

# Special Lecture 6

## Effects of Sleep on Seizures ;

### A Path to sleep neurology (Somno-neurology)

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**Tokyo Bay Urayasi/Ichikawa Medical Center**

**Taiwan Pediatric Epilepsy Congress 2010**

**Dec. 26, 2010, 11:25-11:50**

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- 1. Effects of sleep on epilepsy**
- 2. Effects of sleep on inter-ictal epileptiform discharges**
- 3. Current knowledge on sleep mechanisms**
- 4. Response-reversal**

# Effects of sleep on epilepsy

- According to Gowers (1885), **21%** of *institutionalized patients* had seizures only during **sleep**, **42%** only during the **awake** state, and **37%** had seizures during **both wake and sleep** states.
- In contrast, according to Janz (1962), **45%** of *non-institutionalized patients* had generalized tonic-clonic seizures only during **sleep**, **34%** only during the **awake** state, and **21%** had seizures during **both wake and sleep** states.

- Méndez & Radtke (2001) summarized effects of sleep on epilepsy as follows;
- Awakening epilepsies are primary generalized seizure disorders, **including juvenile myoclonic epilepsy**, childhood and juvenile **absence** epilepsies, and **GTC on awakening**. These seizures are more prominent during the first 2 hours after awakening.
- **Partial seizures with secondary generalization** are sleep epilepsies, as well as other partial seizure disorders with centrotemporal spikes (BECTS) and Landau-Kleffner syndrome.

- Cont.
- **West syndrome**; Despite *the increased epileptic abnormalities during NREM sleep*, there is a marked decrease in the frequency of clinical spasms during sleep. Clinical seizures are most likely to occur before sleep or on awakening.
- **Lennox-Gastaut syndrome**; Seizures occur diffusely throughout the sleep/wake cycle. However, *tonic seizures are facilitated constantly by sleep*.
- **CSWS** (epilepsy with continuous spike-and-wave during slow wave sleep) or **ESES** (Electrical status epilepticus in slow wave sleep); EEG diagnosis.

**Panayiotopoulos syndrome** (Infantile variant of benign epilepsy of childhood with occipital paroxysms)

- More than 95% patients of this syndrome show ***hemiconvulsive and generalized tonic-clonic seizures during sleep.***

# Effects of sleep on inter-ictal epileptiform discharges (IEDs)

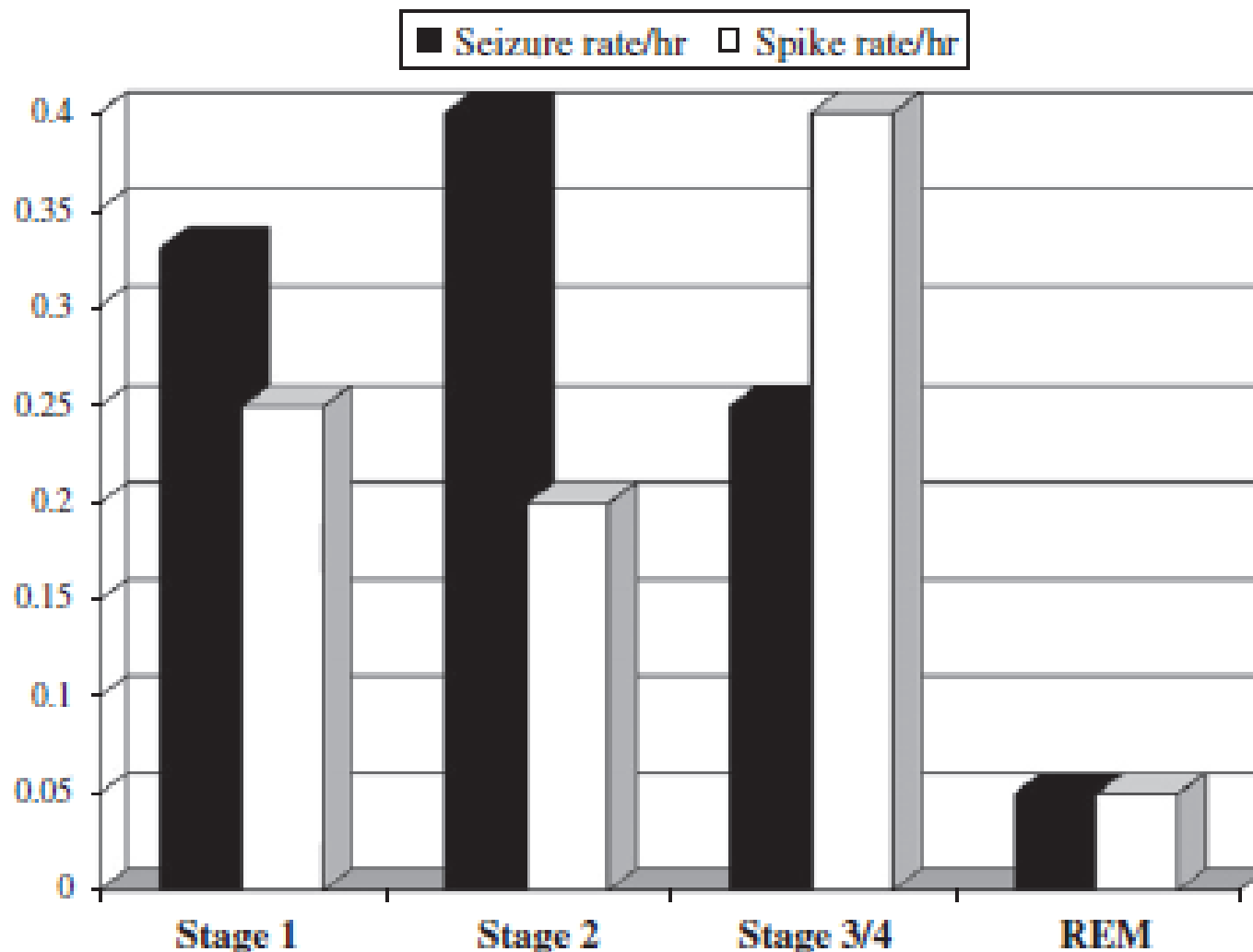
- In contrast to adults whose IEDs are activated by NREM stages 3 and 4, IEDs in children are more prevalent in stage 1 and 2 sleep.
- Focal IEDs that occur during REM sleep are more accurate for seizure localization as compared with other sleep states.

**Sleep and arousal mechanisms in experimental epilepsy:  
epileptic components of NREM and  
antiepileptic components of REM sleep.**

Shouse et al, 2004

Neural generators of synchronous EEG oscillations combine to promote electrographic seizure propagation during NREM and drowsiness, and antigravity muscle tone permits seizure-related movement.

Neural generators of asynchronous neuronal discharge patterns reduce electrographic seizures during alert waking and REM sleep, and skeletal motor paralysis blocks seizure-related movement during REM.



**This slide confirms the former cited paper title that epileptic components of NREM (stages 3 & 4) and antiepileptic components of REM sleep.**

**Fig. 1.** Seizure & spike rate/hour in different stages of sleep.

Minecan D, Natarajan A, Marzec M, Malow B. Relationship of epileptic seizures to sleep stage and sleep depth. *Sleep* 2002;25(8):56–61.

