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Neurological Basis of Sleep

Simon J. Durrant, PhD DPhil



British Sleep Society



UK Multidisciplinary Sleep Professionals



Nederlandse vereniging voor
SLAAP- EN WAAKONDERZOEK
www.nswo.nl



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1. I do not have any potential conflicts to disclose.



2. I wish to disclose the following potential conflicts of interest:

Type of Potential Conflict	Details of Potential Conflict
Grant/Research Support	
Consultant	
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3. The material presented in this lecture has no relationship with any of these potential conflicts, **OR**



4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

- 1.
- 2.
- 3.

Sleep is a very important part of our lives. The neurological control of sleep is an ongoing field of study, but many key mechanisms have already been uncovered.

Wakefulness Systems

- The ascending reticular arousal system.
- The cholinergic pathway.

NREM Systems

- The ventrolateral preoptic area.
- Suppression of wakefulness systems.

The Flip-Flop Model and Orexin/Hypocretin

- The flip-flop sleep/wake mechanism.
- The stabilising mechanism of orexin.

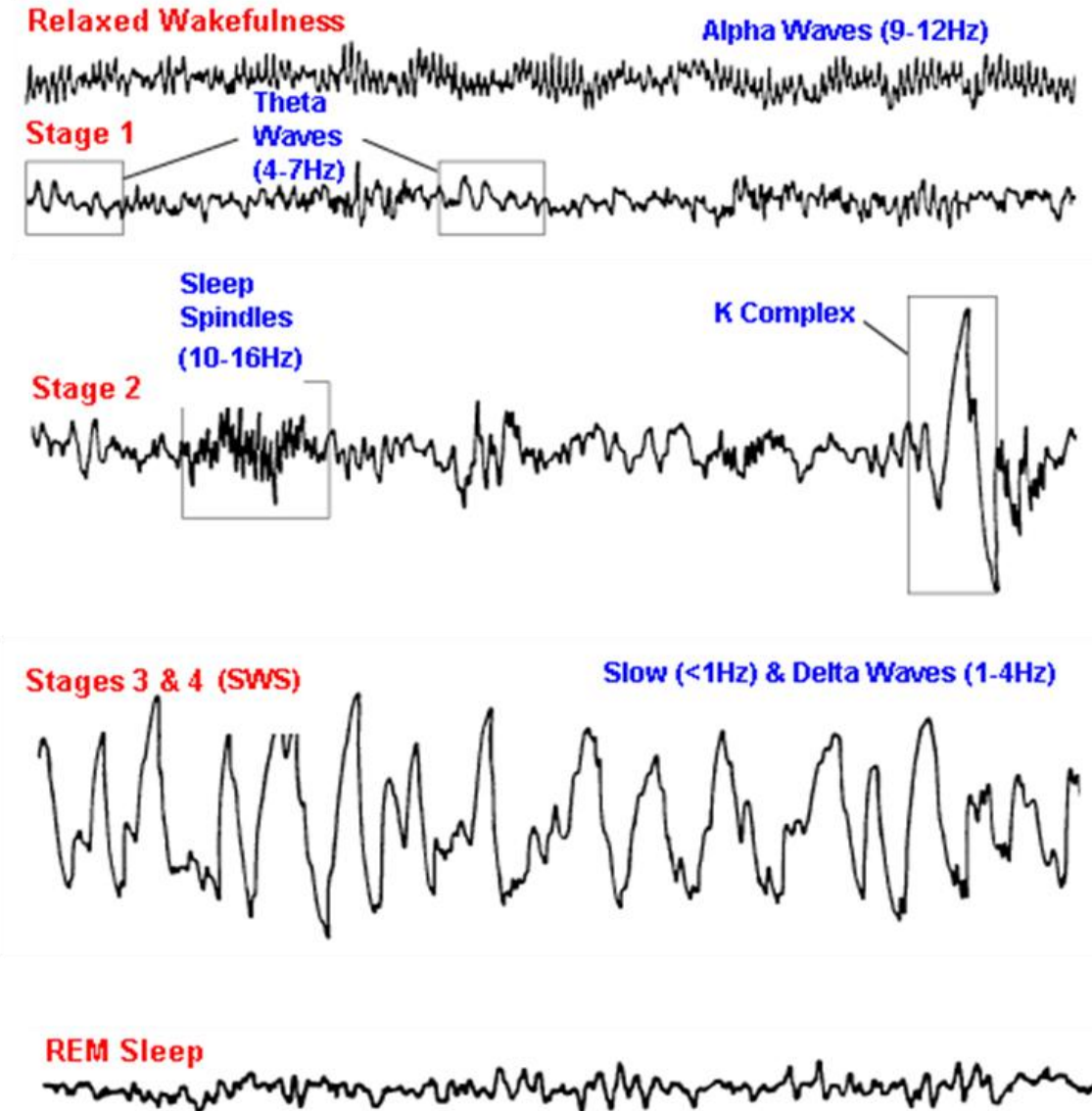
REM Systems

- Disinhibition of REM-suppressing areas.
- Activation of the sublaterodorsal tegmental nucleus.

