SUBCORTICAL MODULATORY SYSTEMS. MECHANISM OF BEHAVIORAL STATE CONTROL
Outline

1) Arousal Concepts
2) Brain Electrical Activity During Waking and Sleep States
3) Mechanism of Arousal: Initial Studies
4) The Brainstem Reticular Formation
5) ‘Diffuse’ Corticopetal Systems
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7) Thalamo-cortical loops in NREM oscillations and their control by brainstem cholinergic input

8) REM sleep

9) The homeostatic process of sleep-wake control

10) Sleep-wake control and circadian entrainment
DEVELOPMENT OF AROUSAL CONCEPTS

• **Waking** is a complex state. It is characterized by: 1) Perceptions that are influenced by external and internal sensory input; 2) Capacity of directing attention and accessing memory faithful to recent history; 3) Readjustment of posture, array of *motor output*; 4) *Emotions* that are focused to percepts and thoughts. (Hobson and Pace-Schott, 2002)

• **1930s**: wakefulness is maintained by afferent input to the brain and sleep ensues when that input is removed, as in the ‘*cerveau isole*’ cat, or falls below a certain critical level, as in normal sleeping (Bremer, Deafferentation theory)

• **1950s**: the brain actively controls its own state by the *ascending reticular activating* system (Magoun-Moruzzi).

• **1965s**: the concept of an undifferentiated reticular formation is gradually replaced by the description of *transmitter-specific cell groups* in the brainstem, the basal forebrain and the hypothalamus that send widely branching axons to the cortex and other parts of the brain.

• **1980s**: thalamo-cortical oscillations; neuromodulators trigger intrinsically generated oscillatory pattern in cooperating cortical cells. *Arousal is a switch from slow to fast oscillatory pattern* (Steriade, McCormick, Llinas, Singer, Buzsaki).

• **1990s**: The subjective experience of various states can tentatively be linked to the accompanying systematic changes in balance between various neuromodulators. The characteristic imaging data in various states are likely to relate to the shifts in regional metabolism and blood flow that are orchestrated by the these neuromodulators.

• **2003** Arousal provides the motivational force that activates behavior (Pfaff)
Behavioral states in humans

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Hobson and Pace-Schott, 2003
Stages of sleep form cyclical pattern

A: EEG recordings during different stages of wakefulness and sleep. B: A typical pattern of sleep in a young adult. REM: black bars (Kandell et al., 1991)
Awake: low voltage-random, fast

Drowsy: 8 to 12 cps- alpha waves

Stage 1: 3 to 7 cps- theta waves

Stage 2: 12 to 14 cps- sleep spindles and K complexes

Deep sleep: 1/2 to 2 cps- delta waves >75 µV

REM sleep: low voltage-random, fast with sawtooth waves
Physiological changes in a volunteer during various sleep states in a typical 8-hr sleep period

From Purves et al., 2004
Alpha rhythm

A: EEG records showing alpha rhythm from four species (Brazier, 1960).

B: Desynchronization of the EEG of a rabbit by an olfactory stimulus (Green and Arduini, 1954).
EEG with brainstem transections

A: Cortical LVFA typical of the alert state in cat (transection at ‘A’).
B: Spindling with cut at ‘B’ (Bremer, 1937).

A: 'encephale isole'
B: 'cervau isole'
EEG with brainstem lesions (Lindsley et al., '49)
Ascending modulatory systems: The past

Magoun, Moruzzi et al, 1951
Lorente de No, 1938
Hypothalamic sleep-wake ‘centers’

Lesion of the anterior hypothalamus resulted in insomnia, lesion of the posterior hypothalamus was associated with comatose state. (Von Economo, 1931)
During period marked by thick line, stimulation of the RF. At arrow, 1mg/kg atropine injected iv. EEG calibration: 0.1 mV, 1 sec (Szerb et al., 1965).
Correlation of EEG and ACh output in cortex and hippocampus in freely-moving cat (Marrosu et al., 1995)
EEG, BEHAVIOR, ATROPINE, RESERPINE

No Drug

Atropine (50 mg/kg, i.p.)