Cited by *S.V Kothare, J. Kaleyias / Sleep Medicine 11 (2010) 674–685*



What is the neuronal background to produce these state dependent alterations of seizures and IEDs?

Pathophysiology of each epilepsy is supposed to be involved in the sleep mechanisms.

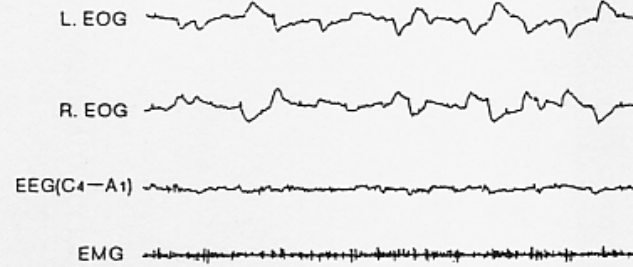
Current knowledge on sleep mechanisms will be shown.

# Polysomnographic features of each sleep stage

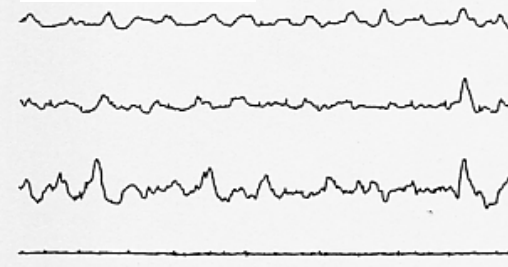
L-EOG  
R-EOG

EEG  
EMG

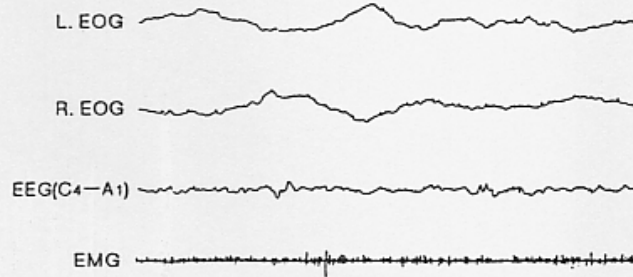
Awake



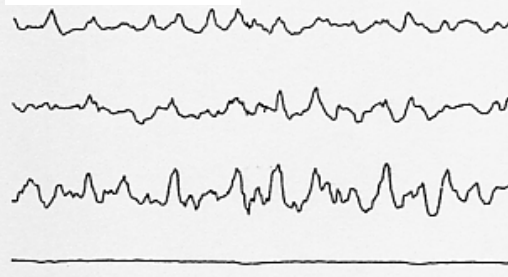
Stage 3



Stage 1



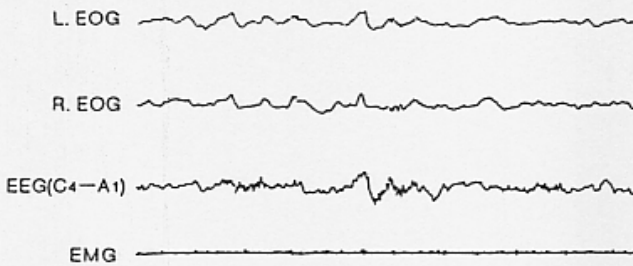
Stage 4



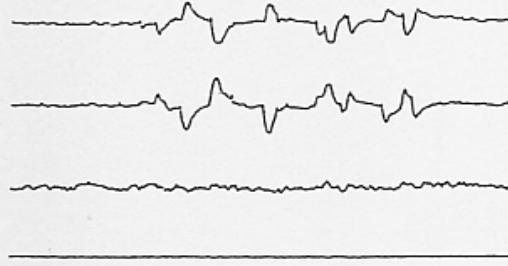
L-EOG  
R-EOG

EEG  
EMG

Stage 2



REM sleep stage



L-EOG  
R-EOG

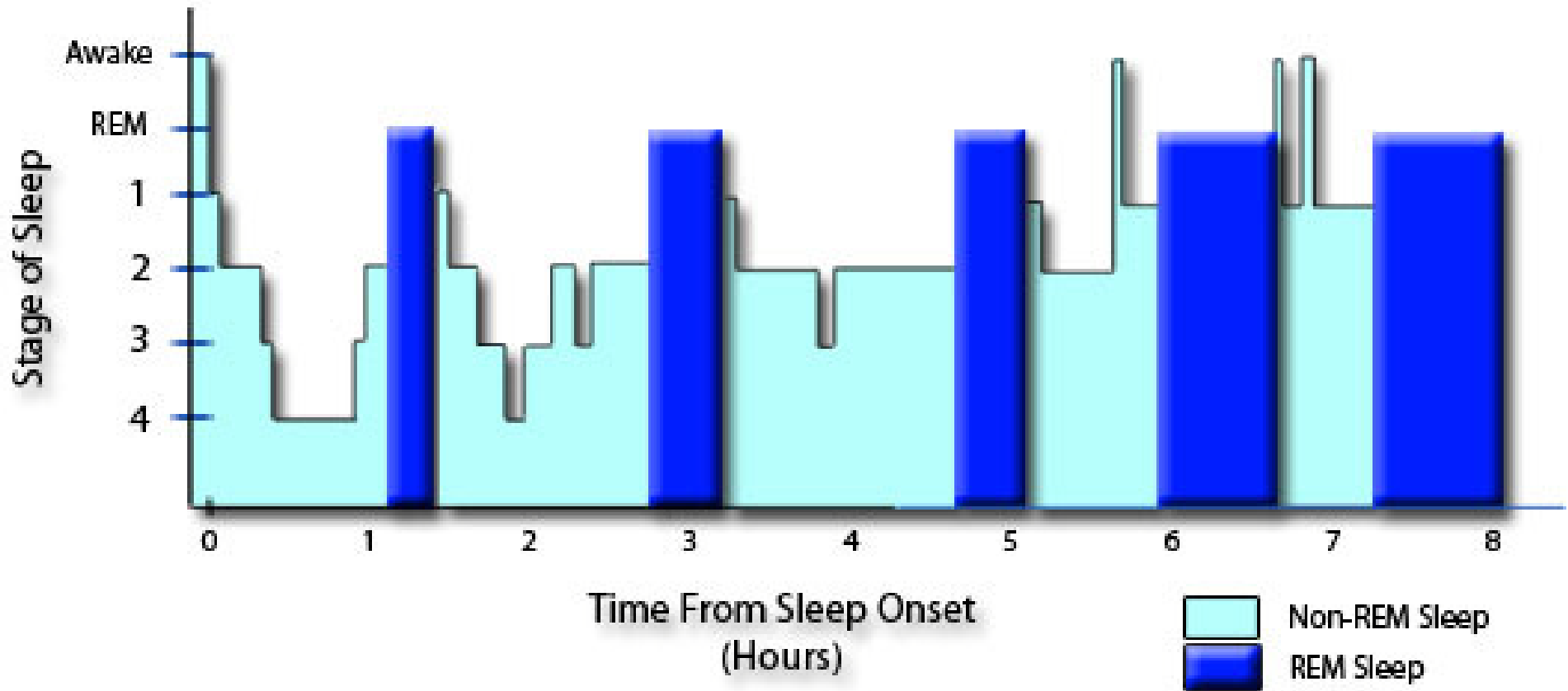
EEG  
EMG

You can see rapid eye movements during awake and REM sleep, high voltage EEG during stages 3 and 4, the high EMG level during awake and stage 1, and the lowest EEG level during REM sleep.