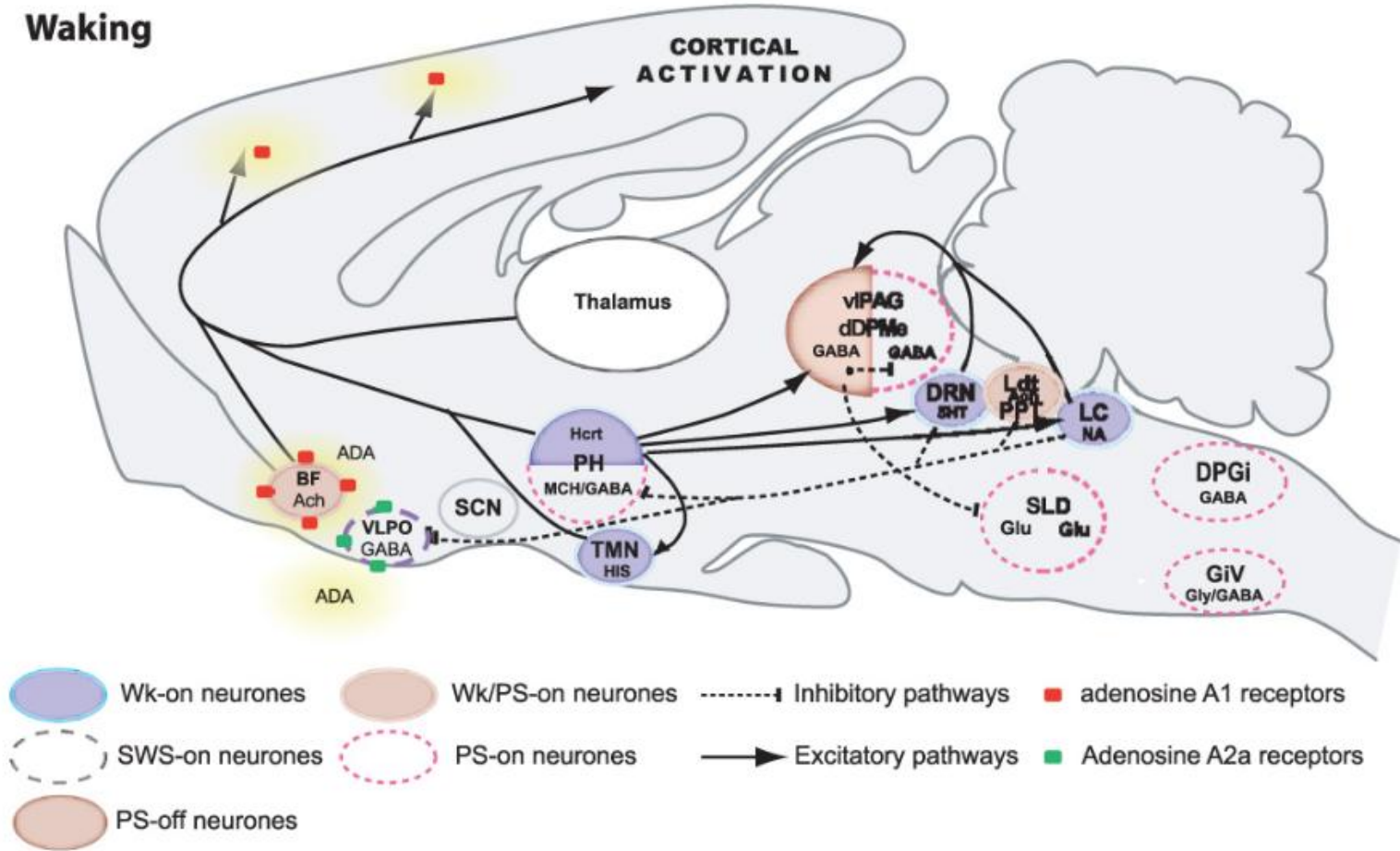
Homeostatic and Circadian Triggers

- Homeostatic effect of adenosine.
- Circadian influence of the suprachiasmatic nucleus.

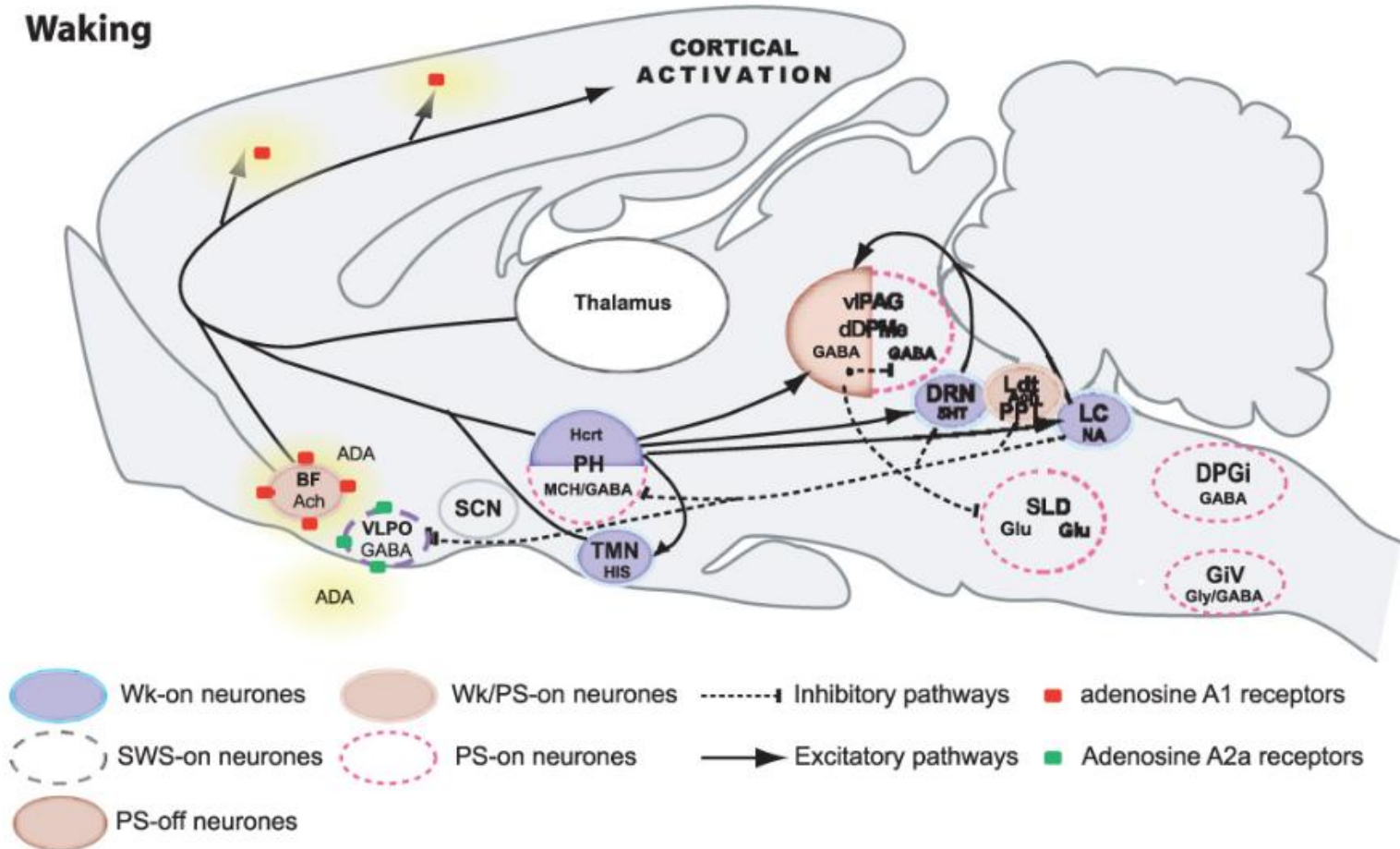
- Insects and Reptiles: two main vigilance states (wake and NREM sleep).
- Birds and Mammals: three main vigilance states (wake, NREM and REM sleep).
- In humans, we typically subdivide NREM further into three (formerly four) states.
- NREM characterised by slow oscillations – thalamocortical default.
- REM (PS) characterised by theta waves, muscle atonia and eye movements.