Reserpine (10 mg/kg, i.p.)
+ Atropine (50 mg/kg, i.p.)
Monoaminergic cell groups and the Brainstem Reticular Formation
The dorsal column-medial lemniscus pathway

Dark shaded are corresponds to the reticular formation
Various cell groups of the reticular formation and the raphe nuclei are indicated.
Fig. 12.4. Orientation of dendrites in the reticular formation. Sagittal section through the medulla (rat). Note the long, straight dendrites, which are typical of the neurons of the reticular formation, in contrast to the neurons of a cranial nerve nucleus (XII) and other specific brain stem nuclei. A long axon (a) with numerous collaterals extending ventrally in the transverse plane is also shown. Collaterals of the pyramidal tract fibers (Pyr.) also enter the reticular formation. P = pontine nuclei; R.gc. = the gigantocellular nucleus of the reticular formation; Ol.i. = the inferior olivary nucleus. From Scheibel and Scheibel (1958).
Classification of neurons according their dendritic arborization

A, B: invertebrates; C-E: brainstem reticular core; F: pyramidal; I: dentate granule; K: Purkinje; L: mitral cell; M: tufted; N: wavy pattern (inferior olive). Monoaminergic cells of the brainstem, cholinergic neurons of the brainstem and basal forebrain show isodendritic arborization.
EVIDENCE FOR THE EXISTENCE OF MONOAMINE-CONTAINING NEURONS IN THE CENTRAL NERVOUS SYSTEM

I. Demonstration of Monoamines in the Cell Bodies of Brain Stem Neurons

by

ANNICA DAHLSTROM and KJELL FUXE

UPPSALA 1964
The monoaminergic cell groups in the brainstem

Dahlstrom, Fuxe, Hokfelt
Monoamine synthesis

ADRENALINE

NORADRENALINE

DOPAMINE

DOPA

TYROSINE

PHENYLETHANOLAMINE N-METHYLTRANSFERASE

PNMT

DOPAMINE OXIDASE

DBH

DOPA DECARBOXYLASE

DDC

TYROSINE HYDROXYLASE

TH

Serotonin (5HT)

Monamine oxidase

5-hydroxyindole acetic acid
The A1-A7 NE cell groups
LC provides a major ascending output to the thalamus and cerebral cortex as well as descending projections to the brainstem, cerebellum and spinal cord.
Noradrenergic pathways in humans
Neuron from the LC (Aston-Jones, 2004)
Effect of LC stimulation (100Hz, 20uA) on neocortical and hippocampal activity in urethane-anaesthetized rat.
Relationship of LC activity to cortical ECoG (A) and hippocampal EEG (HEEG, B) before, during and after peri-LC bethanechol infusion. The raw trigger output from LC activity is shown in the middle trace, and the integrated trigger output (10 sec intervals) is in the bottom trace. As LC activity is seen to increase during the latter part of the infusion, reduced amplitude and increased frequency become evident in the ECoG trace. As LC activity begins to decrease, ECoG amplitude begins to increase and its frequency decreases. Similar changes can be observed in the HEEG (Aston-Jones)
LC activity and attention

A reversal procedure in a visual discrimination task in monkeys reveals responses for LC neurons specific to meaningful stimuli. Target stimuli occur on 10% of trials, and non-target stimuli occur on 90%. Stimuli are presented at vertical dashed lines in each histogram. The animal receives a drop of juice when it responds after a target stimulus.

(a) and (b): Post-stimulus-time histograms (PSTHs) for response of an LC neuron to green (target), but not to yellow (non-target) stimuli. c and d: Similar PSTHs for the same LC neuron after reversal training such that target stimuli are now yellow and non-target stimuli green. Note that green stimuli (c) no longer elicit responses, whereas yellow stimuli (d) now elicit a small response. Thus, the response is selectively elicited by meaningful stimuli. Calibration bar represents 1 sec. (Aston-Jones)
Serotonergic neurons along the midline of the brainstem

A, B coronal, C sagittal sections. Neurons in the B1-B3 groups project to the lower brainstem and spinal cord. Neurons in the raphe pontis (B6), median raphe (B7) and dorsal raphe (B8) project to the upper brainstem, hypothalamus, thalamus and cerebral cortex.
Fig. 24 5HT neurons in the human
DR neuron activity and EEG

Polygraph records showing the activity of a typical dorsal raphe (DR) neuron and gross potentials across the sleep/wake cycle. Note the positive relationship between the firing rate and the level of behavioral arousal, as well as the cessation of unit activity during REM sleep. During REM sleep, ponto-geniculo-occipital (PGO) waves can be seen in the LGN trace and prominent rhythmic slow activity (theta) in the hippocampus (HIPP) trace (Jacobs and Fornal, 1999).
The mesopontine cholinergic nuclei