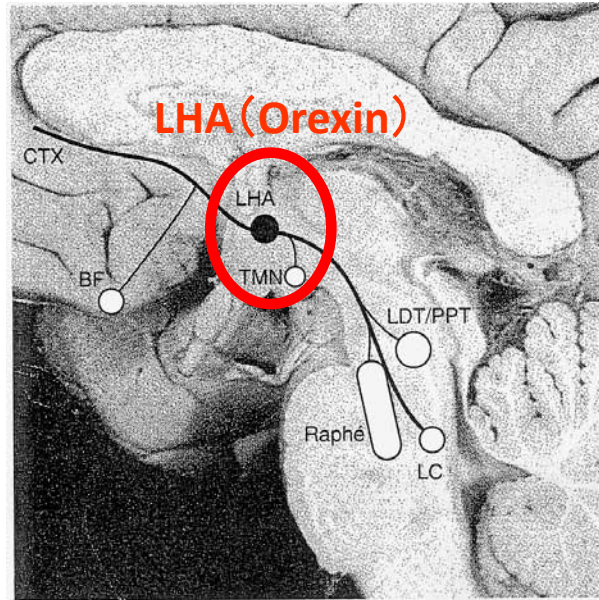
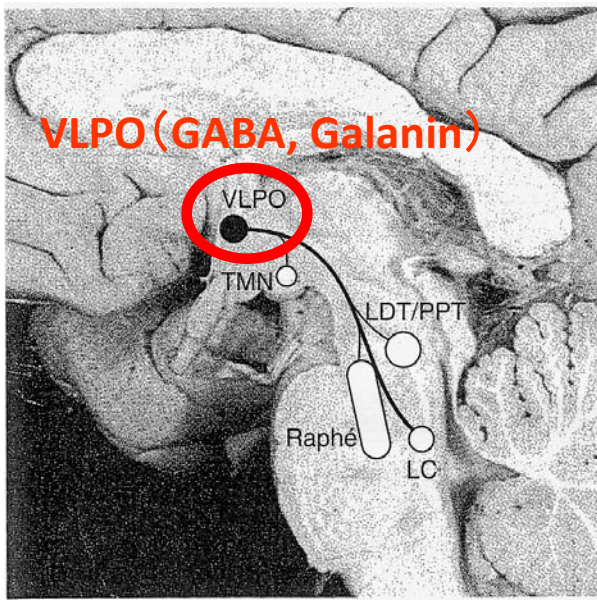
50  $\mu$ V

1 sec.

# Sleep Stages Through The Night

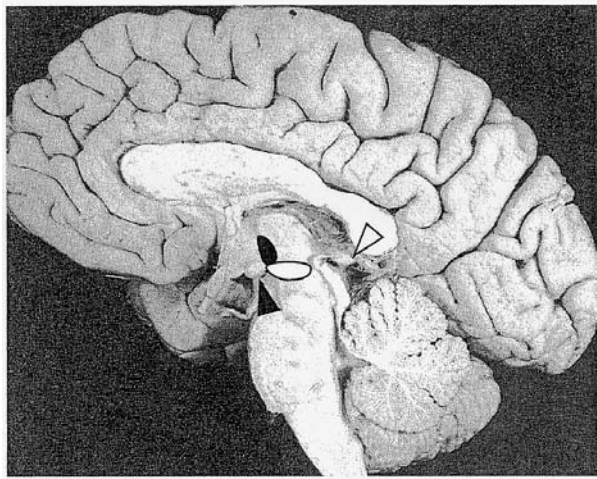


This figure shows the transitions and relative amount of time spent in each stage of sleep in a typical night for a human adult. Notice that deep, slow-wave sleep is most prevalent at the start of the night, and that as the night progresses proportionally more and more time is spent in REM sleep.



VLPO;  
 ventrolateral preoptic area  
 LHA; lateral hypothalamic area  
 CTX; cortex  
 BF; basal forebrain  
 TMN; tuberomammillary nucleus  
 LDT;  
 laterodorsal tegmental nucleus  
 PPT;  
 pedunculo pontine  
 tegmental nucleus  
 Raphe; raphe nucleus  
 LC; locus coeruleus

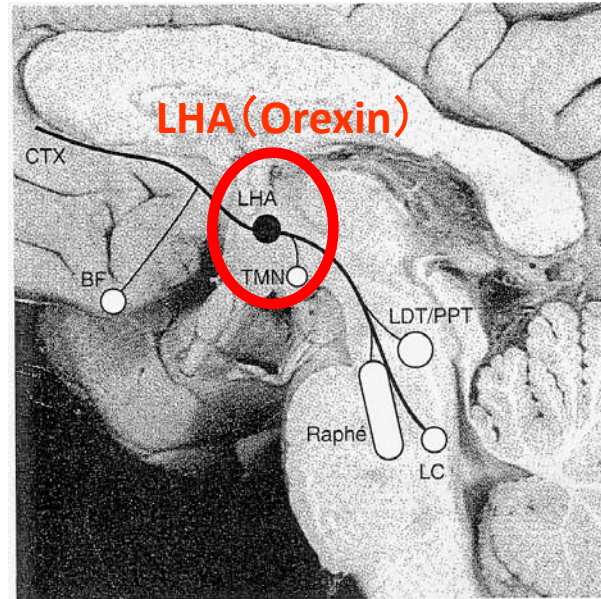
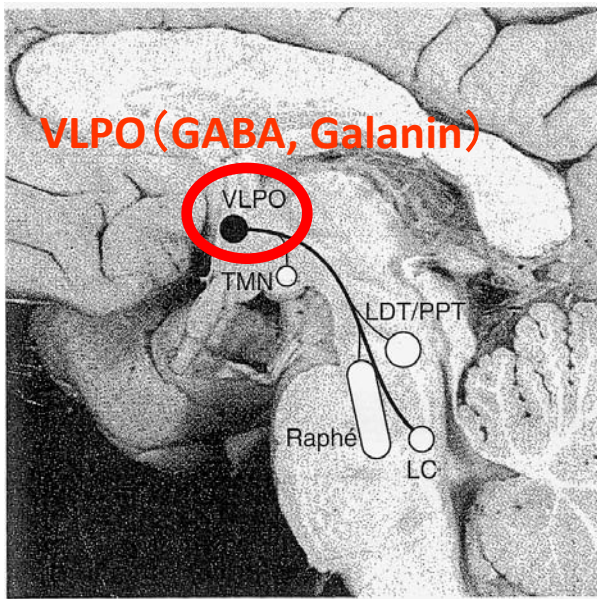
Projections from VLPO (sleep center)(lt) and LHA (waking center) (rt).



Sleep (black) and waking (white) centers proposed by von Economo in 1920s.

