



*"Saint Peter released from prison"
Filippino Lippi*



Fisiopatología de la Narcolepsia

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Departamento de Fisiología



D^r JEAN-BAPTISTE-ÉDOUARD GÉLINEAU

DE LA

NARCOLEPSIE

PAR LE

D^r GÉLINEAU

MEMBRE DE LA SOCIÉTÉ DES MÉDECINS, DU BUREAU DE BIENFAISANCE
DE LA SOCIÉTÉ FRANÇAISE D'HYGIÈNE
DE L'ACADÉMIE DE LA ROCHELLE, ETC., ETC.



J. TESSIER & Eugène TESSIER
IMPRIMERIE DE SURGÈRES
(Charente-Inférieure)

1881

Narcolepsia

“...es una neurosis rara o poco conocida caracterizada por una necesidad imperiosa de dormir, súbita y de corta duración que se reproduce a intervalos mas o menos largos...”

Gelineau, 1880.

“Por primera vez me di cuenta de que tenía un problema cuando **a los 14 años** me dormía en el liceo y era despertado por el profesor.

Fueron **nueve** los accidentes de auto que padecí entre los 16 y 20 años, todos por quedarme dormido mientras manejaba.

A los 21 años me diagnosticaron narcolepsia, pero entre los 21 y 25 años sufrí **seis** accidentes de tránsito, ya que no fui tratado correctamente.

A los 25 años me sentí normal y alerta por primera vez, **gracias a que el tratamiento fue efectivo.**”

Joseph Piscopo
*Chairman of the
American Narcolepsy Association
(1986-1993)*

Epidemiología

- 1 in 2000 (*¿ 1500 pacientes en Uruguay?*).
- Similar en ambos sexos.
- Edad de comienzo: 15 a 35 años.

Clínica

- Hipersomnias (síntoma inicial).
 - ataques de sueño.
 - somnolencia (con automatismos motores).

- Cataplejia (70%). Pérdida repentina del tono muscular.
 - parcial o completa (similar a la atonía del sueño REM)
 - desencadenada por emociones



- Alucinaciones al comienzo del sueño (30%).

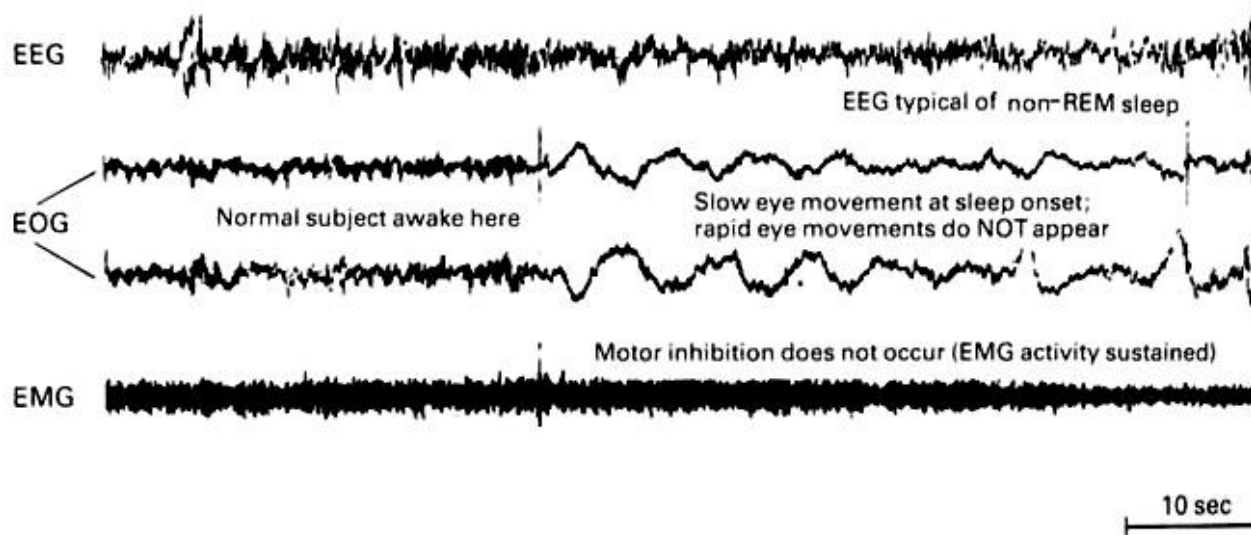
- Parálisis del sueño (25%).

Paraclínica

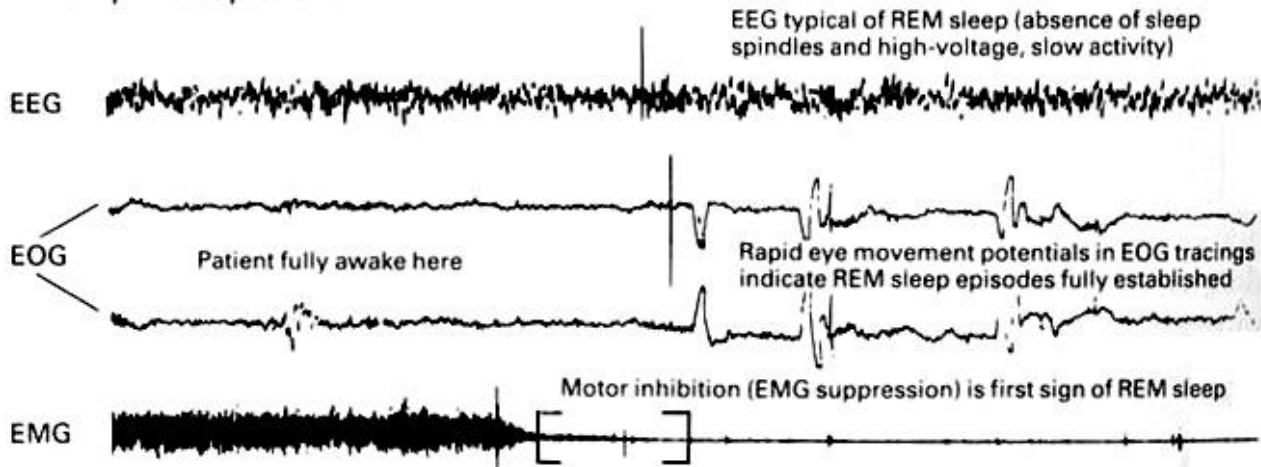
- Polisomnografía
 - sueño fragmentado
 - disminuye la latencia al sueño REM (“sleep onset REM”)