Summary of ascending and descending projections of the latero-dorsal (LTD) and pedunculo-pontine (PPT) tegmental nuclei. The most substantial ascending projections are to the thalamus, including relay and limbic nuclei. This pattern of thalamic innervation is in marked contrast to the surrounding tegmentum which innervates midline and intralaminar nuclei. The PPT also innervates the reticular (RT) nucleus, however, this nucleus also receive a substantial cholinergic innervation from the basal forebrain. A major target of the descending projection is the medial pontine reticular formation (Wainer et al., 1993).
Brainstem PPT neurons of cat increase firing rates in advance of EEG desynchronization during REM sleep. Sequential mean frequency (SMF) of one (A), 14 (B) and eight PPT neurons. S = synchronized sleep, SD = transitional epoch. Time 0 of SD epoch is the appearance of the first PGO wave. The spontaneous firing baseline in S is indicated by dotted line. (Steriade, Data, Oakson, Pare).
HYPOTHALAMO-CORTICOPETAL SYSTEAMES
Histaminergic neurons in the postero-lateral hypothalamus

Histaminergic cells are clustered in the tuberomammillary nucleus in the postero-lateral hypothalamus. The histaminergic neurons innervate the entire neuraxis, from the cerebral cortex to the spinal cord (From Saper, 2000)
Waking-related neuron in the post-lat. hypothalamus

Waking-related neuron in the post-lat hypothalamus, in the area that is rich in histaminergic neurons. Unit firing in waking: 2.03 Hz, NREM: 0.15 Hz and REM sleep: 0.14 Hz. Note the resumption of firing coincident with the appearance of waking in the second trace. (From Steininger et al., 1999).
The orexin/hypocretin system of the lateral hypothalamus

Effect of 0.7 nmol HCRT-1 infused into the lateral ventricle on ECoG and EMG activity. Immediately, prior to the infusion (pre-infusion), the animal spent the majority of time in slow-wave sleep. Following infusion, behavioral, ECoG and EMG indices of waking were observed. Note the decrease in large-amplitude, sSWS activity in ECoG and the increase in EMG activity post-infusion.
Release of hypocretin during waking and sleep states

Sleep-cycle release of Hypocretin. A-C, Location of the tips of dialysis probes in the hypothalamus (HYP), basal forebrain (BF), and LC. CI, Internal capsule; CO, optic chasm; f, fornix; LH, lateral hypothalamus. D-F, Hcrt levels across the sleep-waking states in the HYP, BF, and LC. Sleep-state values differ as a function of state (HYP, $p < 0.003$, $F = 4.7$, df = 3254; BF, $p < 0.03$, $F = 3.2$, df = 3133). Tukey's test; *$p < 0.05$; **$p < 0.02$; ***$p < 0.002$. Hcrt release is maximal during AW (active waking) and REM sleep and minimal during SWS and QW (quiet waking) in the HYP and BF (Kiyashchenko et al., 2002).
Hypocretin modulates LC firing

A: Activation of hypocretin 1 receptors increases the firing rate of locus coeruleus neurons. *Bottom*, Rate meter record demonstrating that *in situ* microelectrophoretic application of hypocretin 1 (1 mg/ml) produced a marked activation of a spontaneously active LC neuron. Calibration: 5 Hz, 5 sec. (Bourgin et al., 2000).

B: Hypocretin innervation of the LC (Aston-Jones, 2004)
Ascending modulatory systems: the present

DRN-5HT (yellow)
LC-NE (green)
PPT-Ach (orange)
TMN-His
Hcrt/Orexin (red)

Sutcliffe and De Lecea, 2002;
THE BASAL FOREBRAIN
CORTICOPETAL SYSTEM
DISTRIBUTION OF CHOLINERGIC CORTICOPETAL NEURONS IN RAT
Basal forebrain cholinergic neurons in human
Basal forebrain cholinergic system in human
Regional Chat activities in rhesus monkey (Mesulam et al., 1986)
Comparing the ACh innervation of motor (4) and sensory regions of the rat, cat, monkey and human). From Avendano et al., 1996
BF stimulation, EEG I.

A, Effective (solid circles) and ineffective (open circles) stimulation sites for eliciting EEG activation in 20 consecutive experiments. Caudal stimulation sites (mean rostrocaudal distance from the anterior commissure, 0.77 mm; range, 0.54–1.04 mm) were more effective (87.5%; n = 14 of 16), whereas rostral stimulation sites (mean distance, 0.28 mm; range, 0.08–0.46 mm) were less effective (25%; n = 1 of 4). Effective stimulation sites lay in middle and ventral aspects of the caudal globus pallidus (GP) and substantia innominata (SI), source of the NB cholinergic projection to auditory cortex (Weak et al., 1980; Saper, 1984). Atlas sections modified from Paxinos and Watson (1986). CP, caudate putamen. B, Glutamate (180 nmol in saline), delivered via a 30 gauge cannula attached to the stimulating electrode, desynchronized the EEG for >1 min (recovery can be seen at end of trace). Portions of the EEG before and during glutamate-induced desynchronization are marked by asterisks and shown below at higher resolution. Subsequent saline infusion of equal volume was without effect.