- Wake-promoting ascending reticular activating system (ARAS).
- Monoaminergic system: locus coeruleus (NA); dorsal raphe nucleus (5-HT); tuberomammillary nucleus (HIS).
- DRN and LC inhibit the GABAergic VLPO (through NA and 5-HT).
- DRN and LC activate ventrolateral periaqueductal grey – suppress REM.



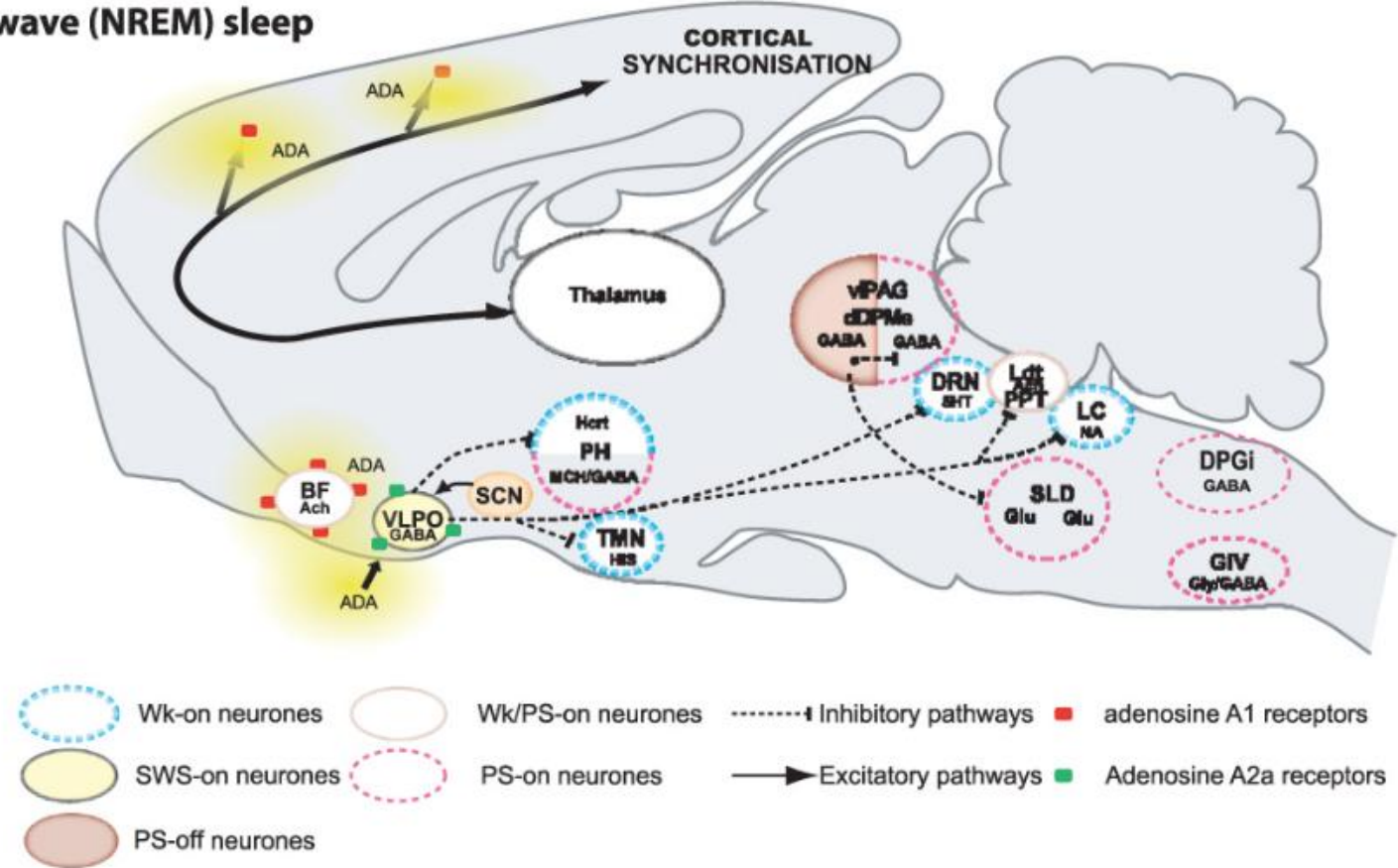
- Cholinergic system: basal forebrain and pedunculopontine tegmental nucleus.
- PPT inhibits the GABAergic VLPO (through Ach).
- Activation of ARAS suppresses sleep-inducing areas (esp. VLPO) and maintains wakefulness.



- Ventrolateral preoptic nucleus (VLPO) central to NREM sleep:-

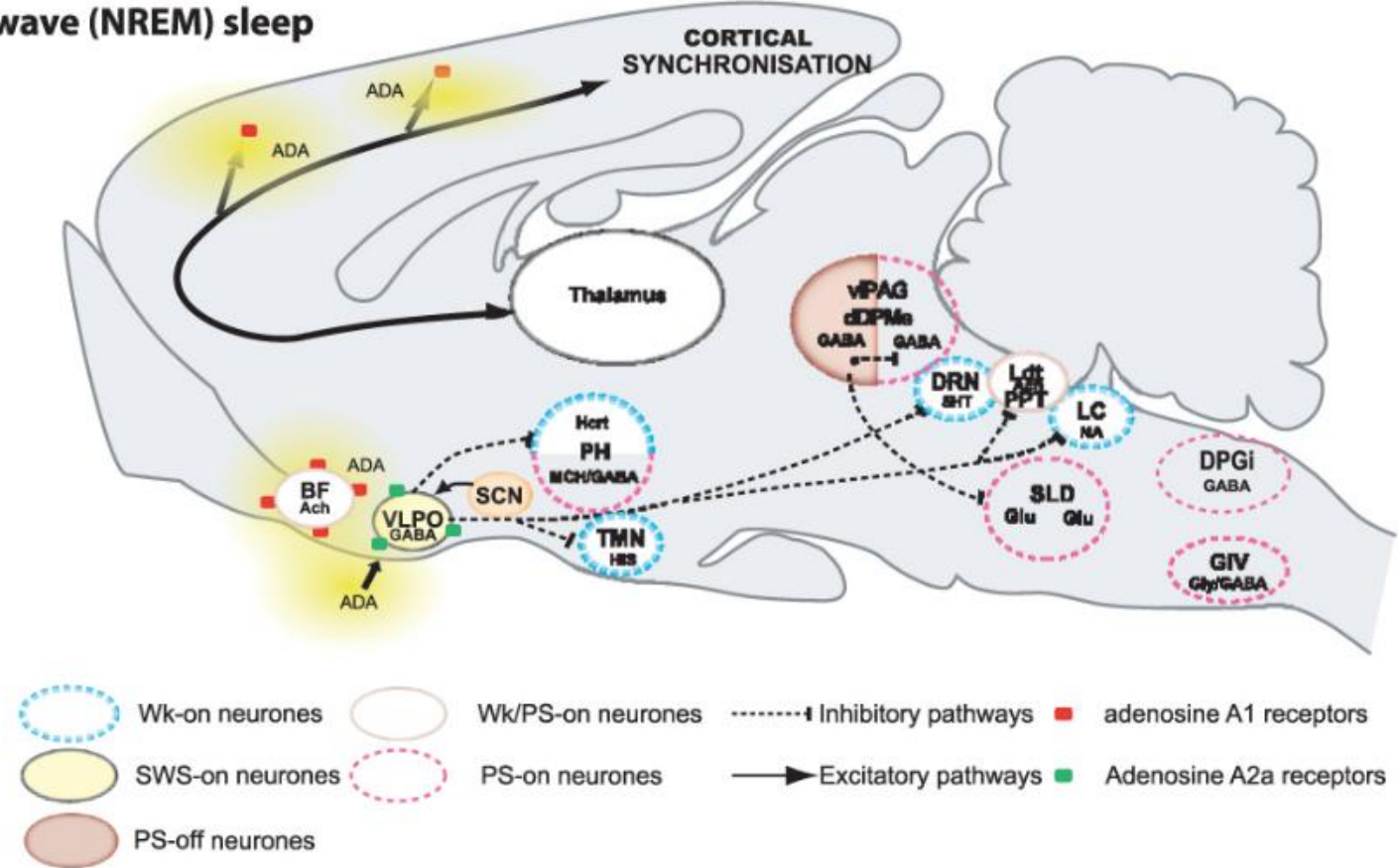
- GABAergic, inhibits ARAS (aminergic)
- Inhibits orexinergic neurons (Hcrt) in the posterior hypothalamus.
- Promotes slow oscillations (SOs); cortical synchronisation.
- Median preoptic nucleus (MnPn) also involved with similar function.