Sleep onset REM

A Normal sleep onset



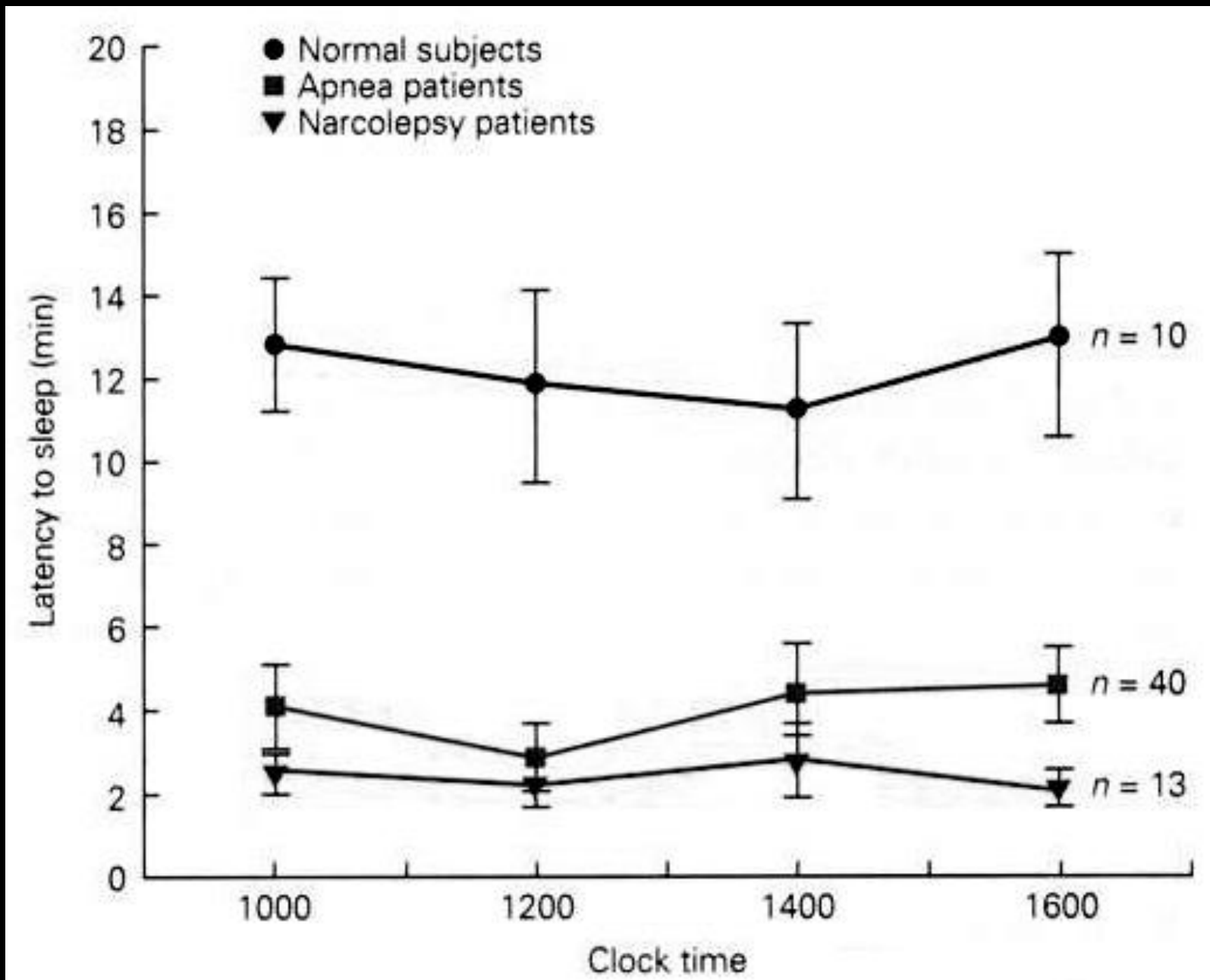
B Narcoleptic sleep onset



“Multiple sleep latency test”

- Latencia \leq 8 minutos
- 2 o mas “Sleep Onset REM”

Disminuye la latencia al sueño en el "Multiple Sleep Latency Test"



Fisiopatología

- **Trastorno en el mantenimiento de la vigilia** (Hipersomnias).
- **Intrusión del sueño REM (o sus signos) durante la vigilia** (“sleep onset REM”, cataplejía, parálisis del sueño, alucinaciones)

Tratamiento farmacológico

- Sustancias promotoras de vigilia (Anfetaminas, metilfenidato, modafinilo, etc).
- Sustancias que inhiben el sueño REM (Antidepresivos).

Historia de las **hipocretinas y la Narcolepsia**: ejemplo de Neurociencia Traslacional (impacto de la investigación básica, para entender y tratar las enfermedades cerebrales)

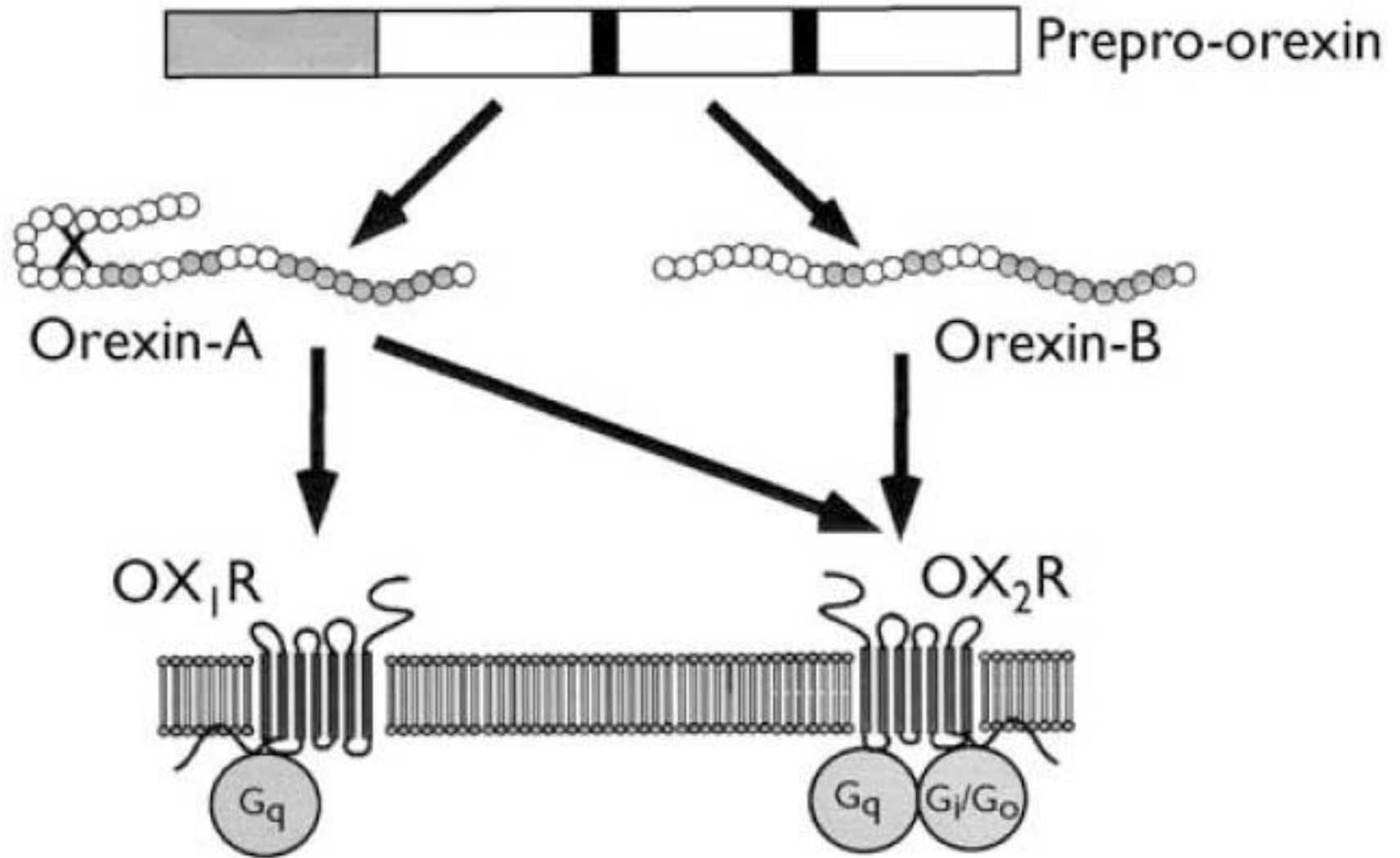
- 1998. - Descubrimiento de las hipocretinas (orexinas).
 - Anatomía del sistema hipocretinérgico.