METHERATE and ASHE, 1992
BF stimulation, EEG II

Metherate and Ashe, 1992

NB stimulation *in vivo* elicited EEG activation mediated by cortical muscarinic receptors. A, NB tetani (200/sec, 500 μA) of increasing number of pulses (arrowheads) elicited correspondingly longer durations of EEG desynchronization. Effect of 60 pulse tetanus is shown at faster speed to the right (duration of tetanus indicated by arrow; artifacts are blanked). Atropine, administered iontophoretically (40 nA) within auditory cortex, enhanced synchronous oscillations and antagonized the effect of NB stimulation. Increasing stimulus intensity (e.g., 100 pulse stimulus) partly overcame the atropine blockade. Recovery was seen at about 1 hr (Post). B, Averaged (n = 5) frequency power spectra show that NB stimulation resulted in increased high-frequency components (Pre-drug spectra; individual functions contributing to each average were normalized to the peak power under that condition, i.e., pre- or posttetanus). NB stimulation also produced decreased power in the 1–5 Hz range (histogram in inset; power normalized to pretetanus value for each experiment). Atropine antagonized the effect of NB stimulation on EEG frequency components and power in the 1–5 Hz range. Note that the increased EEG amplitude and synchrony under atropine (seen in A) resulted in increased power in the 1–5 Hz range relative to control (note change in histogram scale). Data are from five experiments in which (1) atropine was administered within the cortex (either iontophoretically or directly to the cortical surface), and (2) NB-mediated EEG desynchronization endured for longer than 2 sec (to allow for adequate digital sampling).
BF stimulations elicit heterogeneous cortical MUA responses

ACh release from sites in the visual and the somatosen-sory cortex following electrophysiological recordings of the neuronal activity provoked by BF stimulation. A: Eleven pairs of 30-minute samples obtained simultaneously from the somatosensory and the visual cortex. The first five pairs provided the baseline levels for both cortical regions. During collection of the sixth pair of samples the BF was stimulated every 4 seconds with a train of 40 pulses at 100 Hz. ACh release increased more in the somatosensory cortex than in the visual cortex. ACh levels returned to normal over the next hour, and the stimulation was repeated during the ninth sampling period. B: A second experiment showing the same pattern of differential ACh release following BF stimulation. In this experiment the BF stimulation was performed three times using a train of 50 pulses every 4 seconds for the duration of the 30-minute sampling period (sample pairs 7, 10, and 13). A slight, but significant, increase in ACh occurred in the visual cortex, whereas a 600-700% increase occurred in the somatosensory cortex.

Multiunit recordings from the hindlimb somatosensory cortex showing how BF stimulation could provoke a long suppression of spontaneous activity followed by a large and long increase in neuronal activity. The several large neurons in this recording were spontaneously active. A: A 2-second record of spontaneously active neurons discharging in bursts. B: When a 100-ma BF stimulus was administered, all neural activity stopped for about 450 ms after the end of the stimulus; then an intense discharge occurred, lasting for approximately 1.1 second. C: A second example of the inhibitory pause produced by BF stimulation.

Dykes et al, 1997
Effect of cholinergic facilitation on the direction selectivity of a LIV simple cell (A) and a LVI complex cell (B). PSTH showing the response of the cells to an optimally oriented bar of light moving forwards and backwards over the receptive field. (Silito, 1993)

Effects of arousal (noise) from SWS on response selectivity of a cell in LII of the striate cortex. Arousal results in a moderate increase in the response to movement and a virtual elimination of the response to rightward movement (Livingston and Hubel, 1981).
BF neurons are electrophysiologically heterogeneous

Detari et al., 1987
Basal forebrain corticopetal cholinergic neurons are intermingled with non-cholinergic neurons

A: Choline acetyltransferase (ChAT) and Nissl-staining. B: cholinergic neurons (red) are intermingled with Parvalbumin (green), Calretinin (black) and calbindin (blue) neurons
Juxtacellular filling, unit recording, EEG
Identified cholinergic neuron
Identified GABAergic neuron (Parvalbumin)
Identified interneuron (GABA-NPY)
Fig. 38. Putative functional circuitry in the BF
Comparative distribution of ChAT, 5HT, DBH fibers in monkey auditory (first three columns: Campbell et al., 1987) and primary visual cortex (last two columns Morrison et al., 1982)
Effect of neuromodulators on cortical firing in slices