Slow-wave (NREM) sleep



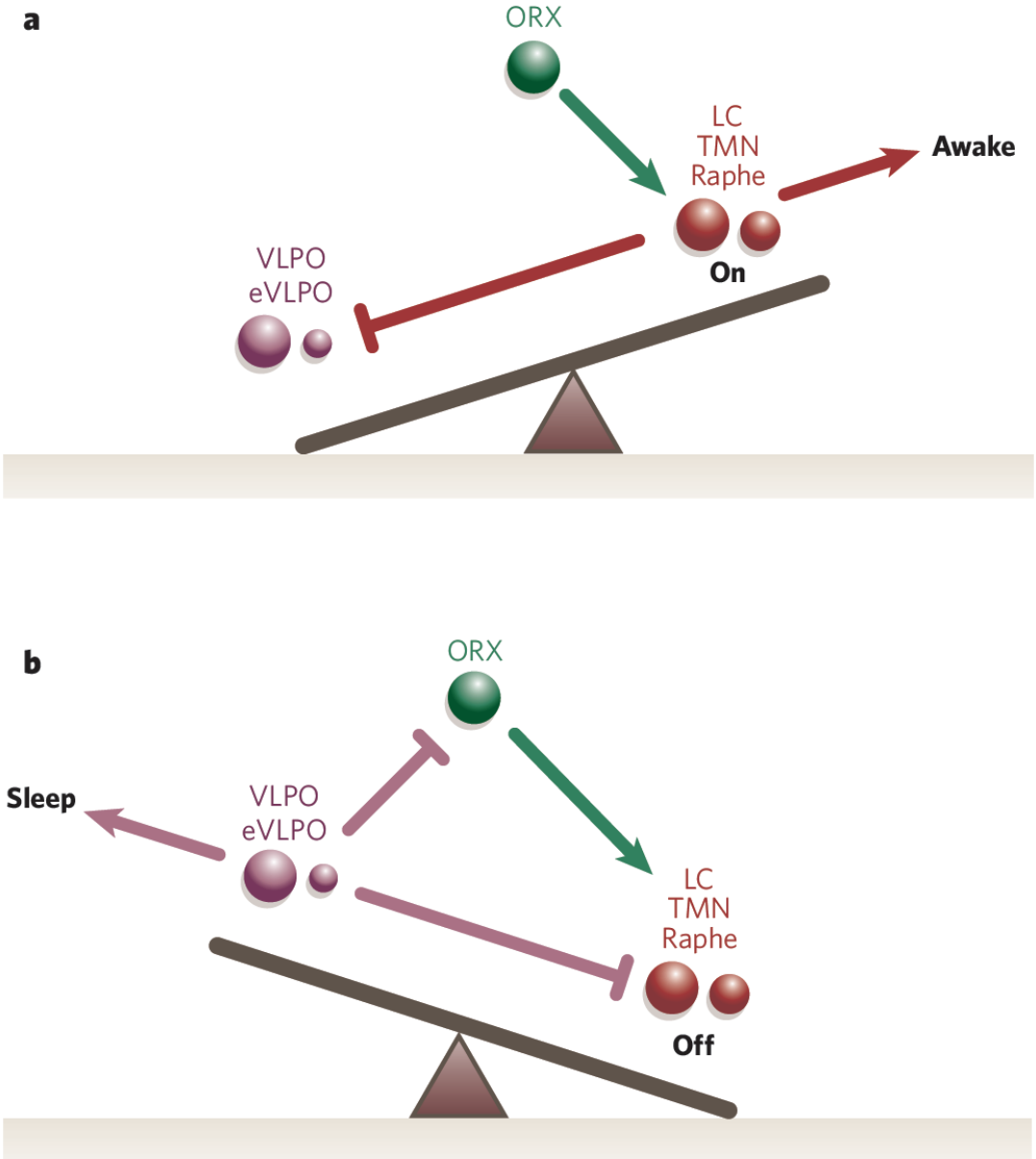
- Cholinergic pathway switched off (BF suppressed by adenosine, PPT suppressed by GABA from VLPO)
- Positive afferents from the SCN (via the dorsomedial hypothalamus).
- Adenosine inputs, especially from the basal forebrain.
- NREM is caused by switching off wake and not switching on REM.