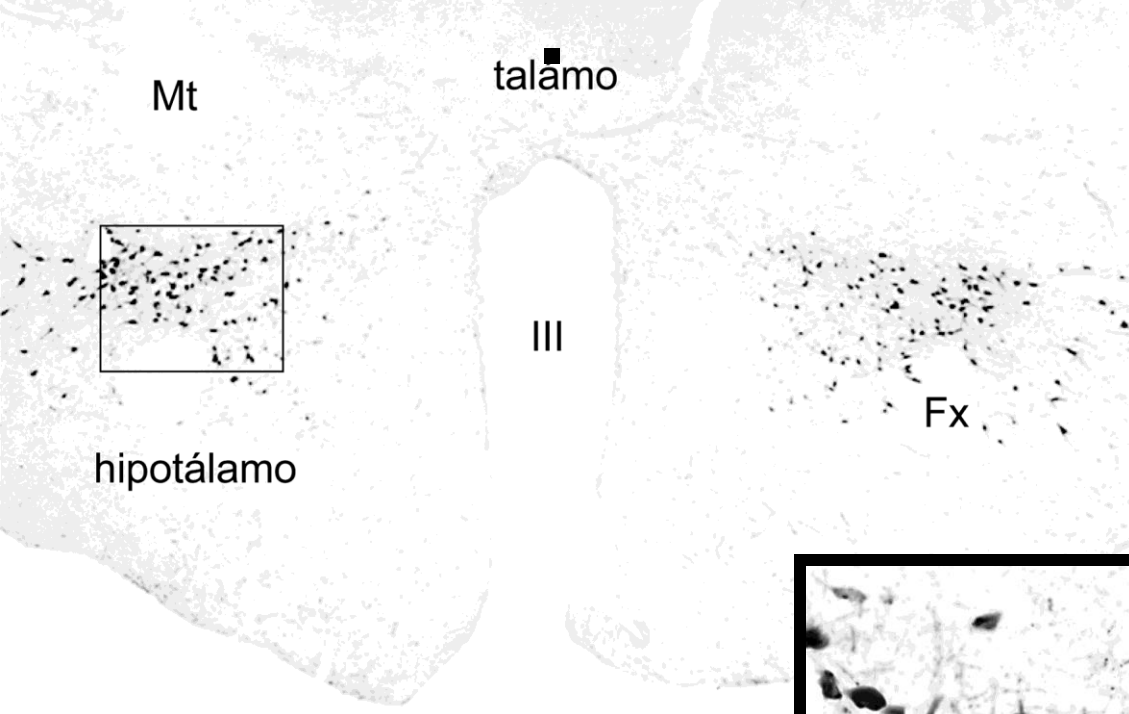
- 1999. - La Narcolepsia familiar canina: mutación en el gen del receptor tipo 2 de la hipocretina
 - Ratones “knock-out” para las hipocretinas presentan un fenotipo narcoléptico.

- 2000. - La narcolepsia humana muestra una degeneración de las neuronas hipocretinérgicas.

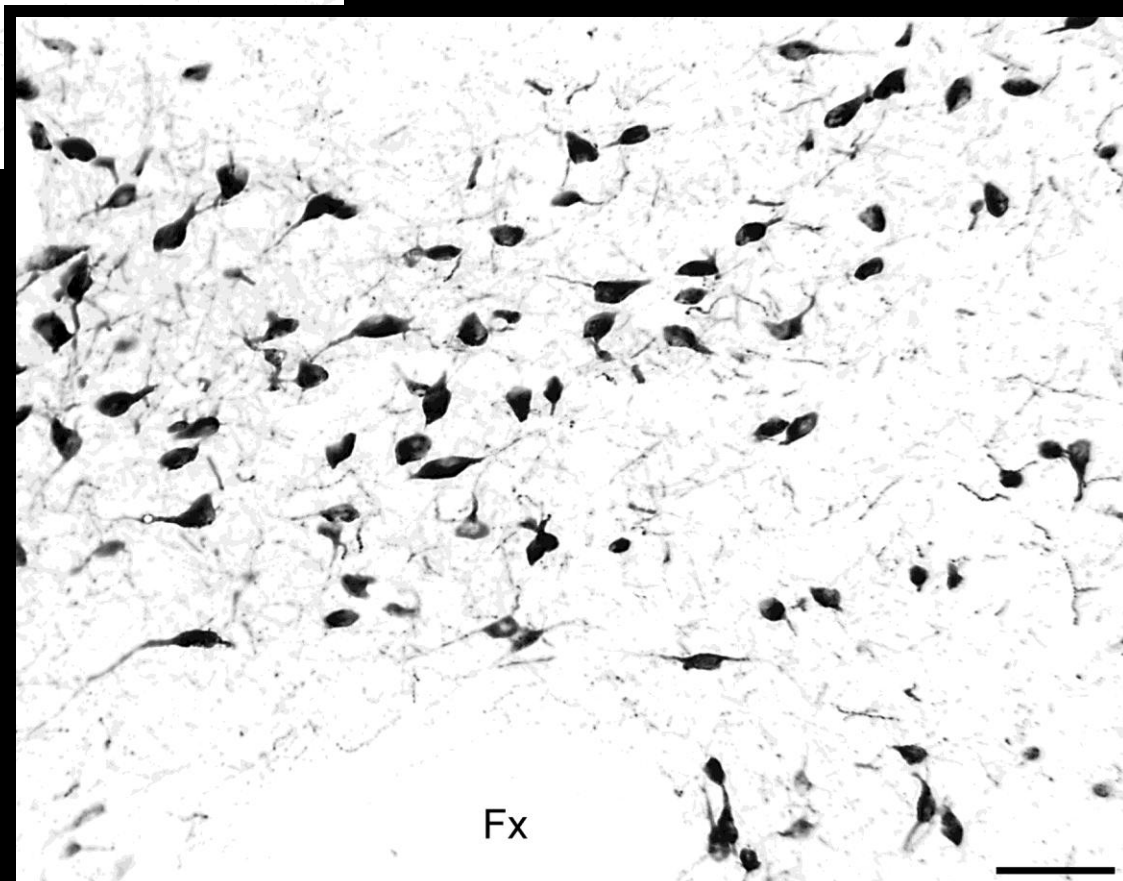
- 2001.
 - Titulación de hipocretinas en el LCR como método diagnóstico de Narcolepsia.
 - Tratamiento de sustitución en modelos animales de Narcolepsia.
 - Tratamiento de sustitución en pacientes Narcolépticos.