A-D: current clamp; E-H voltage clamp mode; McCormick and Williamson, 1989
The ascending modulatory systems are interconnected
Diffuse input to BF: LC axons
LC can affect the cortex via the BF

Dringenberg and Vanderwolf, 1998

Cape and Jones, 1998
CHOLINERGIC NEURONS RECEIVE SYNAPSES FROM THE MIDBRAIN DOPAMINERGIC AREA

Ventral midbrain axons contact CH and PV cells in the BF

Gaykema and Zaborszky, 1996
Mesopontine projections to PV (and CH) neurons in the BF
Corticopetal Vglut2 cells in the brain

Hur and Zaborszky, in press
Diffuse input: Vglut 2 synapses on CH dendrites
Diffuse input to BF: hypocretin axons

Wu, Zaborszky, Hajsan, van den Pol, Alreja, in press

**a:** whole-cell current clamp; **b:** current clamp showing the depolarizing effect of Hcrt. **c:** voltage clamp (-65 mV) in which Hcrt2 induced an inward current that persisted in zero Ca2+, high Mg2+ ACSF.
SLEEP SWITCH, FLIP-FLOP SWITCH
Sleep-active neurons in the VLPO

A: Giemsa-stained section showing a small triangular cluster of cells (ventrolateral preoptic nucleus). b: Fos-ir neuronal nuclei in the VLPO after 1 hr period spent predominantly asleep. C: the VLPO is demarcated as a galanin/GABA positive cell group. Lower right: retrogradely labeled neurons that project to the tuberomammillary nucleus (Sherin et al., 1998).
The cessation of firing of 5-HT raphe neurons is a key controlling event of REM. REM sleep is accompanied by a selective increase in GABA release, but not glutamate in the DRN in naturally sleeping cats (Nitz and Siegel, 1997).

GABAergic afferents to the DRNm using retrograde tracing with cholera toxin B and glutamic acid decarboxylase immunohistochemistry. Stars corresponds to double-labeled cells. Note abundant projection from the medial (MPO) and lateral preoptic area (LPO) and pontine ventral periaqueductal gray (Gervasoni et al., 2000).
The flip-flop switch

A model for reciprocal interactions between sleep- and wake-promoting brain regions, which produces a flip-flop switch. Aminergic regions such as the TMN, LC and DR promote wakefulness by direct excitatory effects on the cortex and by inhibition of sleep-promoting neurons of the VLPO. During NREM sleep, the VLPO inhibits amine-mediated arousal regions through GABAergic and galaninergic (GAL) projections. The inhibition of the amine-mediated arousal system disinhibits VLPO neurons, further stabilizing the production of sleep. Orexin/ (ORX) neurons in the lateral hypothalamic area might further stabilize behavioral state by increasing the activity of aminergic neurons, thus maintaining consistent inhibition of sleep-promoting neurons in the VLPO and REM-promoting neurons in the PPT–LDT (Saper et al., 2001).
THALAMO-CORTICAL INTERACTIONS AND THEIR MODULATIONS BY ASCENDING BRAINSTEM AND FOREBRAIN PATHWAYS
Synaptic organization of the thalamus

RE: reticular thalamic nucleus; Th-cx: thalamocortical n.; Cx: pyramidal n.; L-circ: local circuit n.; Inset: synaptic contacts within a glomerulus (Llinas and Steriade, 1988)
Cholinergic innervation of the thalamus

Cholinergic innervation of the thalamus. A: Choline acetyltransferase staining, B: Adjacent Nissl-stained section (Levey et al., 1987)
Histaminergic innervation of the forebrain, including the thalamus

Distribution of histidine decarboxylase-positive fibers at four level in the forebrain (Inakagi et al., 1988).
NE and/or E innervation of the forebrain

Distribution of dopamine-Beta-hydroxylase immunoreactivity at mid-thalamic level (Swanson and Hartman, 1997).
Different types of NREM sleep oscillations in the thalamocortical circuit

Three rhythmic electrical activities characterize SWS: spindles (7-15 Hz) that are generated in the GABAergic RE neurons, delta waves (1-4 Hz), that are generated in the cortex and thalamus, and slow oscillation (0.5-1 Hz) that is generated intracortically. Note the different time calibrations. (Steriade, 2000). Each of them is blocked by brainstem or forebrain cholinergic system.
State-dependent activities in cortical and thalamic neurons

**In vivo**

- Neurons in the cerebral cortex (A), thalamic reticular nucleus (B) and thalamic relay nuclei (C) change their activities in vivo from periodic and rhythmic spike bursts during natural, SWS to tonic firing of trains of single spikes during waking and REM-sleep in behaving cats with chronic implants (D-F). Similar changes in firing pattern occur in vitro in these neurons in response to various neurotransmitters released by brainstem modulatory systems (Steriade et al., 1993).

