Neural control of arousal: Neuromodulators

- ACH from **pons** and **basal forebrain**
  - Behavioral activity levels correlate with ACH levels
  - Desynchronizes the EEG
  - Controls neural excitability
  - ACH is high in REM sleep

- NE from **locus coeruleus**: vigilance attention
  - Amphetamines (NE agonists) produce arousal
  - waking-> slow wave-> REM-> waking

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

- **Histamines** from **Tuberomammillary Nucleus, Hypothalamus**:
  - Activates the cortex directly and indirectly (through basal forebrain ACH)
  - **Anti-histamines promote drowsiness**

- Orexin (aka Hypocretin) lateral hypothalamus...where it secretes:
  - Excitatory projections to cortex and many neuromodulatory centers.
  - **Wakefulness promoting**
  - Indirect arousal effects
  - Causes narcolepsy when damaged

Neural Control of Sleep
(What makes us go/transition to sleep?)

- **Adenosine Hypothesis**: adenosine accumulation during awake period
  - Sleep promoting substance
  - Awake state: Glycogen depletion→ increases in adenosine→ progressive increase in general inhibition→ increases 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.
  - Systems in turn inhibit the VLPOA

- **Flip-Flop circuitry:**
  - Can be unstable: narcolepsy, sleep, attacks (low arousal state)
  - Either asleep (OFF) or awake (awake) never both

  - **Turning Flip-Flop on:** Orexin neurons
    - Orexin neurons active during awake state and project to arousal systems on: motivation to remain awake, stimulus driven; mediated by external signals: Biological clocks, hunger signals

  - **Turning Flip Flop off:** The adenosine Hypothesis is
    - **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 most active
    - Adenosine is inhibitory → decrease brain stem activity → increase VLPOA → SWS

    - **OFF:** also related to food consumption: Satiety signals inhibit orexin neurons

Therapeutic Manipulators of SWS?

- Prolonged total of sleep deprivation leads to loss of body weight, temp. Deregulation and (eventually) death
- However: 1 night sleep deprivation (total, or 2nd half of night) has antidepressant effect.

Neural control of Sleep: REM

- Dreams = windows to the ‘Psych’ 65%: sad, angry, 20% happy, excitement, 1% sexual
- Executive Mechanism (switch, ‘flip-flop’)
  - ACH levels are high during REM (and awake) from pons
  - REM-on cells
  - Active just before REM onset: cause REM?

  *Dreams are constructions of the brain*

  Typical transition to REM (fetal position)

- REM flip-flop
Mutual inhibition: Sublaterodorsal nucleus (SLD) and Ventrolateral PAG (VLPAG)
- Orexin neurons also influence the REM flip-flop cataplexy

### Neural Control of REM Sleep
- SLD projections explain normal features of REM sleep:
  - **Cortical Activation**: Thalamus (dream content) Medial Pontine Reticular Formation (dream density)
  - **REM**: tectum (Superior colliculi)
  - **Genital Activity**: lateral preoptic area (sexual preparedness)?
  - **Atonia**: medulla, prevents acting out of dreams
  - Lesion of paralysis neurons (in medulla) yield REM without atonia
  - When orexin neurons are damaged: Emotional stimuli take over (cateplexy) amygdala and hypothalamus

### Biological Rhythms:
- **Internal Clocks**
  - Infradian (less than 1 day)
  - **Circadian** (1 day): Sleep/Wake cycle ~25 hours free running
  - Supradian (more than one day): menstrual cycle
  - Circannual (1 year): Hibernation
- **Suprachiasmatic Nucleus**: Circadian/Supradian
  - Time scale: day → month
  - Small (8600 cells), within 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 study indicates SCN uses chemical non-s
- Scn sends inputs to SWS flip-flop
  - Inhibits VLPOA (decreases drowsiness)
  - Invite orexin neurons (promote wakefulness)
- SCN ticking =slow production of a self-inhibiting protein
- Normal sleep onset: 10-11pm average length is 8 hours.
- Advanced sleep phase syndrome: Sleep onset 6-7pm, wakeup is 3-4am. genetic mutation
- Delayed sleep phase syndrome: sleep onset 2-3am, wake up 10-11am. Genetic mutation
  - Normal genetic variations may explain ‘normal’ variations in sleep onset time and sleep duration.

### Circadian Rhythm
- **Pineal Gland**: Circadian/circannual
  - In midbrain (near cerebellum). Secretes melatonin (during night)
  - Melatonin has slow (cumulative)actions in periphery (sympathetic systems): seasonal time keeper in most animals.
  - Melatonin: increase levels **before bedtime**
  - Melatonin helps jet-lag (take before bedtime)
    - Side effects: depression, low sex drive, weight loss
  - Melatonin helps blind people to sleep better