Slow-wave (NREM) sleep

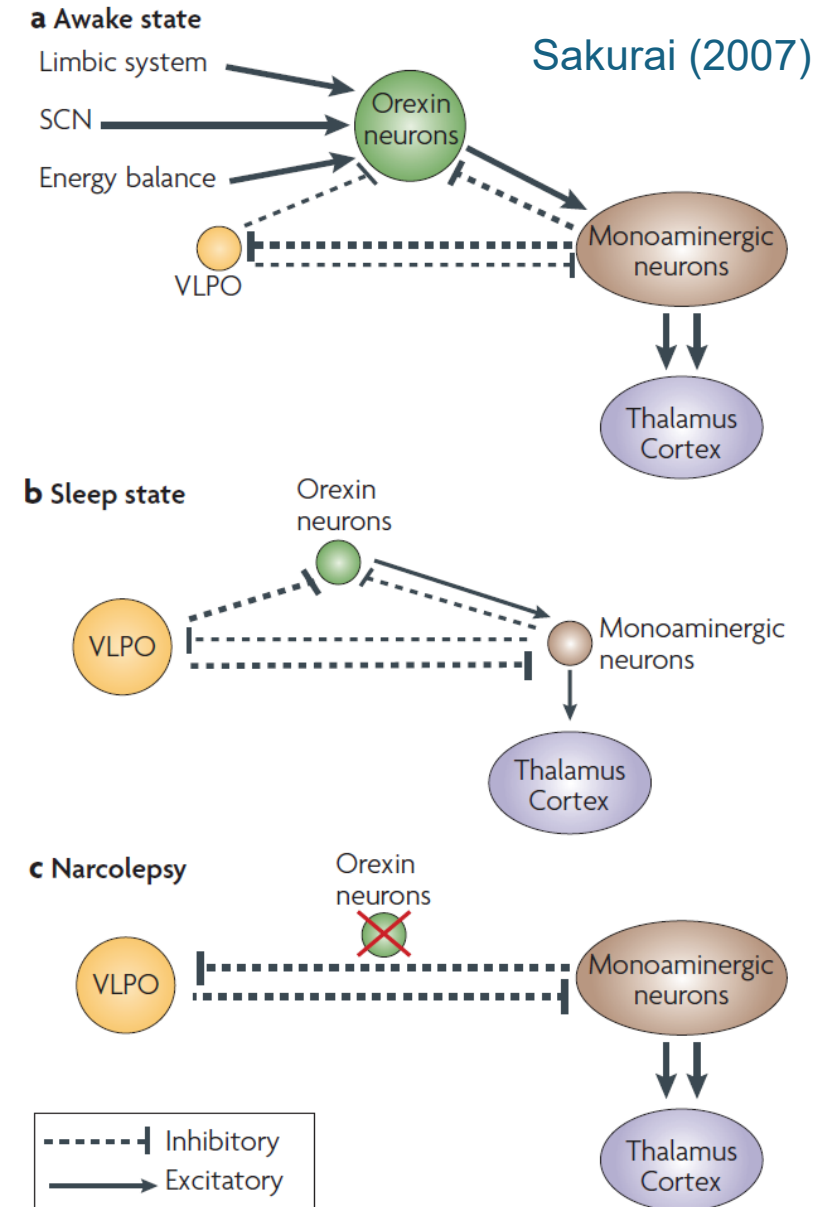


- During wake, the monoaminergic areas of the ARAS inhibit the VLPO.
- During sleep, the GABAergic neurons of the VLPO inhibit the ARAS wake-promoting areas.
- This mutual inhibition is inherently unstable; a small change in one creates a feedback loop that magnifies the effect and creates a state change.
- In order to stabilise the system, an asynchrony is required. This is given by orexin.

Saper et al. (2005)

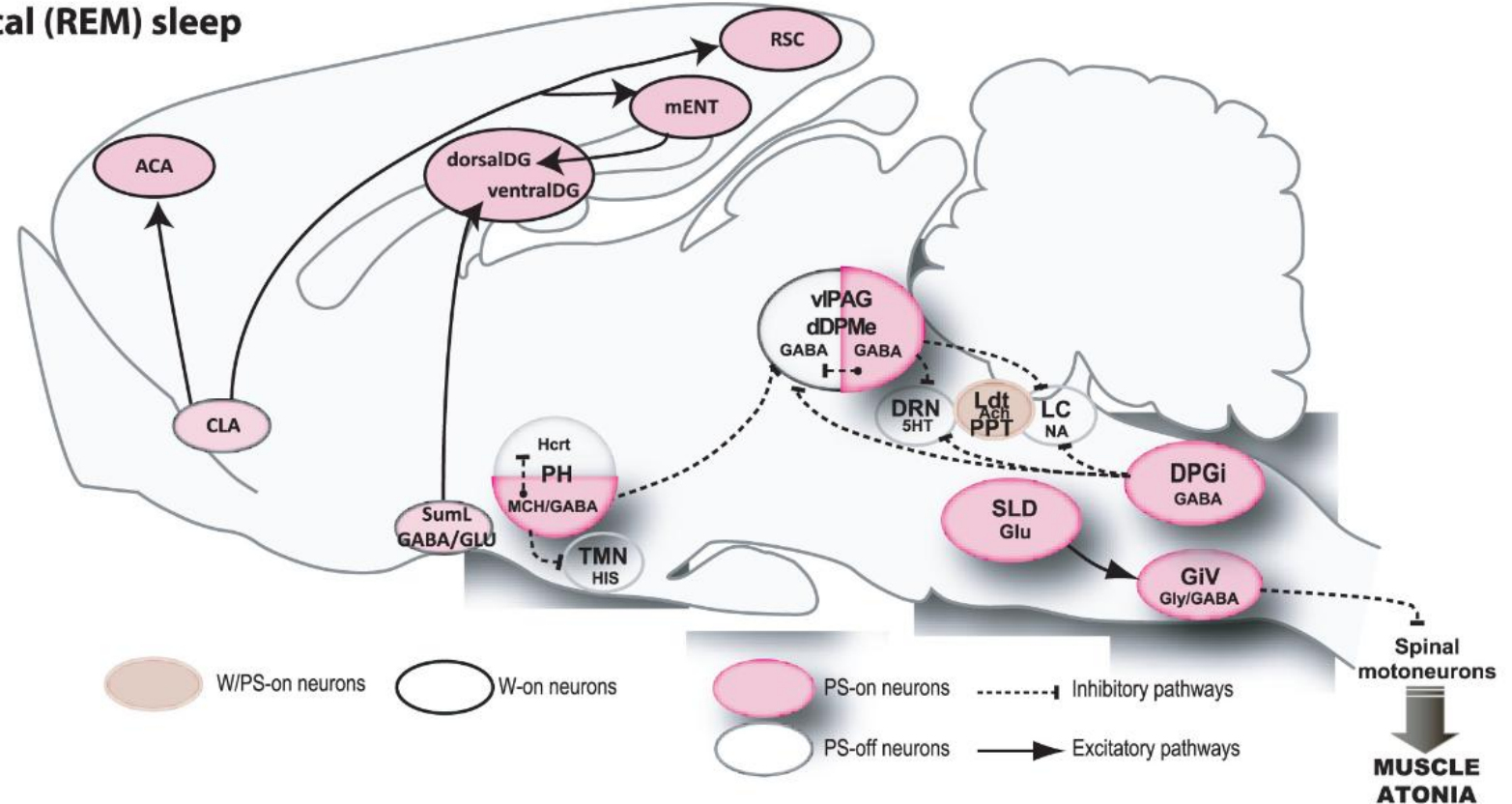


- Orexin stabilises the flip-flop model, particularly during wake.
- Active orexinergic neurons strengthen wake-promoting areas, which in turn inhibit orexin, establishing a balance/equilibrium.
- If wake areas become slightly less active, the orexinergic neurons become stronger and maintain wakefulness.
- During sleep, this mechanism is reduced, and sleep is more likely to be interrupted by wake than vice versa.
- The loss of orexin neurons typically results in narcolepsy, where the unstable flip-flop behaviour is in evidence with rapid wake-sleep transitions.