**In vitro**

- ![Graphs showing firing patterns](image)
Intracellular aspects of spindling in the thalamocortical system

Spindle oscillations in reticular (RE), thalamocortical (Th-Cx, VL) and cortical (Cx, motor) neurons. **A:** Circuit of 3 neurons. **B:** Two rhythms (7-14 Hz and 0.1-0.2 Hz) of spindle oscillations in cortical EEG. **C:** Intracellular recording in cats under barbiturate anesthesia. Note rhythmic spike-bursts of RE neuron during a spindle sequence and concomitant IPSPs leading to post-inhibitory rebound bursts in Th-Cx and Cx neurons. (Steriade, 2002). The spikes in cortical cells is evident in the EEG as spindles.
Blockage of thalamic spindle oscillation by peribrachial stimulation

Blockage of spindle oscillations in intracellularly recorded thalamocortical and reticular thalamic (RE) neurons of unanesthetized encephale isole cats with deafferentation of trigeminothalamic pain pathways. A: an Lateral geniculate relay neuron. B: a neuron recorded in the perigeniculate sector of the RE. Arrowhead: brainstem mesopontine cholinergic (peribrachial) area stimulation. The disruption of spindles occur in the RE where sleep oscillation is generated (Hu, Steriade, Deschenes, 1989).
The brainstem activate thalamocortical and neocortical neurons via two routes. Thus, in contrast to the original idea of M-M, either a cholinergic-PPT/LDT–thalamocortical glutamatergic or the mesopontine-glutamate-basal forebrain cholinergic neurons are sufficient to activate the cerebral cortex.
freely moving rat, L means recording from the pyramidal cell layer, S means recording from the cortical surface
positivity in L (down-state) is accompanied by inhibition of neuronal activity
negativity in L (up-state) is not that obvious, but it is associated with neuronal firing
these changes are less obvious in the surface recording (S), but are opposite to L – negativity corresponds to down-state, positivity corresponds to up-state
there was much speculation about the source of the large deep-positive waves, associated with silence in pyramidal cells
first it was supposed to be caused by IPSPs, but all interneurons were shown to be silent together with the pyramidal cells
Buzsáky suggested that large AHPs in pyramidal cells contributed to this waves
Metherate, stimulating the BF, suggested that the up-states were caused by ACh blockade of different K⁺-currents, which
Steriade suggest that the up-states are caused by mutual excitation of pyramidal cells and/or activation of the mesopontine or basal forebrain cholinergic system. The down-states results in by disfacilitation when this mutual excitation goes down – it is supported by the increased membrane resistance during down-states

Buzsáki et al., 1988
unanesthetized cat

Upper panel: Transition from SWS to wakefulness. In SWS EEG is characterized not by irregular delta waves, but bipolar deflections (up-, an down-states)

Lower panel: SWS and Wake, the membrane potential in SWS shows bimodal distribution.

Steriade, M., et al., 2001
Suppression of the clock-like delta oscillation in a thalamocortical cell by stimulation of the PPT and simultaneous activation of the appearance of fast (40Hz) activity. Cat, urethane anaesthesia. Intracellular recording from TC cell in the LP thalamus together with EEG from postcruciate gyrus. A: a pulse-train to PPT; B: 5 pulse trains to PPT.
Thalamocortical cells and thalamic reticular cells can generate action potentials either as rhythmic bursts or as tonic, single-spike activity, depending upon the membrane potential of the cell. Activation of muscarinic, alfa1-adrenergic, H1-histaminergic or metabotropic glutamate receptors (mGluR) results in depolarization of relay neurons through reduction of $I_{KL}$. This depolarization subsequently shifts these neurons to the single-spike mode of action potential generation. Similarly, activation of alfa1-adrenergic, 5-HT2 receptors, mGluR receptors has similar effect in the thalamic reticular neurons (McCormick, 1997).

In contrast, activation of muscarinic receptors in the thalamic reticular neurons or local GABAergic neurons results in inhibition of their output through an increase in potassium conductance ($I_{KG}$) (McCormick).