Patients with insomnia had black lesions → sleep center (anterior hypothalamus)  
**VLPO (GABA, Galanin)**

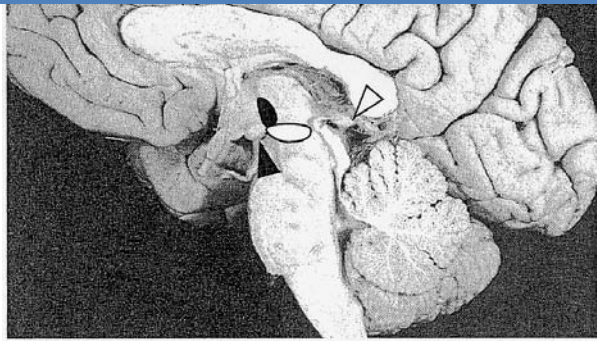
Patients with hypersomnia had white lesions → waking center (posterior hypothalamus)  
**LHA (Orexin), TMN (Histamine)**



VLPO;  
 ventrolateral preoptic area  
 LHA; lateral hypothalamic area  
 CTX; cortex  
 BF; basal forebrain  
 TMN; tuberomammillary nucleus  
 LDT;  
 laterodorsal tegmental nucleus  
 PPT;  
 pedunculo pontine  
 tegmental nucleus

Projections from VLPO (sleep center)(lt) and LHA (waking center) (rt).

# Sleep is not a passive state but an active state.

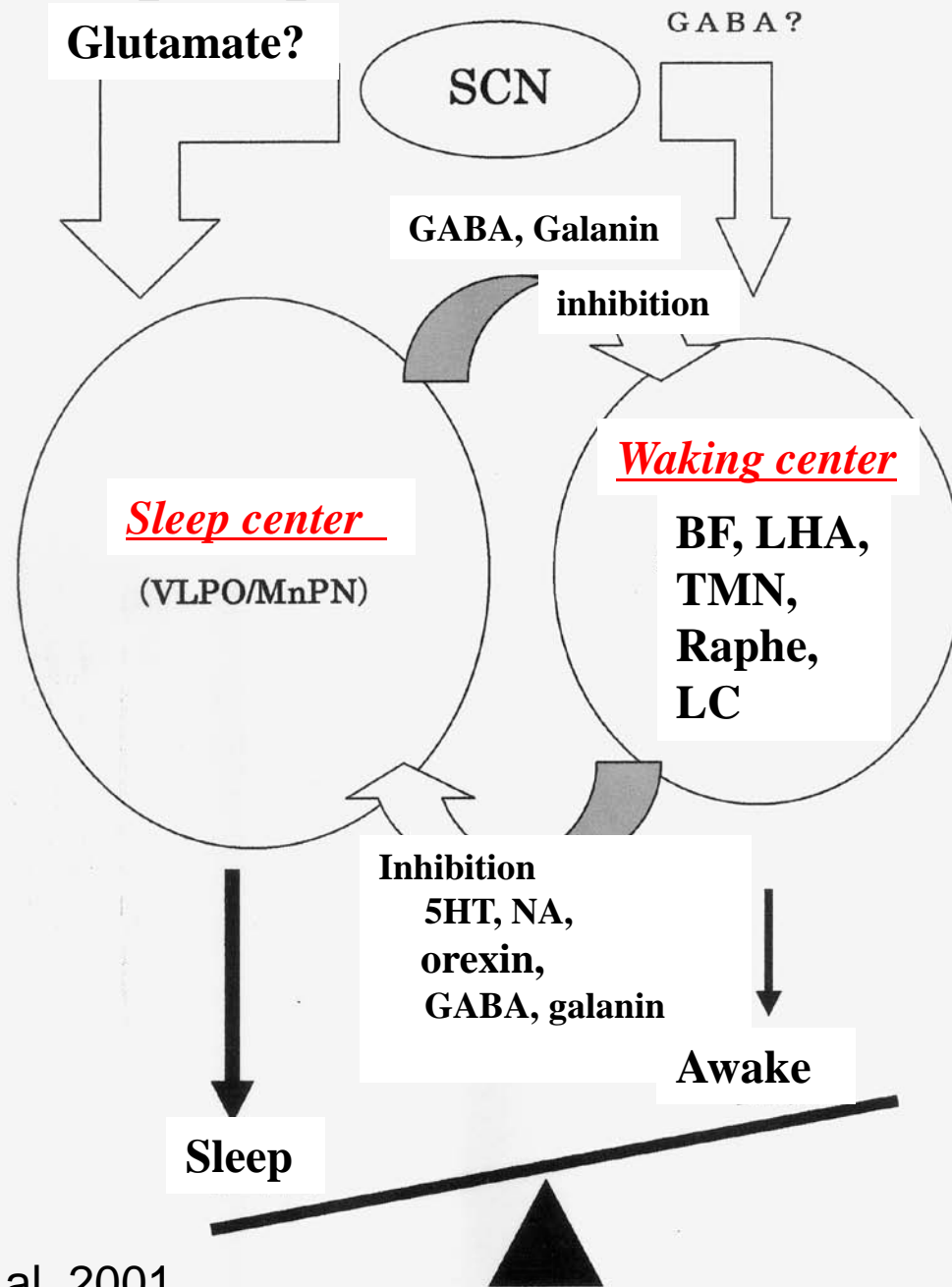


Sleep (black) and waking (white) centers proposed by von Economo in 1920s.

Patients with insomnia had black lesions →  
 sleep center (anterior hypothalamus)  
**VLPO (GABA, Galanin)**

Patients with hypersomnia had white lesions →  
 waking center (posterior hypothalamus)  
**LHA (Orexin), TMN (Histamine)**

# A flip-flop model on the control of wake and sleep



VLPO; ventrolateral preoptic area  
LHA; lateral hypothalamic area  
CTX; cortex  
BF; basal forebrain  
TMN; tuberomammillary nucleus  
LDT; laterodorsal tegmental nucleus  
PPT; pedunculopontine tegmental nucleus  
Raphe; raphe nucleus  
LC; locus coeruleus  
SCN; suprachiasmatic nucleus

**Since both centers are inhibited each other, once the activation of one of centers begins, this activation will continue.**

