Class 13-Sleep continued

Neural Control of Arousal

- Neural control of arousal: neuromodulators
  - ACh from the pons and basal forebrain. Behavioral activity levels correlate with the ACh levels. Desynchronized the EEG. Controls neural excitability. ACh high in REM sleep.
  - Norepinephrine from the locus coeruleus: Vigilance, attention. Amphetamines (NE agonists) produce arousal

**Figure 8.10

- 5HT (Serotonin) from the raphe nuclei (in the Pons). Correlates with sleep stages. Active during the transitions out of REM sleep.
- Histamines (Tuberomammillary nucleus, hypothalamus):
  → activate the cortex directly, and indirectly (through basal forebrain ACh).
  Anti-histamines promote drowsiness
- Orexin (aka Hypocretin, lateral hypothalamus):
  → Excitatory projections to cortex and many neuromodulatory centers.
  Wakefulness promoting. Indirect arousal effects. Narcolepsy when damaged.

**Figure 8.12
Neural Control of Sleep

- What makes us go/transition to sleep?
  - **Adenosine Hypothesis**: adenosine accumulation during the awake period. Adenosine as a ‘sleep promoting substance’
    - Awake state: adenosine secreted by astrocytes. Astrocytes providing glycogen (fuel) to neurons if needed. Astrocytes providing neurons with energy
      **Glycogen depletion → increase in adenosine → progressive increase in general inhibition → increase in sleep tendency**
  - Sleep state: Glycogen → Astrocytes

Neural 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
  - **Flip-Flop circuitry**: **Figure 8.13**
    - If flip-flop is on, meaning the sleep-promoting region in vLPOA is inhibited, you’re in alert waking state, if flip-flop is off, you’re in slow-wave sleep because the sleep-promoting region in vLPOA is activated
  - 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...

**Figure 8.14**
-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
   - (eventually) death
-However: 1 night sleep deprivation (total, or 2\textsuperscript{nd} half of 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’)
-\(\text{ACh}\) levels are high during REM (and awake). From Pons

\*\*Figure 8.16\*
-REM position: likely in the ‘fetal’ position while asleep
-REM flip-flop
  -Mutual inhibition: sublaterodorsal nucleus (SLD) and ventrolateral PAG (vlPAG)
  -Orexin neurons also influence the REM flip-flop. Cataplexy.

**Figure 8.17**

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**Neural Control of REM Sleep**

- 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

**Figure 8.20**

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**Neural Control of Sleep**

- When Orexin neurons are damaged: Emotional stimuli take over (cataplexy). Amygdala and hypothalamus
  - i.e. guy who was playing the ‘slap the hand’ game and falls asleep from high arousal

**Figure 8.18 and 8.19**
Biological Rhythms

- Internal clocks
  - InfraDian (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 (8,600 cells), within the Hypothalamus
  - Reset by light (retino-hypothalamic tract). Melanopsin 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
Figure 8.21

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

Figure 8.24

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

Figure 8.26

Circadian Rhythms
- Pineal Gland: Circadian/Circannual
  - In midbrain (near cerebellum).
    → Secretes Melatonin (during night)
Melatonin has slow (cumulative) actions in the periphery (sympathetic system):
Seasonal time keeper in most animals (humans?)
-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