In the cerebral cortex, activation of muscarinic, alfa1-adrenergic, or mGluR results in abolition of burst firing of layer V burst generating neurons and a switch to tonic, single-spike mode of action potential generation. In regular spiking cells, activation of muscarinic, beta-adrenergic, Hz-histaminergic, serotoninergic and mgluR receptors results in a decrease in spike frequency adaptation by blocking $I_{AHP}$ (and $I_M$ for Ach and 5HT). These responses allow ascending modulatory transmitter systems to prepare thalamocortical systems for sensory transmission, processing (McCormick).

The three brain rhythms (spindle, delta and slow oscillation) are obliterated by brainstem cholinergic and n. basalis cholinergic and GABAergic actions exerted on thalamocortical, thalamic reticular and neocortical neurons. The blockade of low-frequency (<15 Hz) sleep oscillations, which are widely synchronized, is accompanied by the occurrence of fast (20-60Hz) rhythms, which are synchronized over restricted cortical territories and well defined corticothalamic systems. The fast rhythms appear during the sustained depolarization of thalamic and neocortical neurons in wakefulness and REM sleep, as well as during the depolarizing phases of the slow oscillation in non-REM sleep. Thus, fast rhythm are voltage dependent and do not necessarily reflect high cognitive and conscious processes (Steriade, 2004).
THE REM SLEEP
EEG desynchronization results from a net tonic increase in reticular (cholinergic) ascending, thalamocortical and cortical neuronal firing rates. PGO waves are the results of tonic disinhibition and phasic excitation of burst cells in the lateral pontomesencephalic tegmentum. Rapid eye movements are the consequence of phasic firing of vestibular cells; the latter excite ocolomotor neurons.
Diagram of the circuitry involved in the decreased sensation and muscle paralysis that occurs during REM sleep (Purves et al., 2004)

Muscle atonia is the consequence of tonic postsynaptic inhibition of spinal anterior horn cells by the pontomedullary reticular formation. Muscle twitches occur when excitation by reticular and pyramidal tract motorneurons phasically overcomes the tonic inhibition of the anterior horn cells.
REM – non-REM oscillation I

A  REM-off  Structural model  REM-on cells

RN (5-HT)  
LC (NE)

- 5HT NE

Ach

PPT  LDT  mPRF
(Ach)  (glut)

5HT NE

Ach

B  Dynamic model

REM-off

REM-on

C  Activation level (A)

Wake  NREM  REM

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5HT inhibition in the PPT

Digitized inkwriter record of **REM-on** unit discharge in the PPT area of naturally sleeping cats. Note the low level of unit activity in active wakefulness, which continues in non-REM sleep, but increases more than two-fold in REM sleep. 8-OH-DPAT, a selective 5-HT1A agonist dramatically suppressed unit activity in the same REM-period. (Thakkar et al., 1998).
The reciprocal-interaction model of REM-NREM alternation. **REM-on cells** are the cholinergic cells in the PPT/LDT area, GABAergic local or projection neurons neurons in the ponto-medullar reticular formation (DPGi), periaqueductal gray (PAG), and in the substantia nigra pars reticularis. There are also putative glutamatergic REM-on neurons in the reticular formation. **REM-off cells** are the noradrenergic locus coeruleus (LC) and the serotoninergic (5-HT) raphe (RN) neurons. Note that there are self-inhibitory cholinergic autoreceptors in the mesopontine cholinergic nuclei. Also, the noradrenergic (NA) and 5-HT fibers inhibit the wake-REM-on neurons (Pace-Schott and Hobson, 2002).
THE HOMEOSTATIC
REGULATION OF SLEEP-WAKE CYCLE
The homeostatic regulation of sleep-wake cycle

C: The hypothalamic preoptic area (POA/VLPO) contains sleep-active neurons and send inhibitory projections directly to all major monoaminergic cell groups and indirectly to the cholinergic (PPT, LDT, BF) and lateral hypothalamic neurons. AD can activate neurons in the POA via an inhibition of presynaptic GABA release onto the putative sleep-active neurons. Functionally, these two mechanisms are complementary, ie. Increased AD levels in either area is predicted to reduce W and promote the transition to sleep (Strecker et al., 2000).