Las hipocretinas/orexinas son neuromoduladores peptídicos

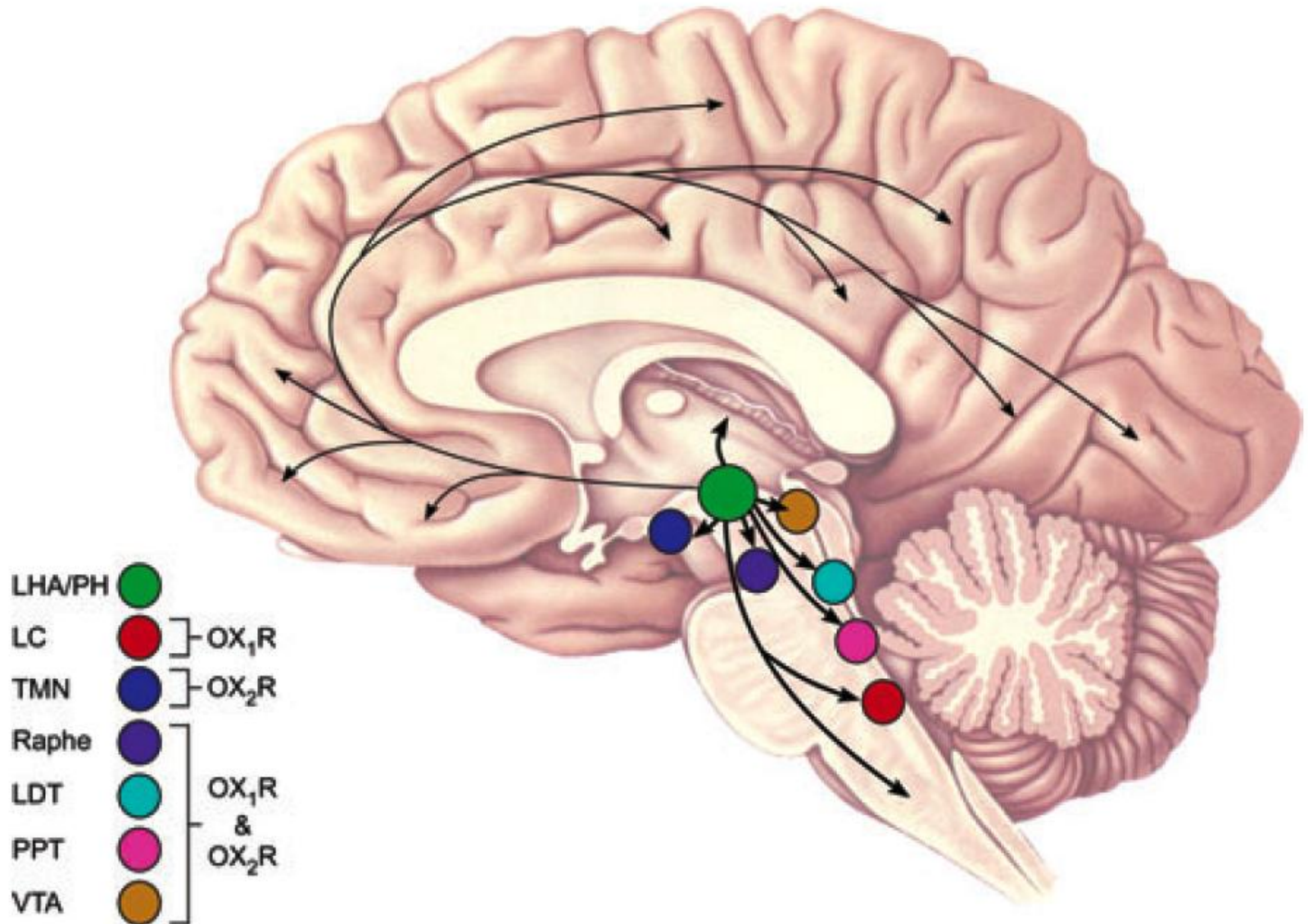


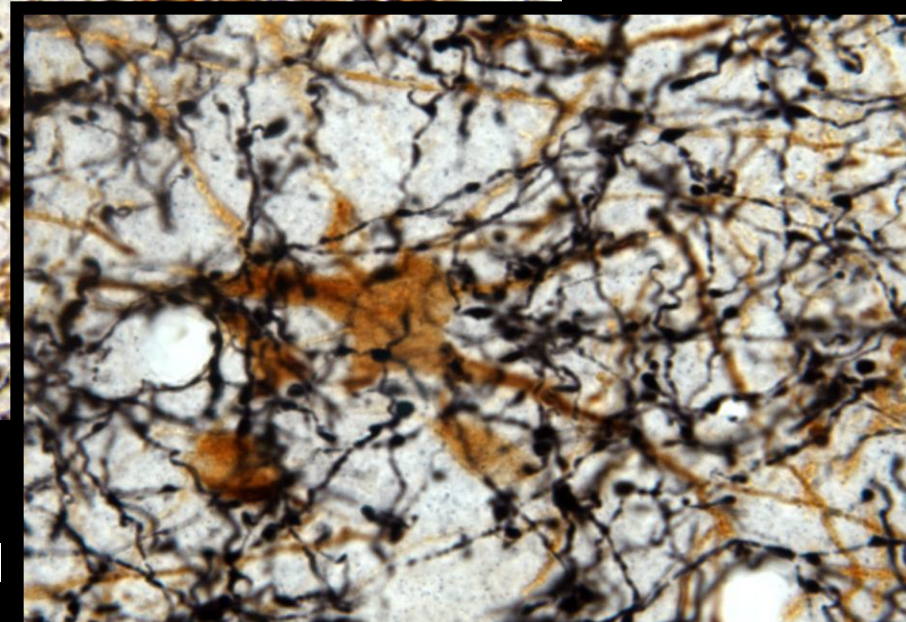
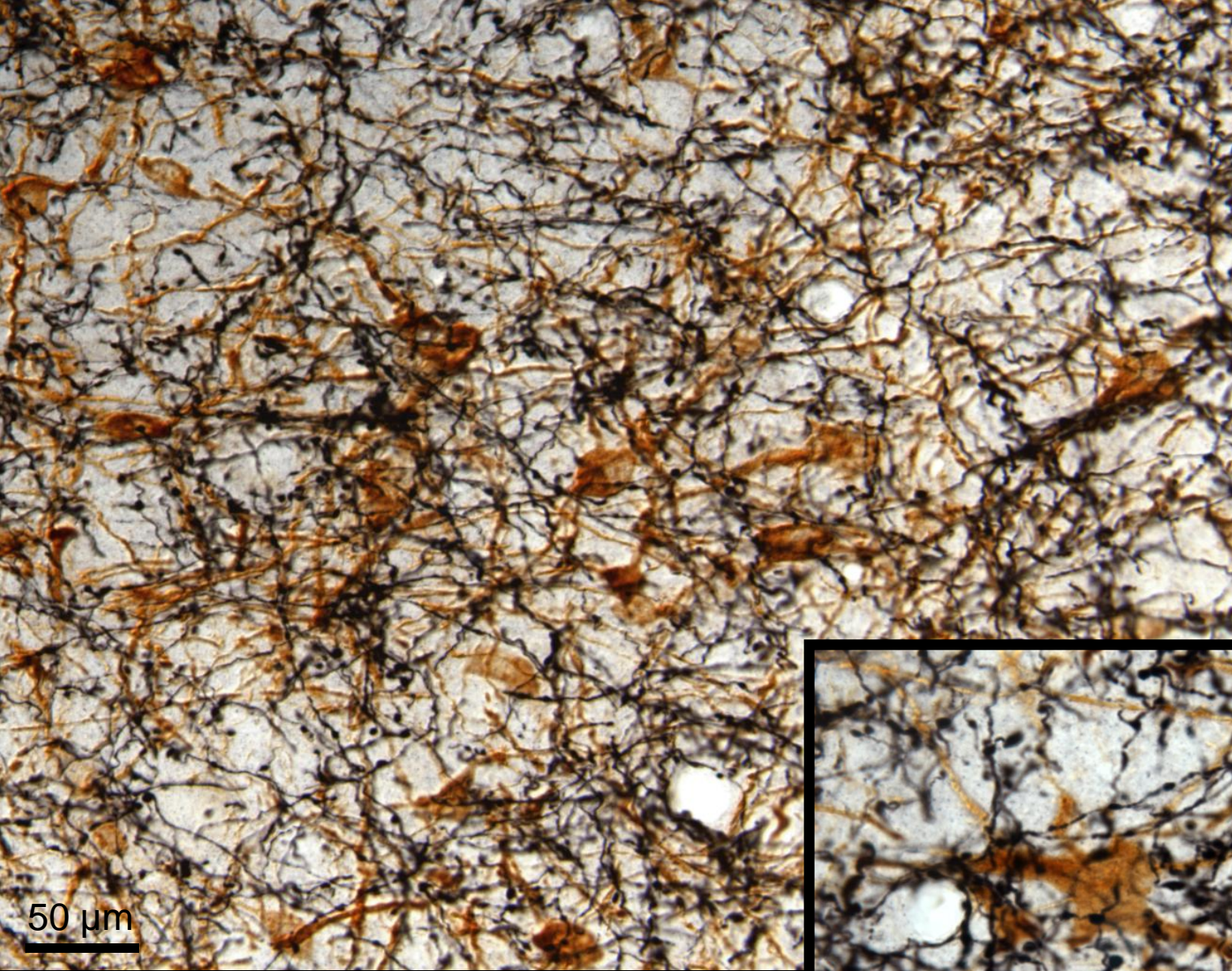


