Neural control of arousal: neuromodulators
- 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 (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): activate the cortex directly, and indirectly (through basal forebrain Ach). Anti–histamines promote drowsiness.
- Orexin (aka hypocretin, from lateral hypothalamus): excitatory projections to cortex and many neuromodulatory centers. Wakefulness promoting. Indirect arousal effects. Narcolepsy when damaged.

Neural control of sleep
Central question: what makes us go/ transition to sleep?
- Adenosine hypothesis: adenosine accumulation during the awake period. Adenosine as a ‘sleep promoting substance’

Awake state

<table>
<thead>
<tr>
<th>Adenosine</th>
<th>Neurons</th>
<th>Glycogen</th>
<th>Fuel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytes</td>
<td></td>
<td>Glycogen</td>
<td>(fuel)</td>
</tr>
</tbody>
</table>

Glycogen depletion -> increase in adenosines -. Progressive increase in. general inhibition -. Increase in sleep tendency

Sleep state: restorative process

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:
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’, mediated by external signals: biological clocks

Turning the flip-flop ‘OFF’: the adenosine hypothesis
- Activate state: glucose consumption from blood
- When blood glucose not sufficient, use glycogen
- Glycogen -\(\rightarrow\) (locally) glucose + adenosine (nucleoside transmitter)
- Adenosines accumulate in those parts of the brain that were most active
- Adenosine is inhibitory -\(\rightarrow\) decrease brain stem activity -\(\rightarrow\) increase vLPOA -\(\rightarrow\) SWS.

Off: also related to food consumption: satiety signal (that your belly is full) inhibit orexin neurons.

Therapeutic manipulators of SWS?
- Prolonged total sleep deprivation leads to loss of body weight, temperate deregulation and (eventually) death.
  - However: 1 night sleep deprivation (total or 2\(^{nd}\) half of night) has antidepressant effect.

Neural control of Sleep: REM
- Dreams= windows to the ‘psyche’. Psychoanalysis. 65%: sad, angry, 20% happy excitement, 1% sexual.

Executive Mechanisms (‘switch’, flip flop)
- ACh levels high during REM (and awake) from pons.

Neural basis of REM sleep- REM flip- flop
Mutual inhibition: Sublaterodorsal nucleus (SLD) and ventrolateral PAG (vlPAG)
  (Pons) (Tegmentum, midbrain)

Orexin neurons also influence the rem flip flow. Cataplexy (REM sleep disorder.)
SLD projections explain the normal features of REM sleep:
- Thalamus (dream content), Medial Pontine Reticular Formation (dream, intensity) -\(\rightarrow\) cortical activation
- REM: tectum (superior colliculi)
- Genital activity: Lateral preoptic area (sexual preparedness?)
- Atonia (loss of tone, don’t contract any muscle): medulla, prevents the ‘acting out’ of dreams. Lesion of ‘paralysis neurons’ (in medulla) yield REM without atonia.

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

Biological Rhythms
- Internal clocks
  - infradian (less than 1 day)
  - circadian (one day): sleep/wake cycle. Approx. 25 hrs. free running
  - supradian (more than 1 day): e.g. menstrual cycle.
  - circannual (1 yr.): hibernation
**Suprachiasmatic Nucleus: circadian/Supradian**
- time scale: day -> month
- small (8600 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.

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

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

**Pineal gland: circadian/circannual**
- In midbrain (near cerebellum). Secretes melatonin (during night)
- Melatonin has slow (cumulative) actions in the periphery (sympathetic system): seasonal timekeeper in most animals (humans?)
- Melatonin: highest levels just before bedtime
- Melatonin helps jetlag (take before adjusted bedtime). Side effects: depression, low sex drive, weight loss.
- Helps blind people sleep better.