**Some extra stimulation (from the SCN?) could produce alteration on this situation.**

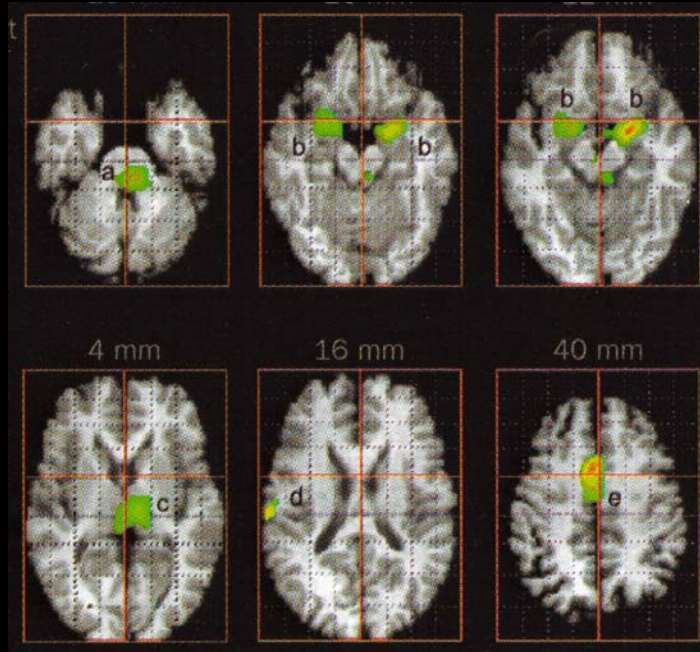
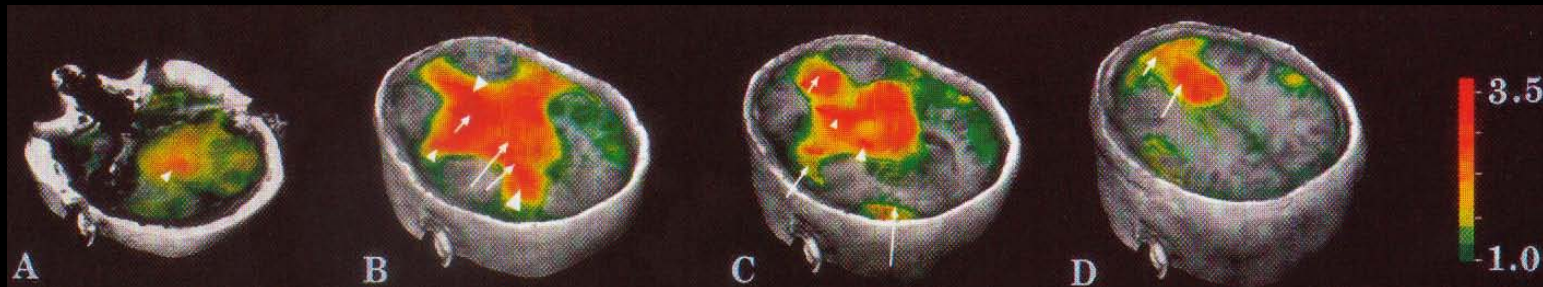
**This model could explain the continuity of the state, but fail to explain state change.**

What does happen during REM sleep?

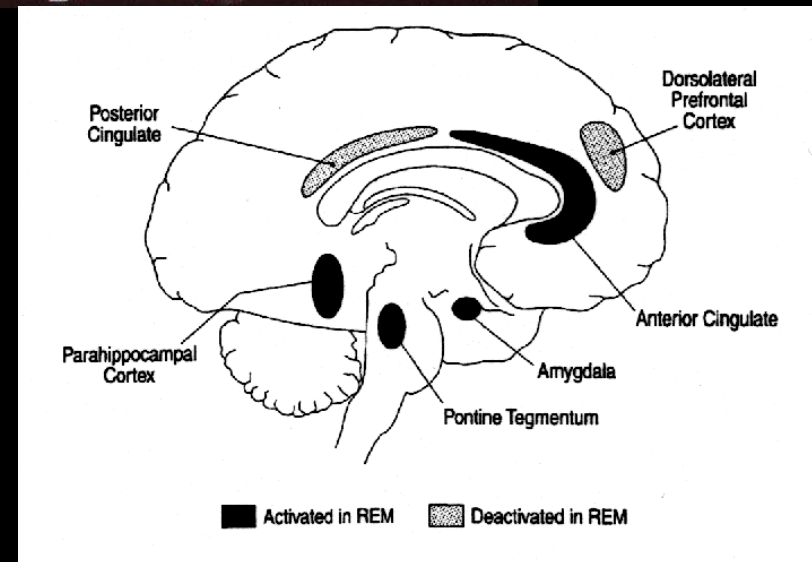
# PET studies on REM Sleep and brainstem

Activations of pontine tegmentum, amygdala and secondary optic area are known during REM sleep.

Braun et al 1997



Maquet et al 1996



Hobson et al 1998



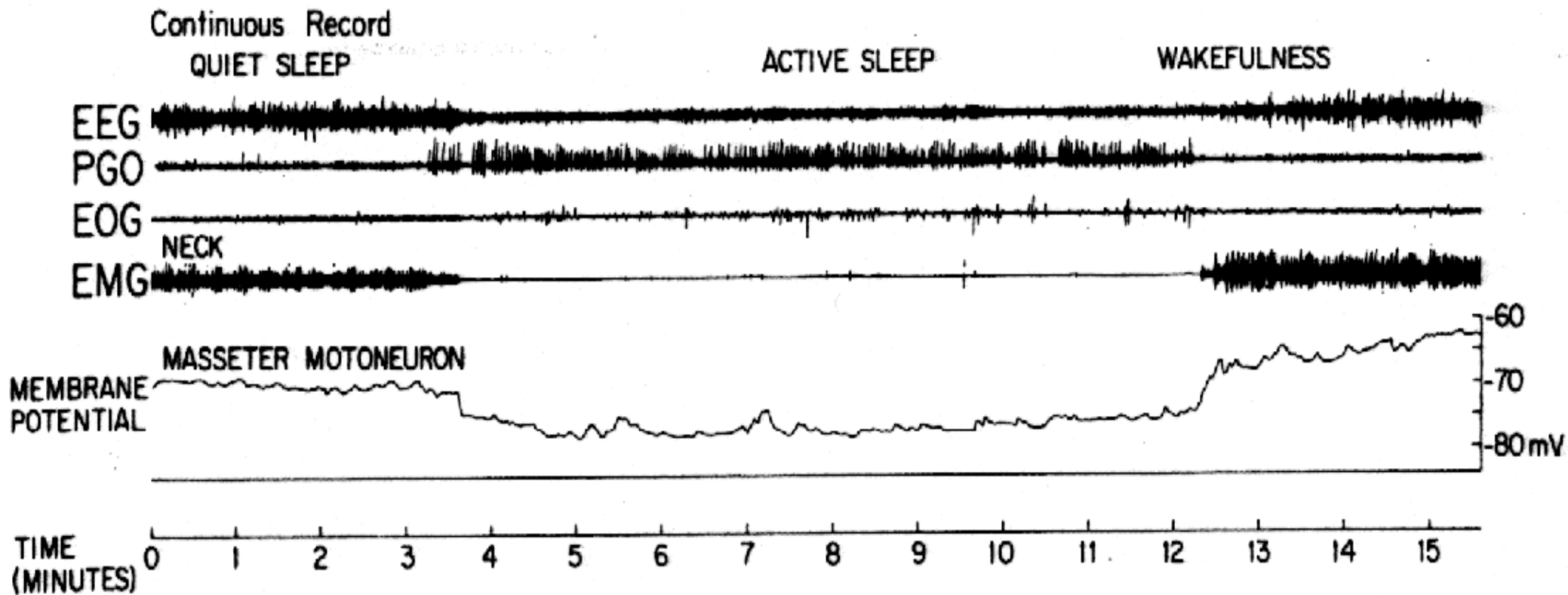
# PET studies on brain activities during sleep