Las neuronas hipocretinérgicas se encuentran en la región perifornical de hipotálamo



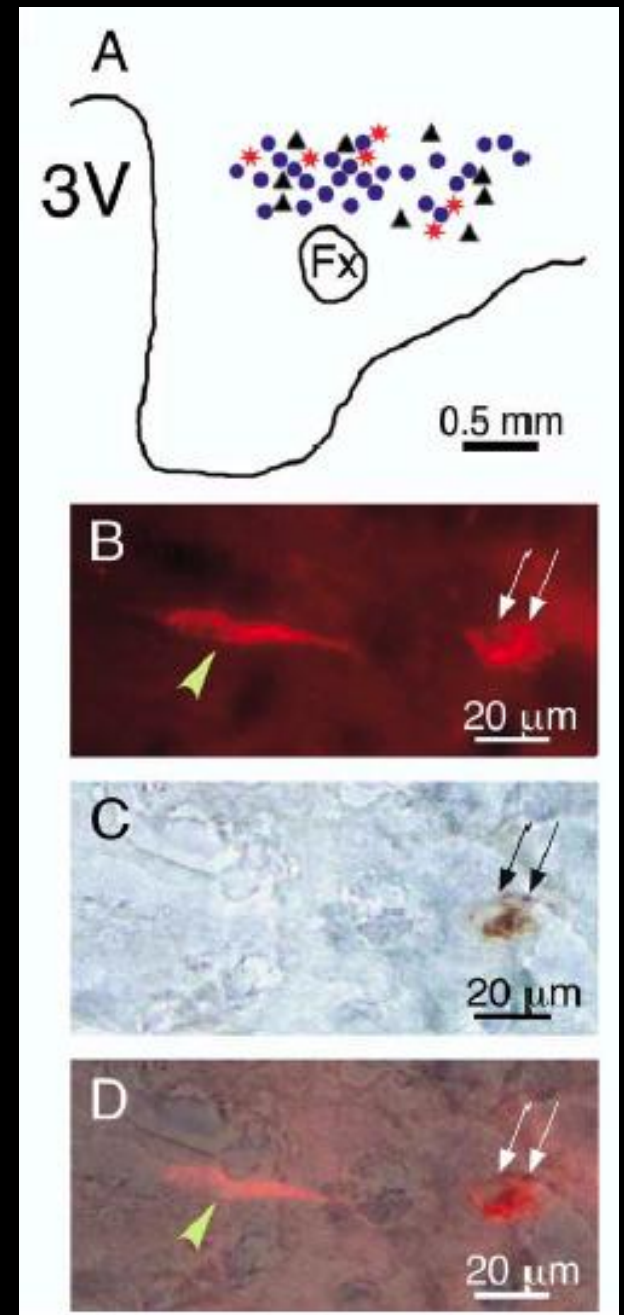
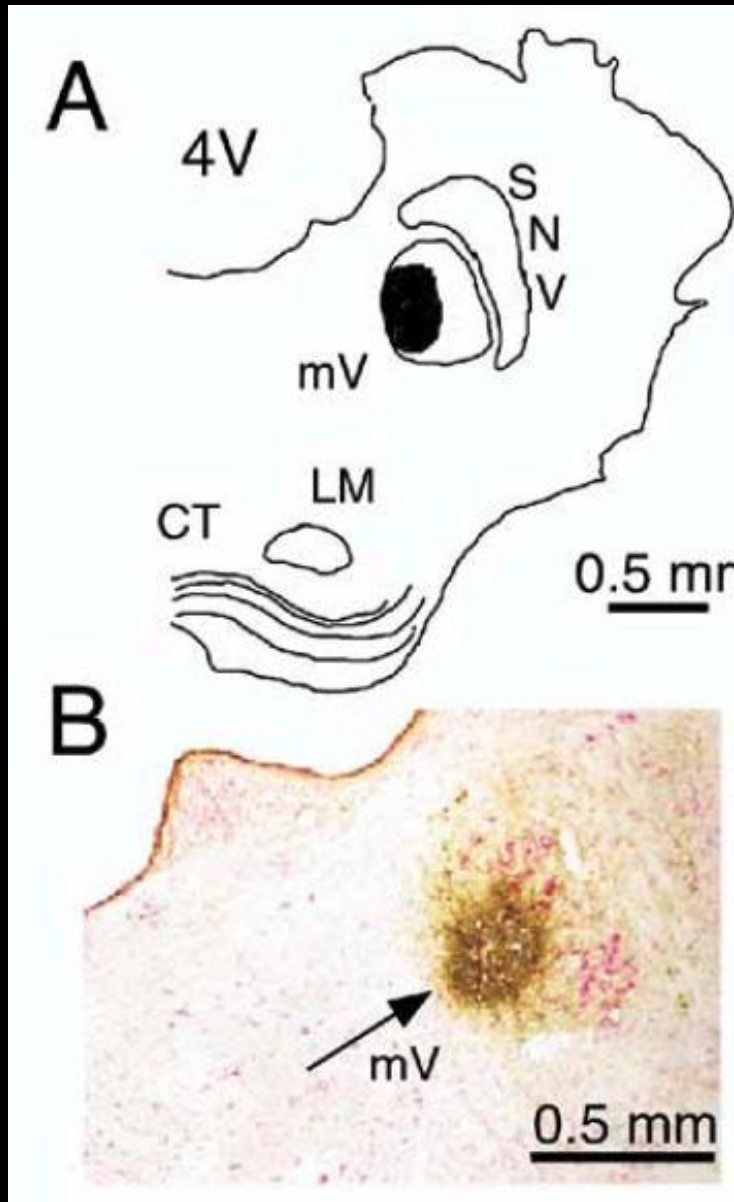
Las neuronas hipocretinérgicas proyectan a amplias regiones del SNC