- During wake, ARAS suppresses PH and ventrolateral periaqueductal grey through GABA.
- During NREM, intrinsic PH and vLPAG GABA inhibition remains on.
- REM triggered by disinhibition of PH, which then disinhibits vLPAG/dDPMe, and dorsal paragigantocellular nucleus
- These in turn disinhibit the sublateralodorsal tegmental nucleus (Glu).

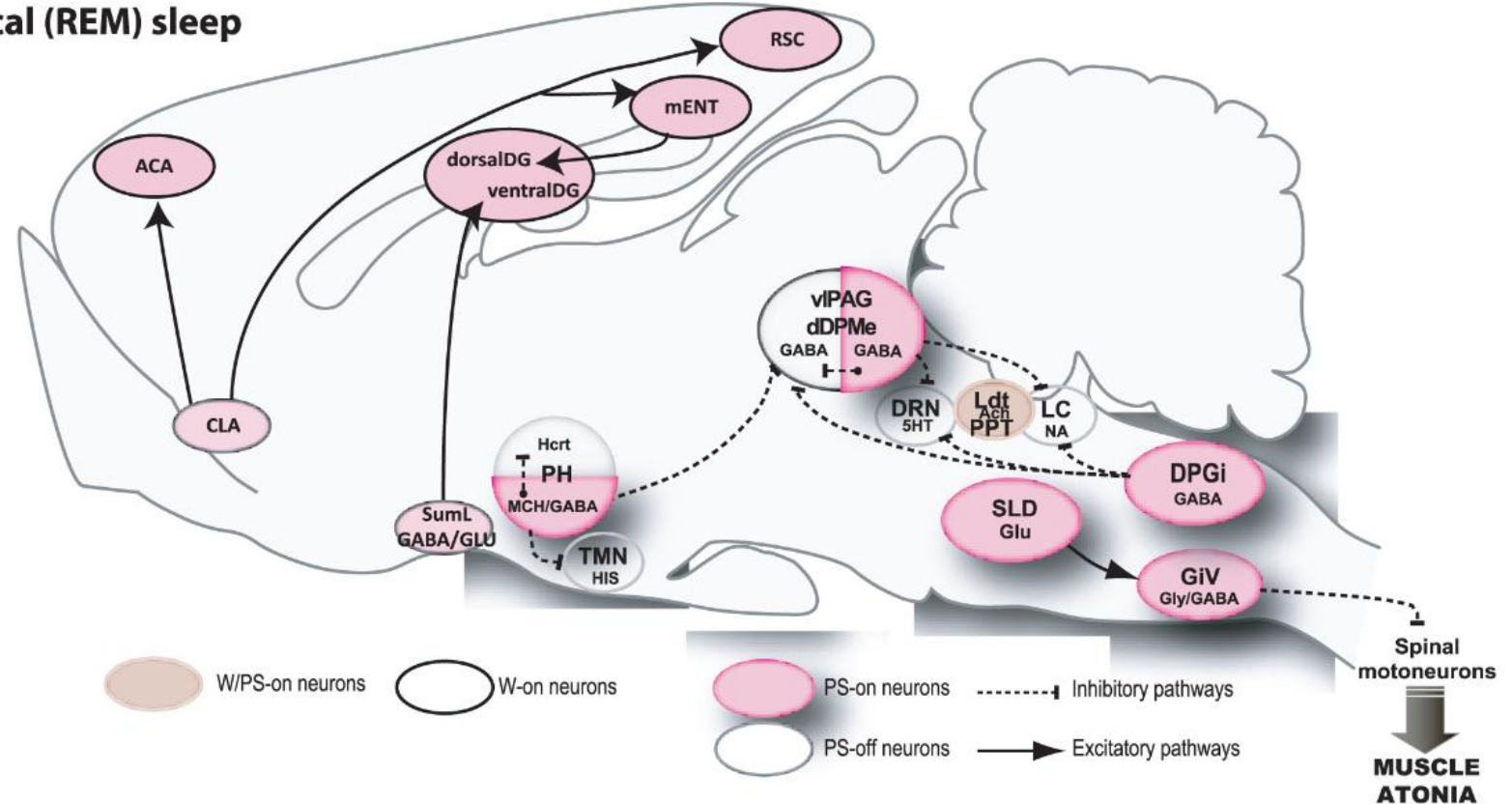
Paradoxical (REM) sleep



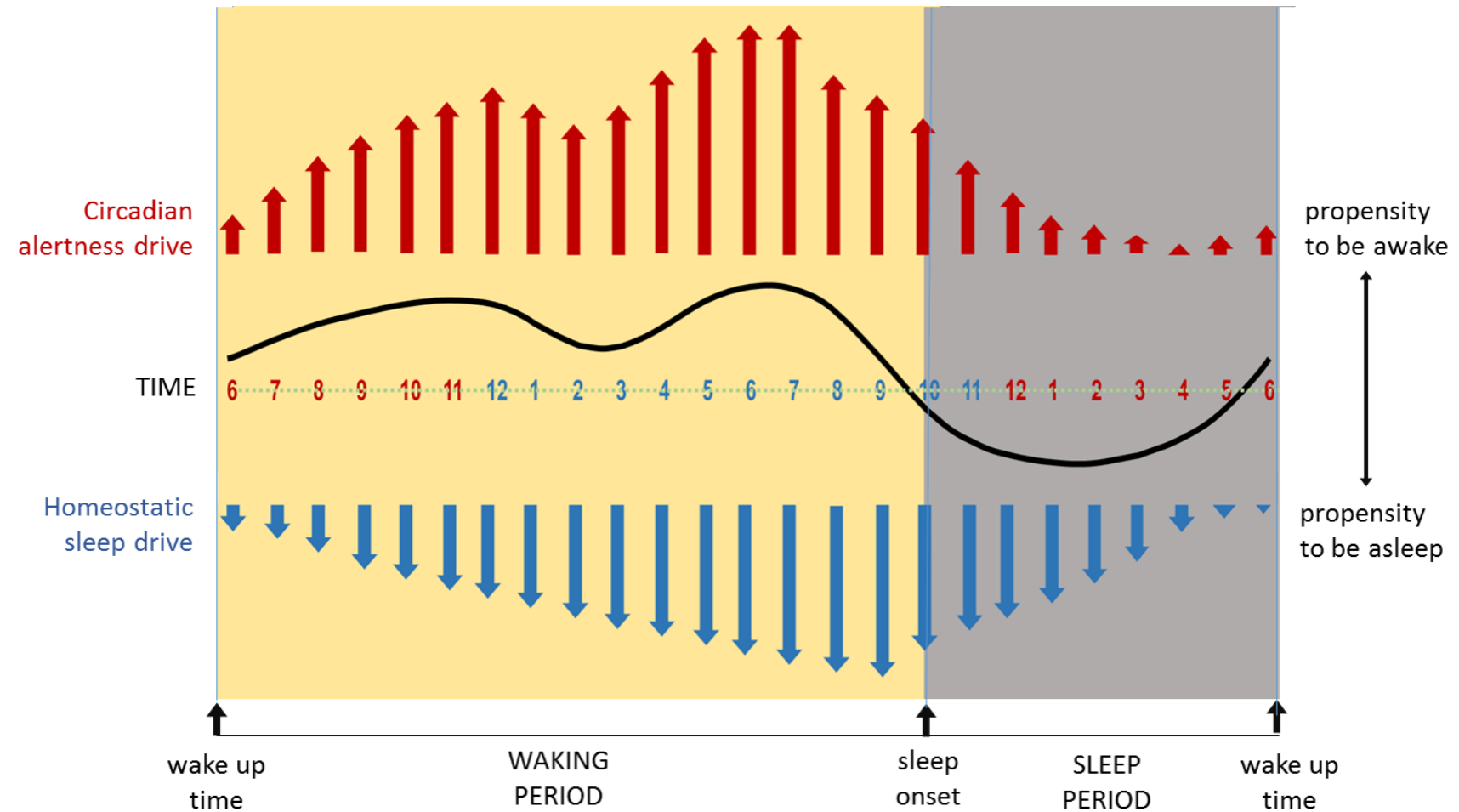
- Activation of glutamatergic SLD activates:-

Paradoxical (REM) sleep