	Light NREM	Deep NREM	REM
Maquet et al, 1997		↓ ; pons, midbrain, basal brain, orbito-prefrontal Cx	↑ ; pontine tegmentum, lt thalamus, amygdala, ant. cingulate gyrus ↓ ; frontal association Cx, post. cingulate gyrus
Braun et al 1997		↓ ; brainstem, thalamus, basal forebrain, frontal/parietal association Cx	↑ ; secondary optic area ↓ ; frontal association Cx
Kajimura et al, 1999	↓ ; pons, cerebellum, thalamus, putamen, ant. cingulate gyrus	↓ ; portions during light NREM+ midbrain, hypothalamus, basal forebrain, caudate, post. cingulate gyrus	
Summary		↓ ; pons, thalamus, basal forebrain, association Cx	↑ ; pontine tegmentum, amygdala, sencandary optic area ↓ ; association Cx

# PET studies on brain activities during sleep

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Summary		<b>↓ ; pons, thalamus, basal forebrain, association Cx</b>	<b>↑ ; pontine tegmentum, amygdala, sencandary optic area</b> <b>↓ ; association Cx</b>

# Anyway, what occurs during REM sleep is inhibition of motoneurons.



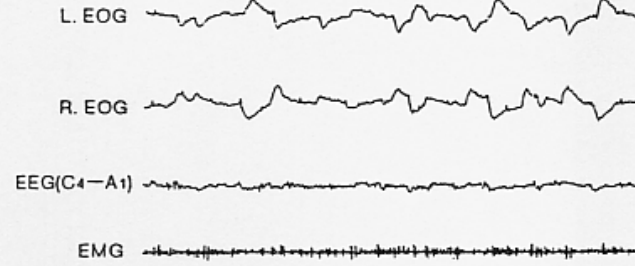
Intracellular recording from a masseter motoneuron

# Polysomnographic features of each sleep stage

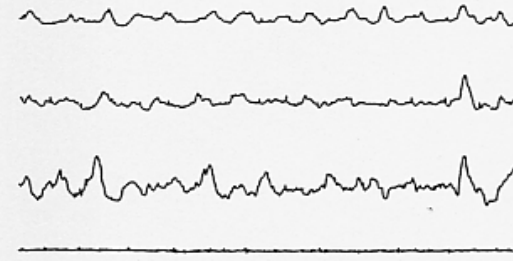
L-EOG  
R-EOG

EEG  
EMG

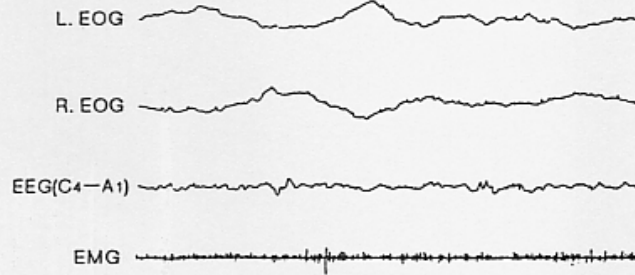
Awake



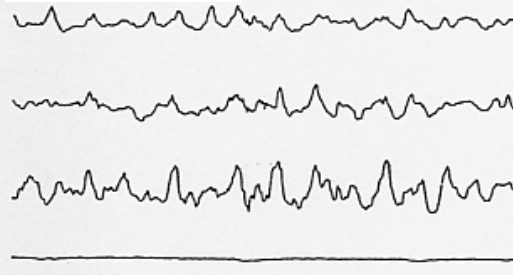
Stage 3



Stage 1



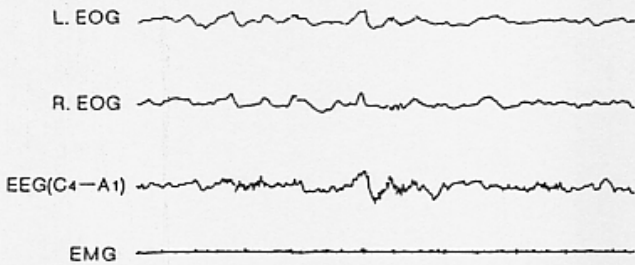
Stage 4



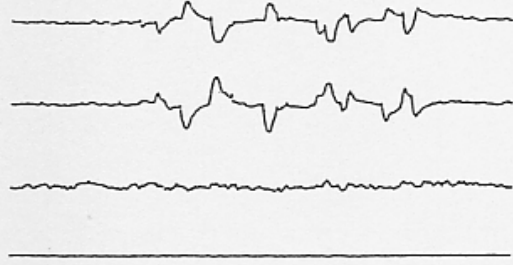
L-EOG  
R-EOG

EEG  
EMG

Stage 2



REM sleep stage



L-EOG  
R-EOG

EEG  
EMG

**Because of the tonic inhibition, muscle atonia occurs during REM sleep.**

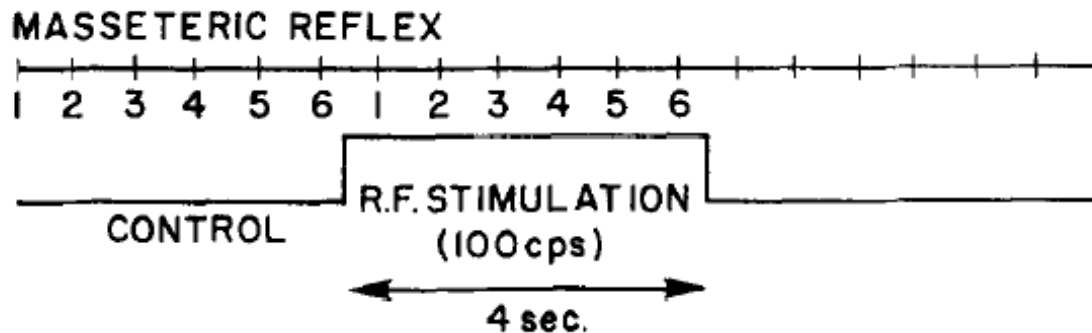
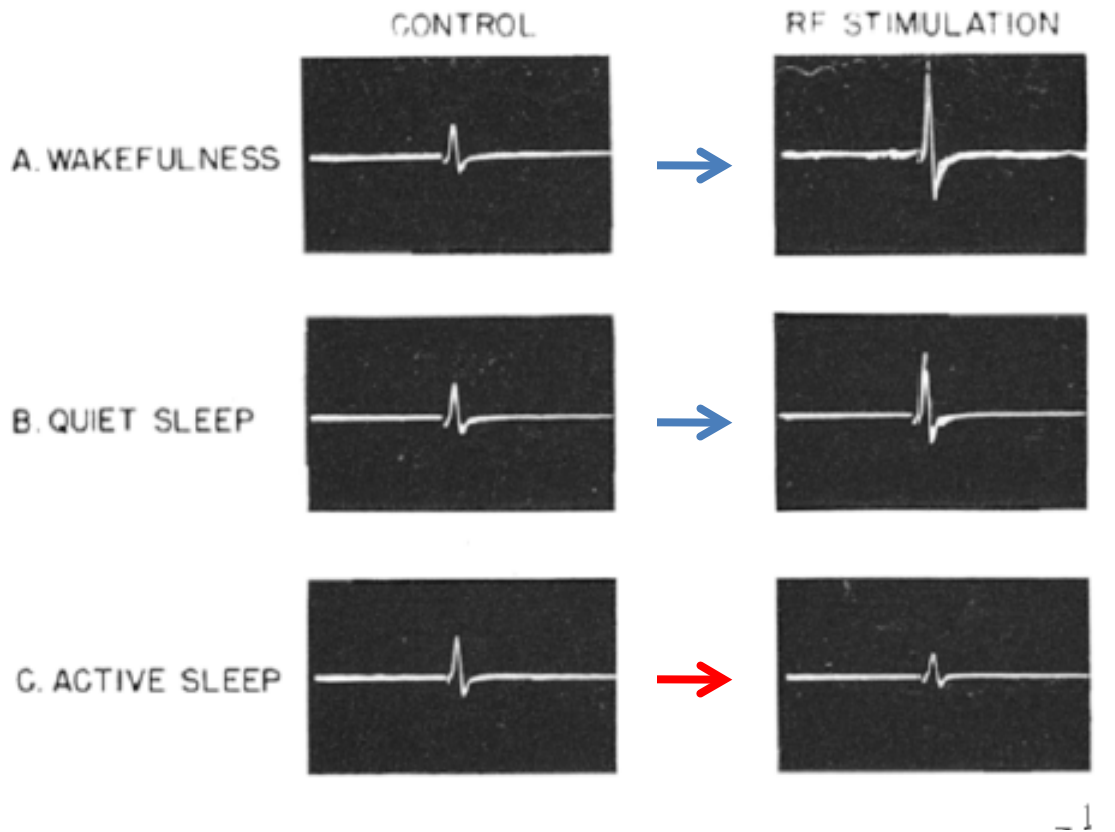
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1 sec.