A: Schematic of the main intra- and extracellular metabolic pathways of adenosine. A1, A2 adenosine receptor subtypes. B: The BF region contains numerous cholinergic and non-cholinergic wake-active neurons that project to the cortex and thalamus and whose activity is thought to promote cortical activation. Adenosine is proposed to inhibit the activity of these neurons possibly via A1 receptor mediated hyperpolarization.
Intracellular pathways of adenosine effects. The A1 adenosine receptor (A1 R) is coupled to Gi3 protein that can either activate the pathway B, by inhibiting adenylate cyclase (AC), or increase in adenosine levels might activate another pathway A by activating PLC, resulting in the activation of PKC due to the mobilization of internal Ca2+ by IP3. PKC can phosphorylate I-B, releasing NF-B dimer to be translocated into the nucleus. The phosphorylated I-B is degraded in the cytoplasm. The NF-B dimer regulates transcription of several genes that have the NF-B consensus sequence upstream from their promoter. It is postulated that this pathway may result in the production of proteins, including the A1 adenosine receptor, that may play a role in producing the long-term effects known as sleep debt (Basheer et al., 2001).
I. During prolonged wakefulness, accumulating adenosine inhibit specific GABAergic anterior hypothalamic and BF neurons, which have been inhibiting the sleep-active VLPO neurons during waking. II: Disinhibited sleep-active GABAergic neurons of the VLPO then inhibit the wake active histaminergic neurons of the TMN, and the serotoninergic DRN and noradrenergic LC and cholinergic PPT/LDT neurons, thereby initiating NREM sleep. III: Forebrain activation by ascending aminergic and orexinergic arousal systems is disfacilitated. IV: Once NREM sleep is thus established, the executive networks of the pons initiate and maintain the ultradian REM/NREM cycle.
THE CIRCADIAN REGULATION OF SLEEP-WAKE CYCLE
Overview of the basic organization of the circadian timing system. Information from the light-sensitive, melanopsin-containing (RGC) neurons of the retina reach the SCN, the circadian pacemaker. Inset shows RGCs and their axons, labeled with a tau-lacZ marker, connecting with the SCN in mouse brain (Hattar et al., 2002).
The light phase response curve (PRC). With animals maintained in constant dark, activity is recorded (horizontal bars) and light pulses are given as indicated. Light establishes both the phase and the period of the pacemaker and thus, is the dominant entraining stimulus of the circadian system. The pacemaker can be viewed as a somewhat inaccurate clock, which must be reset repeatedly. It free runs with a period that is slightly off 24 h in the absence of light-dark cycle. The light-dark cycle sets the exact timing of the pacemaker. The PRC shows that the pacemaker responds differently to light at different times of the day (Moore, 2002). The left side of the figure provides a schematic illustration of how individual SCN neuron is able to mimic the day (L) signal with its molecular clock, resulting in membrane depolarization. This membrane depolarization results in propagation of the light signal to target neurons of the SCN and to phase shift of the molecular clock: phase delay (red arrow) or phase advance (green). Without the molecular clock, the light signal will still be transmitted to SCN targets. However, without the SCN, no signal will activate SCN target structures,(Buis and Kalsbeek, 2001).
This is a record of activity of an albino rat maintained in a light-dark cycle. From the top of the record to the arrow, the animal exhibits a normal rhythm of activity, indicated by dark areas. The record is double plotted, which means that each line shows the preceding day and the new day to ease evaluation of the record. At the arrow, a bilateral SCN lesion was performed. Activity is distributed randomly thereafter, meaning circadian organization of rest-activity has been lost (Moore, 2002). In the absence of the SCN the total amount of sleep is unchanged, but there is no day/light variation (timing) in sleep.
Rhythm of waking (blue lines) and sleeping (red) of a volunteer in an isolation chamber with and without cues about the day-night cycle. Numbers represent the mean+SD of a complete w-s cycle in each condition (Scchmidt et al., 1983)
Lesion of the n. DM eliminate the circadian firing of the LC

From Aston-Jones, 2004
Possible connections between the circadian pacemaker and the sleep/wake control systems. The circadian timing signal generated in the SCN is transmitted through nuclei in the anterior hypothalamus to sleep/wake control systems of the diencephalon (blue) and then to structures in the brainstem controlling REM-NREM cycling (yellow). BFB=basal forebrain. BRF=brainstem reticular formation. Circadian influence can reach the VLPO either directly from the SCN or through the dorsomedial hypothalamic nucleus that receive dense projections from the SCN (Pace-Schott and Hobson, 2002; Colwell and Michael, Nature Neurosci, 6, 1005, 2003).
Sleep disturbances in degenerative disorders

1) During aging, there is a progressive loss of neurons in VLPO, associated with difficulty falling a sleep

2) Narcolepsy (degeneration of orexin neurons), unwanted transitions to sleep while awake, as well as more frequent transitions to wake while asleep; cataplexy: sudden onset of atonia

3) REM behavior disorder (dopaminergic deficiency, often in PD patients), they fail to engage atonia during REM sleep and may act out their dreams. Many of these patients also have periodic limb movement during sleep and restless legs syndrome in the evening, also indicative of failure to suppress motor activity when at rest.