- Ventral gigantocellular reticular nuclei (glycine; GABA); this in turn suppresses spinal motor neurons and creates muscle atonia.
- Thalamus (relative to NREM sleep), which further activates the neocortex and some limbic structures (such as MTL areas including entorhinal cortex and the dentate gyrus).

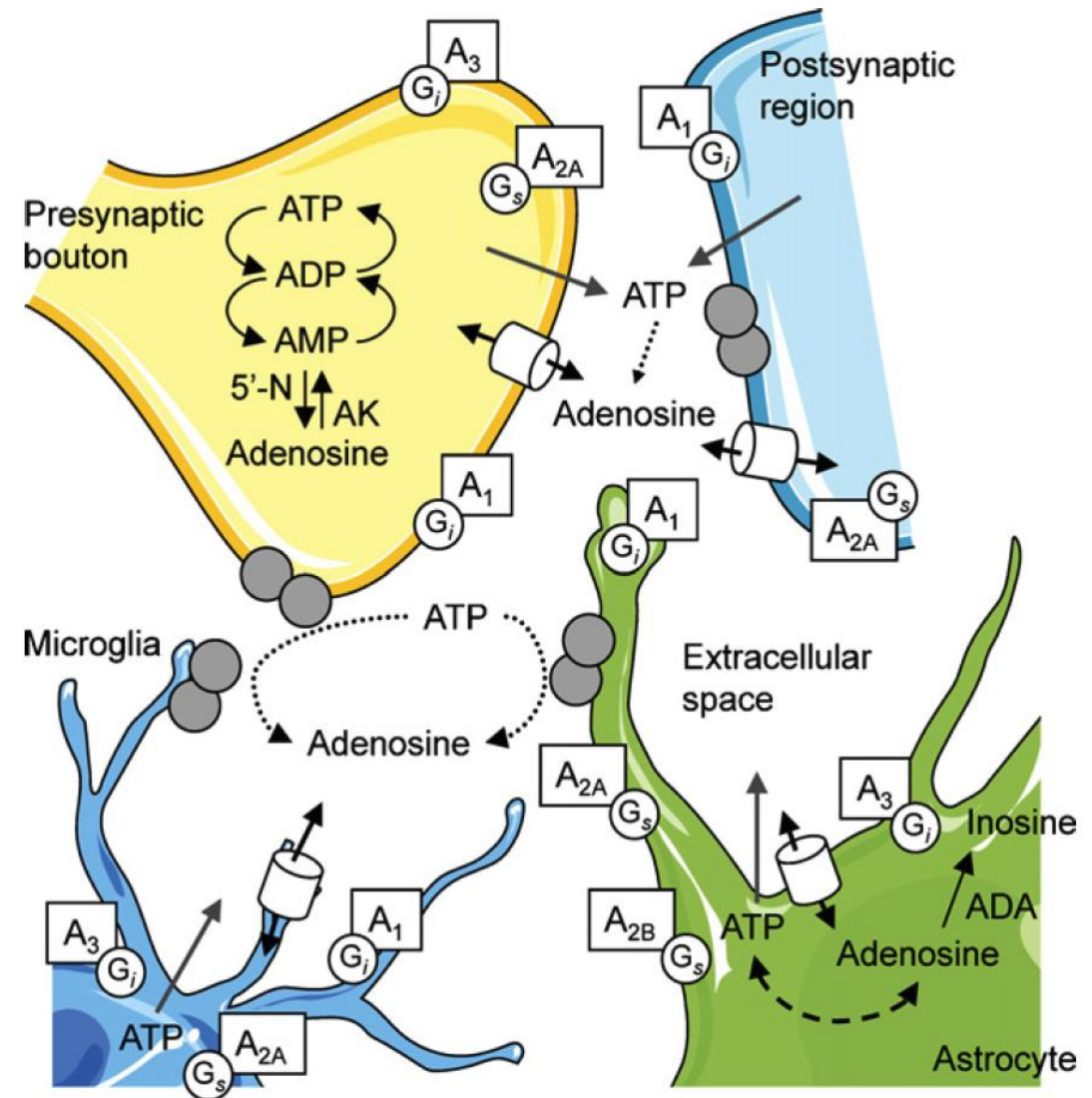


- What are triggers for sleep-wake state transitions? Two Processes:-
 - **Homeostatic sleep drive** – depends on time since last deep sleep.
 - **Circadian alertness drive** – depends on time of day.