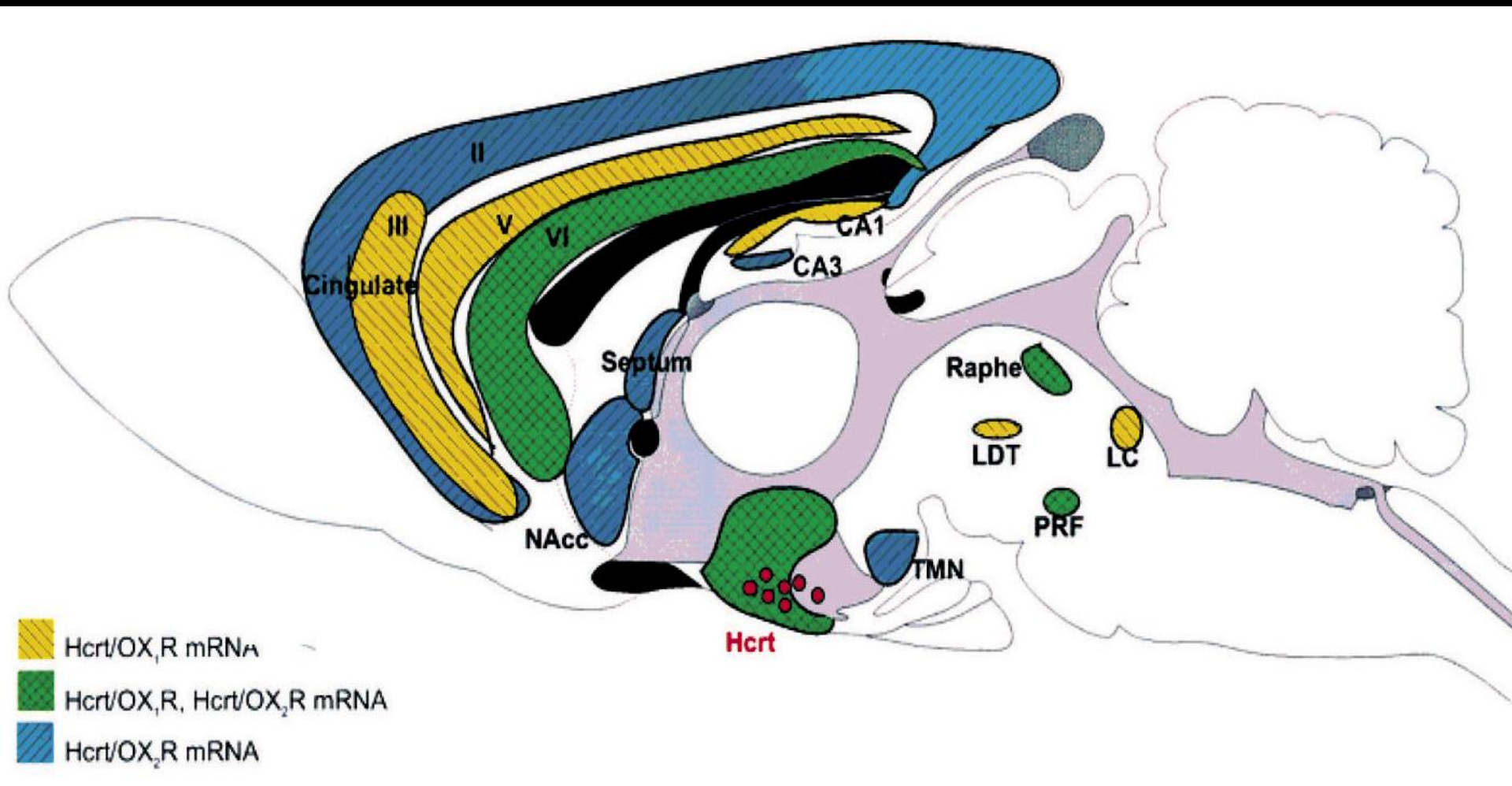


Fibras hipocretinérgicas en el
area tegmental ventral caudal-PAG rostral

Neuronas hipocretinergicas proyectan a los núcleos motores



Distribución de receptores hipocretinérgicos tipo 1 y tipo 2



Narcolepsia canina:

- Cataplejia desencadenada por emociones
- Hipersomnia
- Sueño fragmentado
- “Sleep onset REM”
- Responden a los mismos fármacos que la narcolepsia humana.

Narcolepsia canina



Narcolepsia canina familiar:

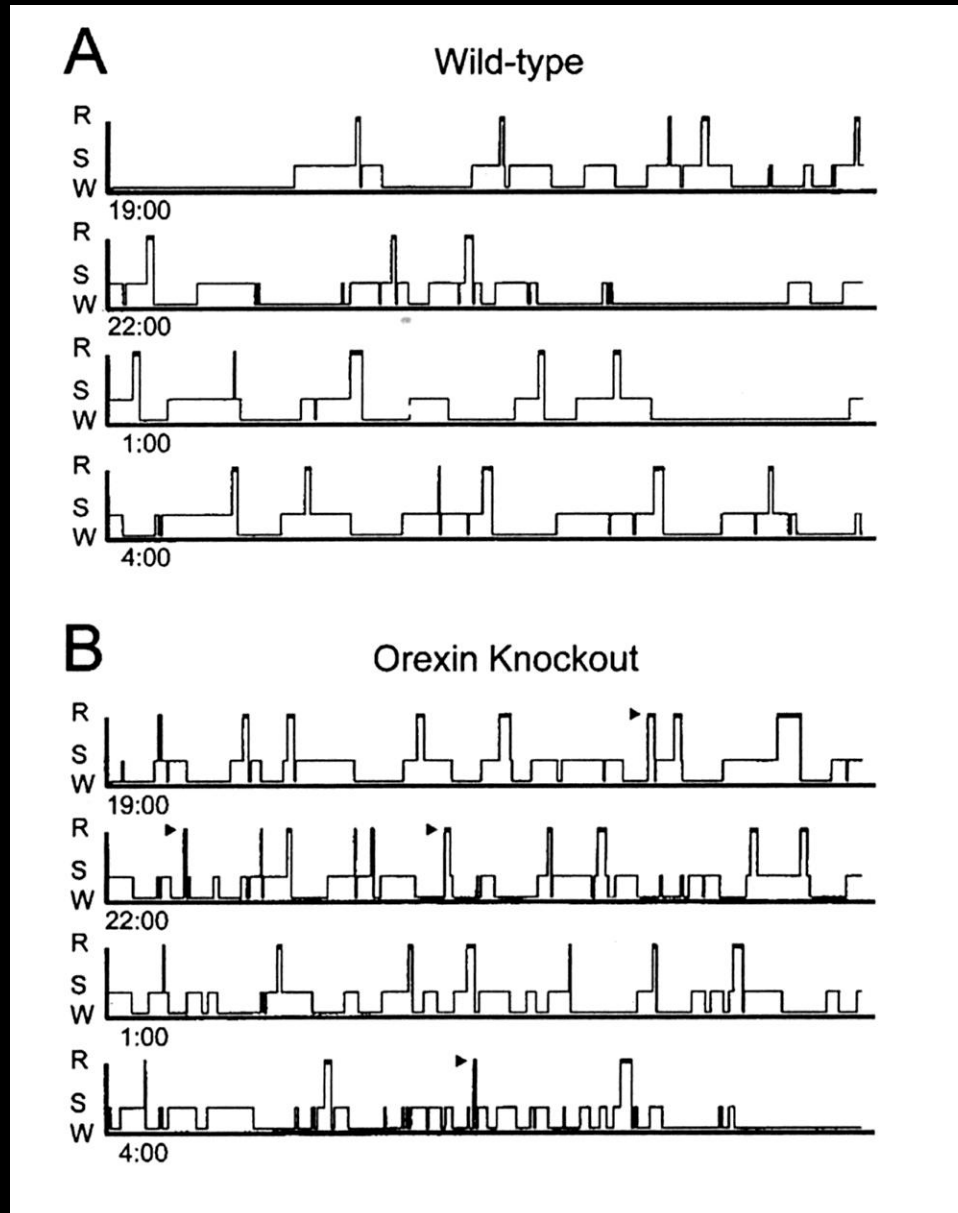
- Mutación en el gen del receptor tipo 2 de la hipocretina (Lin et al. 1999).

Narcolepsia canina espontánea:

- Niveles de hipocretinas no detectables en el LCR (Ripley et al. 2001).

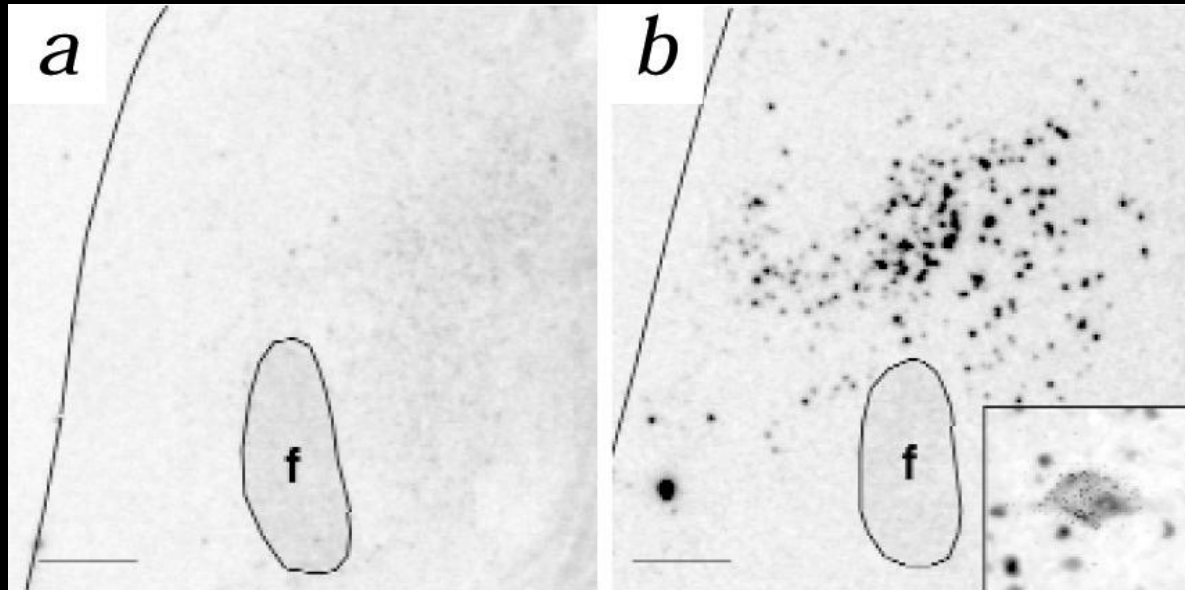
Ratones “knock-out” para la preprohipocretina