# Response-reversal

- Stimulation of the pontomesencephalic reticular formation resulted in two distinct changes in masseteric reflex excitability which were dependent on the behavioral state of the animal.
- During wakefulness and quiet sleep, reticular stimulation resulted in an increase in reflex excitability.
- However, during active sleep, the identical stimulus delivered to the same reticular site led to profound reflex suppression.

# Example of response-reversal



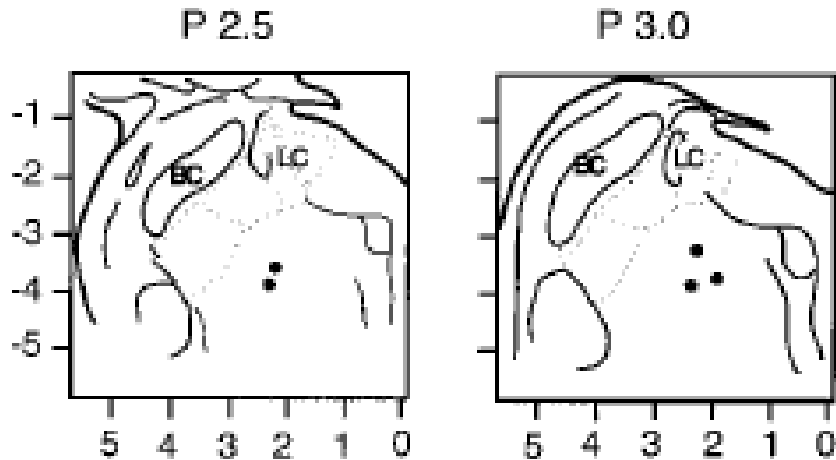
The amplitude of the brainstem masseteric (jaw closing) reflex (mososynaptic reflex), induced continuously in freely-moving adult cats, served as a baseline control for this analysis of reflex modulation.

At randomly-spaced intervals, high frequency stimulation was applied to the ponto-mesencephalic reticular formation for 4-sec periods.

In the states of wakefulness and quiet sleep, the amplitude of the masseteric reflex increased significantly during superimposed reticular stimulation (→).

When the animal entered into active sleep, however, the result of reticular stimulation (using identical parameters) was a profound decrease in reflex amplitude (→). Chase et al., 1976

## A Effective Injection Sites



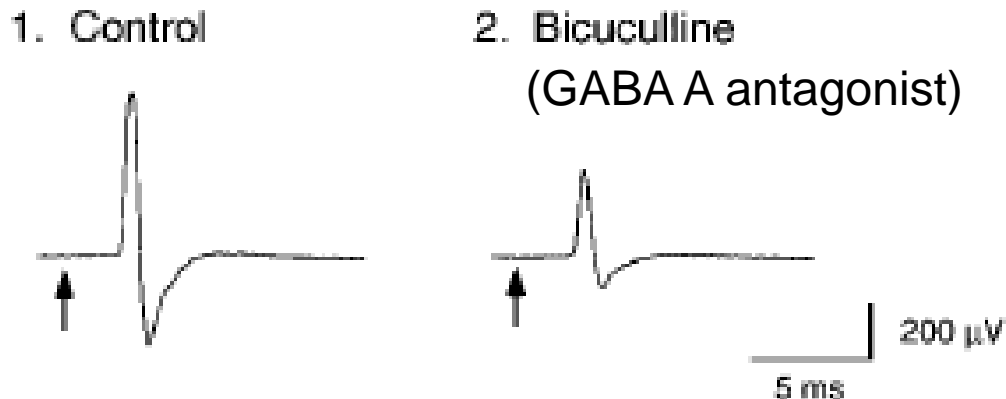
Suppression of the Ia-monosynaptic reflex following the injection of bicuculline into the nucleus pontis oralis (NPO).

*A: anatomical location of effective injections site in the rostral.*

*B: examples of individual reflexes, elicited by electrical stimulation of the L7 dorsal root before and after bicuculline injection.*

Reflex amplitude was reduced after bicuculline administration (*B2*).