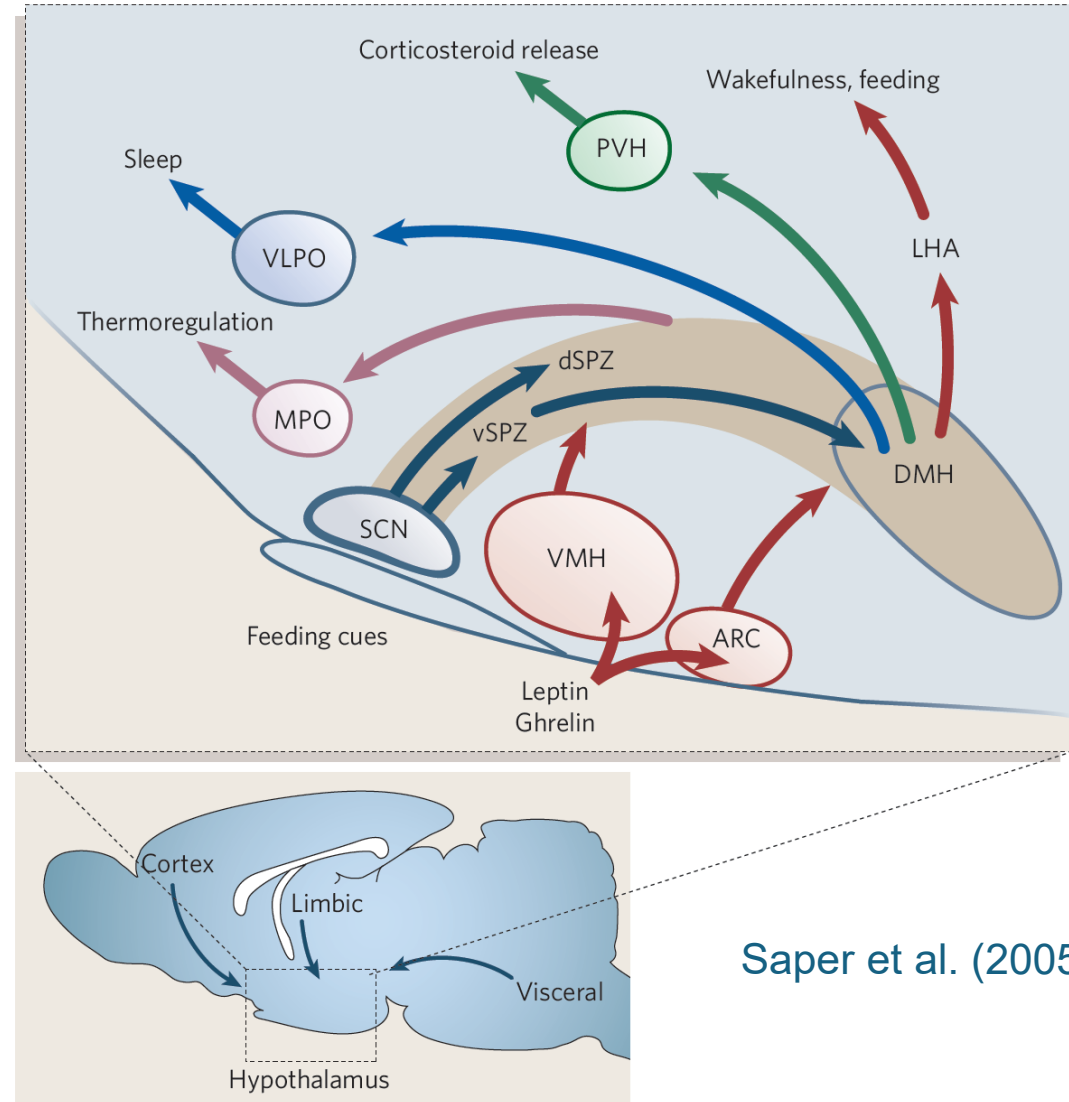


- ATP is the principal energy unit of cells.
- Breaks down into ADP and AMP, but can be converted back.
- Ultimately breaks down to adenosine.
- Binds to various receptors, of which A_1 and A_{2A} are important for sleep homeostasis.
- Caffeine a competitive antagonist for A_{2A} .
- ADA G/A gene variant in 20% of population - reduced adenosine breakdown; more SWS and stronger SWA.
- ACh basal forebrain neurons important for this

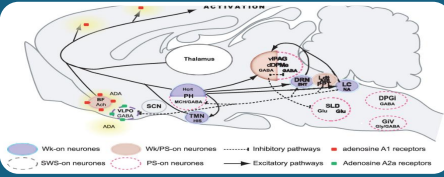
Landolt (2008)



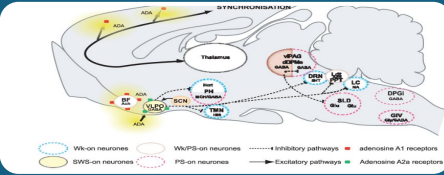
- SCN projects through the ventral subparaventricular zone to the dorsomedial hypothalamus.
- DMH projects to VLPO and synchronises that with SCN.
- DMH also projects to orexin and melanin-concentrating hormone neurons in the lateral hypothalamus to promote wake.
- Also influences thermoregulation, feeding behaviour and corticosteroid release.



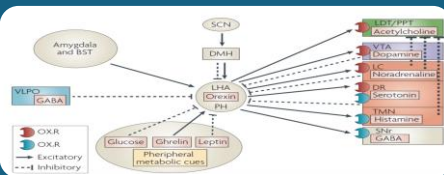
Saper et al. (2005)



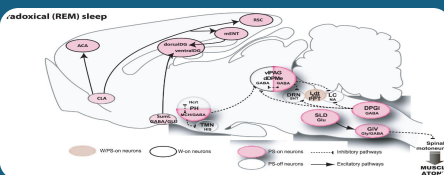
Wakefulness is maintained by the ascending reticular activating system (ARAS).



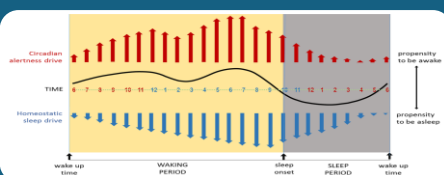
NREM is largely controlled by ventrolateral preoptic nucleus which suppresses ARAS.



Sleep-wake states uses a Flip-Flop model stabilised by orexin/hypocretin.



REM is triggered by disinhibition of REM-suppressing areas; activates muscle atonia.



Sleep-wake transitions are influenced by homeostatic and circadian mechanisms.

Thanks for
Listening!

Any
Questions
?

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