Los ratones “knock-out” para la preprohipocretina entran al sueño REM directamente desde vigilia

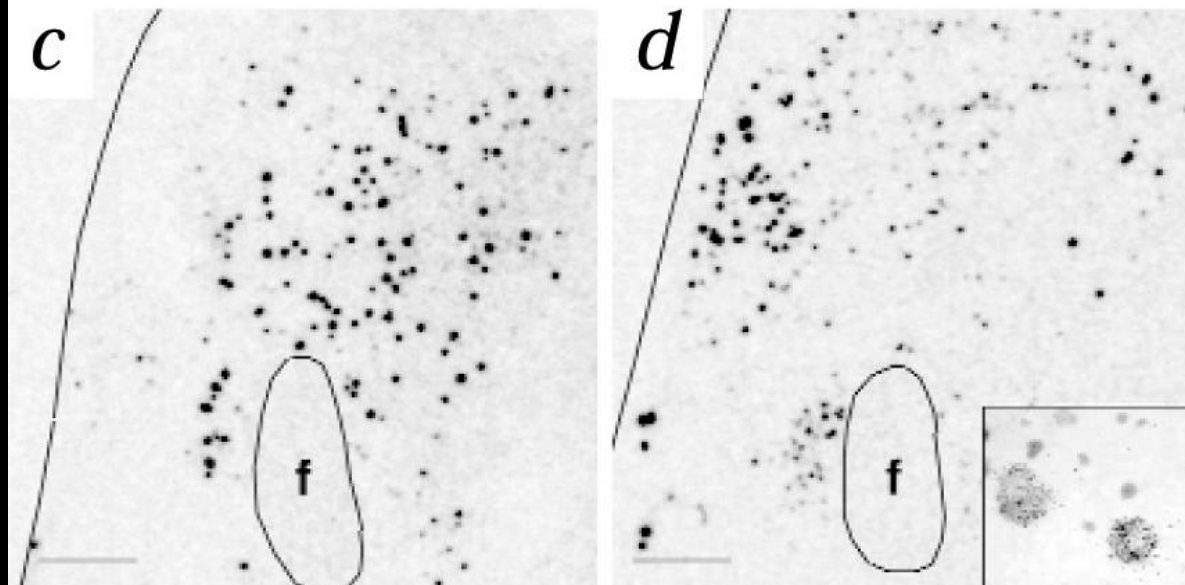


Los pacientes narcolépticos presentan una degeneración de las neuronas hipocretinérgicas

Hipocretinas



MCH



Etiología

Sospecha de etiología autoinmune, muy localizada, dirigida a algún antígeno presente en las neuronas hipocretinérgicas.

Como es la actividad de las neuronas hipocretinérgicas durante la vigilia y el sueño ?



Michael Chase

Department of Physiology, UCLA School of Medicine

Sleep Research Online 4(1): 25-32, 2001
<http://www.sro.org/2001/Tortero/25/>
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1096-214X
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Hypothalamic Neurons that Contain Hypocretin (Orexin) Express *c-fos* During Active Wakefulness and Carbachol-induced Active Sleep

Pablo Torterolo, Jack Yamuy, Sharon Sampogna,
Francisco R. Morales and Michael H. Chase

Department of Physiology and the Brain Research Institute, UCLA School of Medicine, Los Angeles, CA 90095

Hypothalamic hypocretinergic neurons have been implicated in the control of a variety of behavioral states. However, the activity of these neurons during sleep and wakefulness has not been described. Consequently, we examined Fos immunoreactivity (as a marker of neuronal activity) in hypocretinergic neurons during the following behavioral states: a) quiet wakefulness (QW), wherein the cats were awake and restrained in a head-holder device; b) active wakefulness (AW), wherein the cats were freely exploring a new environment and exhibited almost continuous locomotor activity; and c) carbachol-induced active sleep (AS-carbachol), wherein prolonged periods of active sleep were induced by the microinjection of carbachol into the nucleus pontis oralis. The majority of hypocretinergic neurons expressed *c-fos* during AW (184.7 ± 19.6 , 79%), whereas only a small number of these cells expressed *c-fos* during QW (3.0 ± 1.9 , 2%). Surprisingly, a large portion of the hypocretinergic neurons were Fos immunoreactive during AS-carbachol (60.3 ± 11.0 , 34%). The significant difference ($p < 0.0001$) between QW and AW in the number of hypocretinergic neurons that expressed *c-fos* indicates that these neurons are not involved in the maintenance of wakefulness *per se*, but more likely to play a role in arousal-type behaviors that accompany locomotor-explorative activity. In addition, the intriguing finding that a larger number of hypocretinergic neurons express *c-fos* during AS-carbachol than during quiet wakefulness suggests that these neurons play a role in active sleep-related processes.

CURRENT CLAIM: Hypocretinergic neurons are active during arousal accompanied by locomotor explorative activity and during carbachol-induced active sleep.

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The hypocretins (orexins) mediate the “phasic” components of REM sleep: A new hypothesis