## B Monosynaptic Reflex



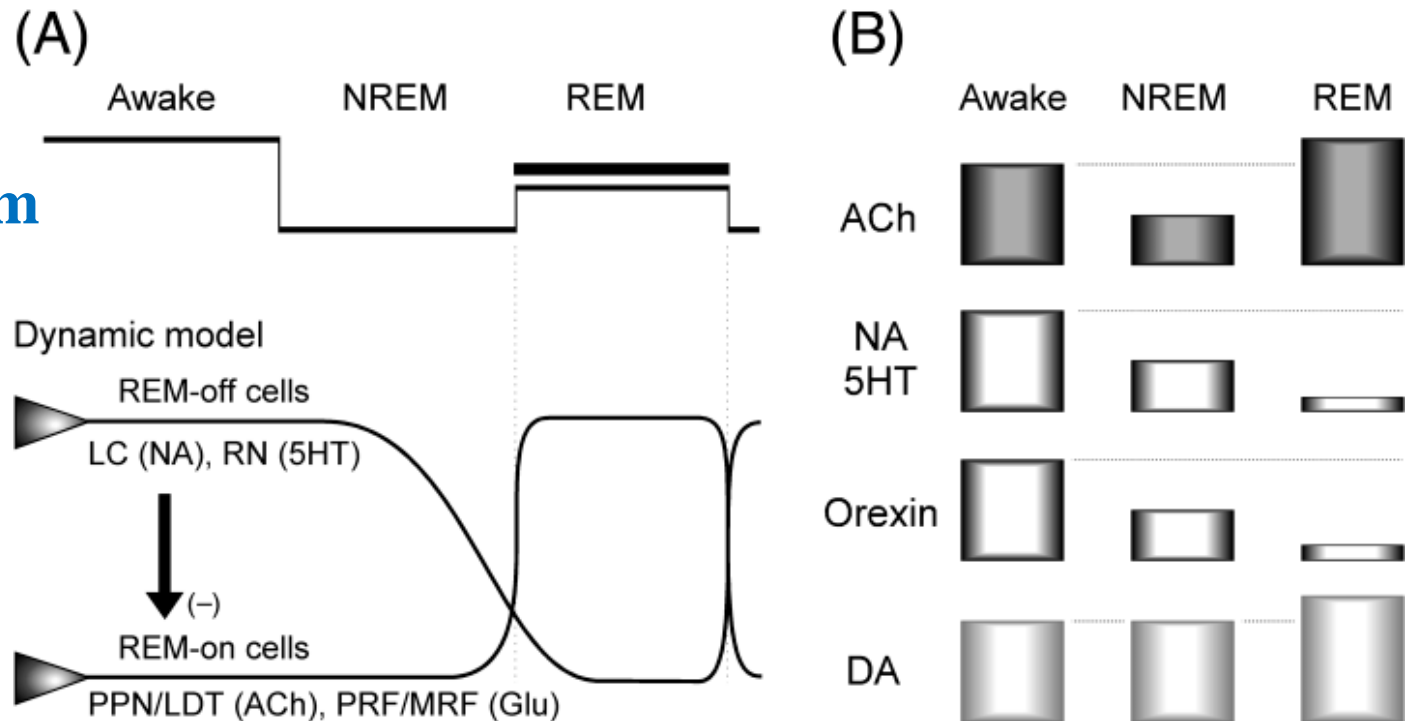
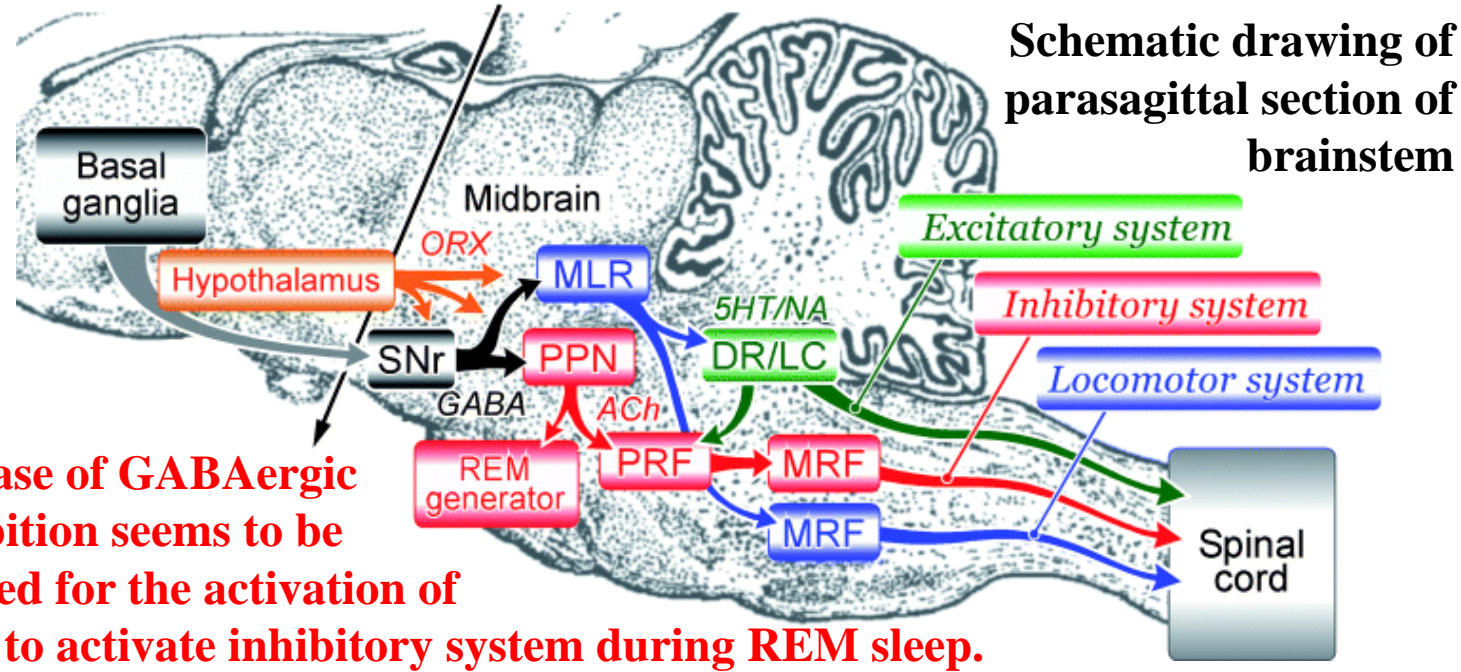
**Response-reversal affected by states could be mimicked by modulation of chemical agents.**

The Motor Inhibitory System Operating During Active Sleep Is Tonically Suppressed by GABAergic Mechanisms During Other States  
Ming-Chu Xi, Francisco R. Morales and Michael H. Chase  
*J Neurophysiol* 86:1908-1915, 2001.

**Functional connections affected by intrinsic chemical substances are altered remarkably among states.**

**Activity of each system is modified by states (the balance among intrinsic chemical substances).**

Takakusaki et al., 2006





# Sleep neurology (Somno-neurology)

- The stimulation delivered during wakefulness to a specific brainstem site produce an effect. The same stimulation to the same site during REM sleep could produce different effects. This phenomenon is termed as response-reversal.
- Recently, this modulation (response-reversal) affected by states could be mimicked by modulation of chemical agents.
- Although the anatomical connection in the central nervous system seems stable from a macrostructural viewpoint, functional connections affected by intrinsic chemical substances are altered remarkably among states.
- A state is determined by the balance among intrinsic chemical substances.

# Sleep neurology (Somno-neurology) cont.

- Most neurologists pay their attention mainly on neurological symptoms during wakefulness, and few of them are interested in symptoms during sleep or the alteration of symptoms occurring by state switches. The latter is an area of sleep neurology.
- Sleep occupies one thirds to fourths of our life.
- I showed you dynamic changes of neuronal activities during sleep.
- Some epileptic disorders exhibit marked wake/sleep dependency.
- Sleep neurology (somno-neurology) is important not only for the solution of epilepsy but also for the elucidation of sleep mechanisms.
- I believe epilepsy is a useful situation to open a path to this new and fascinating area; sleep neurology.

# Special Lecture 6

## Effects of Sleep on Seizures ;

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- 1. Effects of sleep on epilepsy**
- 2. Effects of sleep on inter-ictal epileptiform discharges**
- 3. Current knowledge on sleep mechanisms**
- 4. Response-reversal**