 hours
- Supradian – More than 1 day (menstrual cycle)
- Circannual – 1 year (hibernation)

Suprachiasmatic Nucleus: Circadian/ Supradian

- Time scale – day -> month
- Small (8600 cells) within the hypothalamus
• Reset by light (retino-hypothalamic tract) melanism 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 circadian rhythm
• Transportation studies indicate the SCN uses the Chemical non-synaptic connection to affect its targets
• SCN ticking – slow production of a self-inhibiting protein
• Normal sleep onset: 10-11PM average 8 hours
• Advanced sleep phase syndrome: sleep onset 6-7PM wakeup 3-4AM, genetic mutation
• Delayed sleep phase syndrome: sleep onset 2-3AM, wakeup 10-11AM genetic mutation
• Normal genetic variations may explain normal variations in sleep onset time and sleep duration

Circadian rhythms
• Pineal gland: circadian/circannual