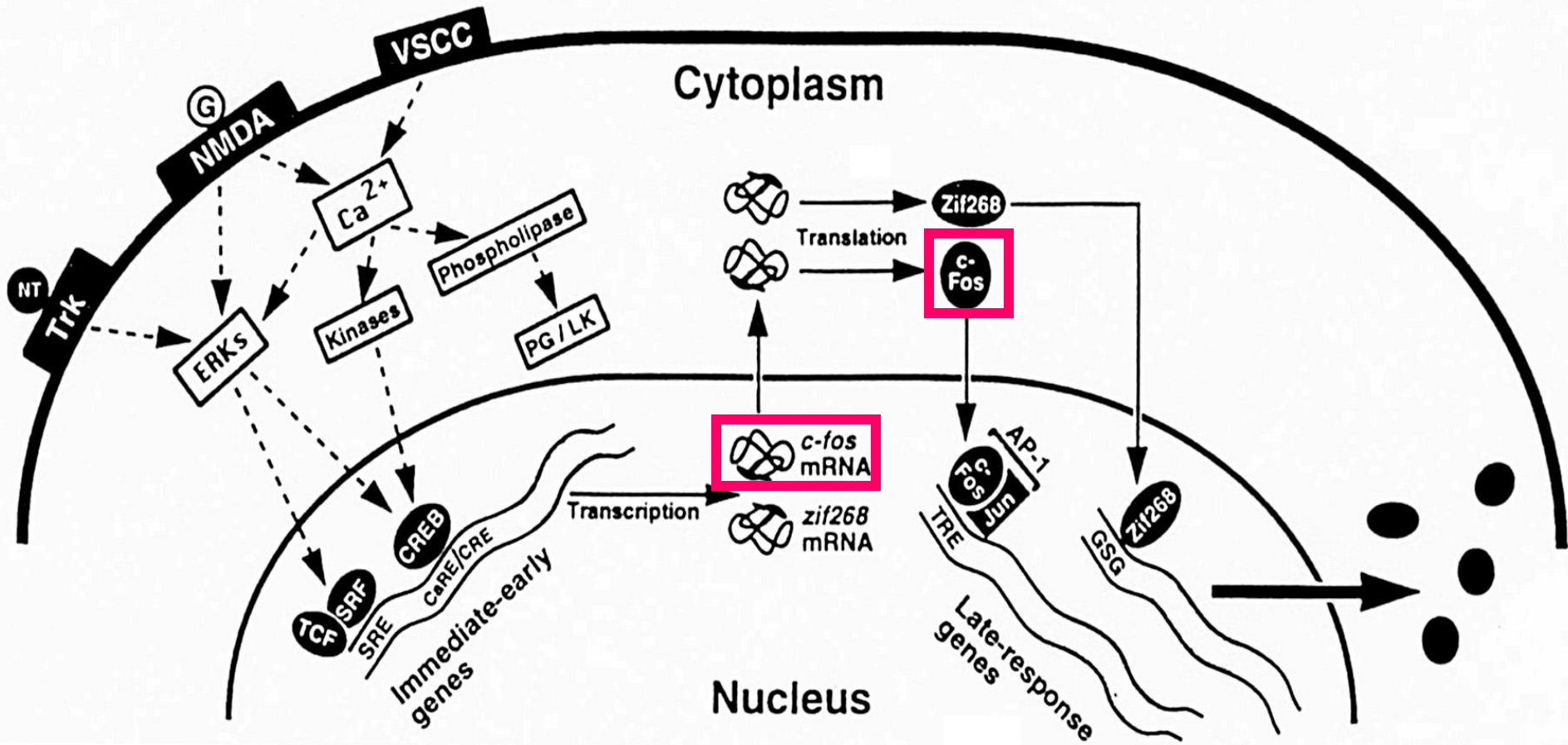
Pablo Torterolo^{a,*}, Michael H. Chase^{b,c}

^aLaboratorio de Neurobiología del Sueño, Departamento de Fisiología, Facultad de Medicina, Universidad de la República, General Flores 2125, 11800 Montevideo, Uruguay

^bWebSciences International, Los Angeles, USA

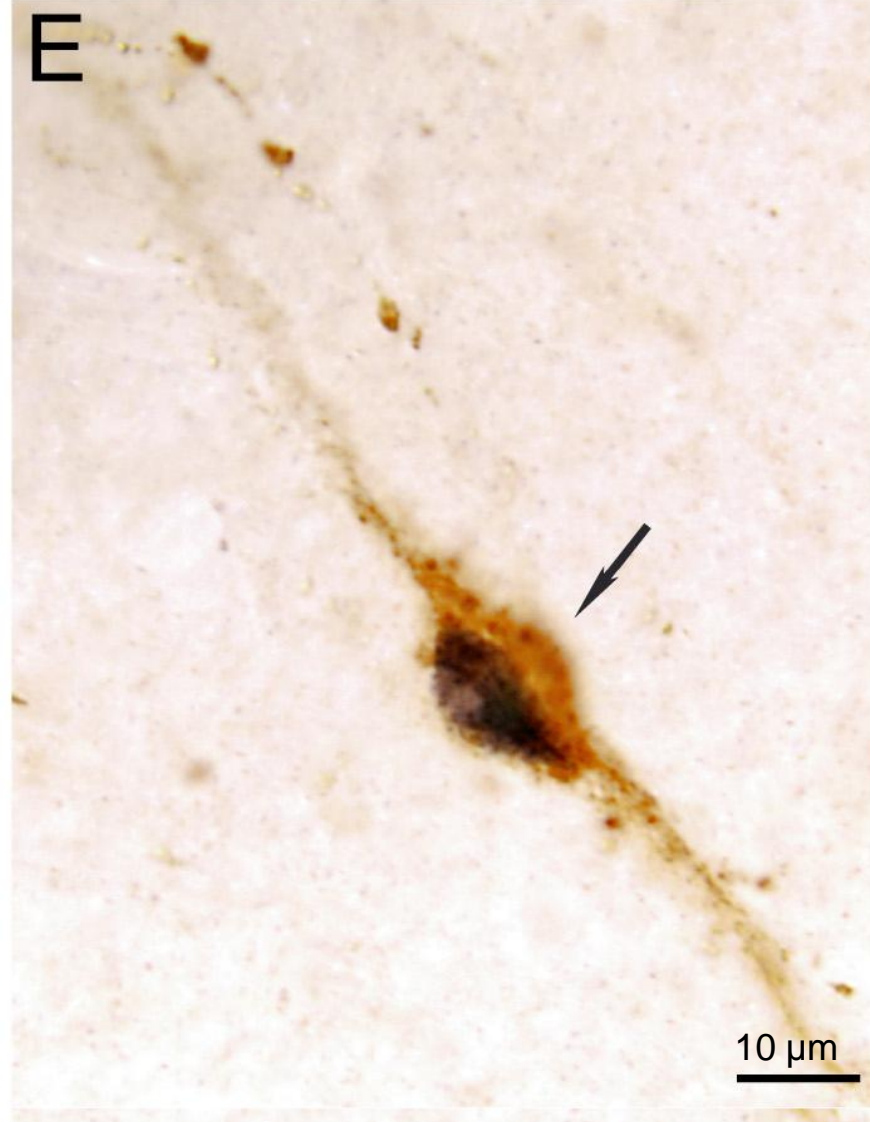
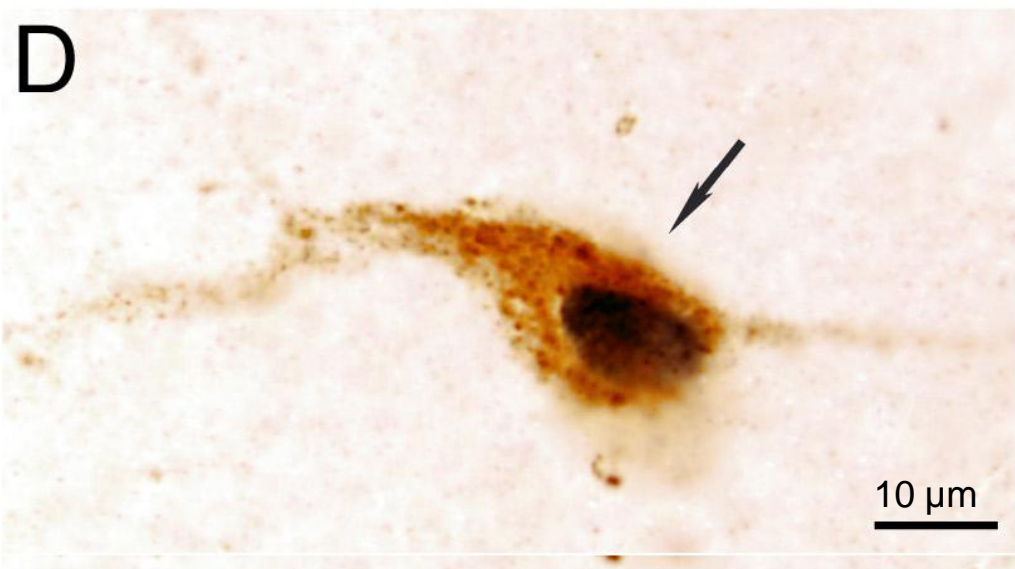
^cUCLA School of Medicine, Los Angeles, USA

Proteína Fos como índice de actividad neuronal



Chaudhuri (1997). Neuroreport, 8:13

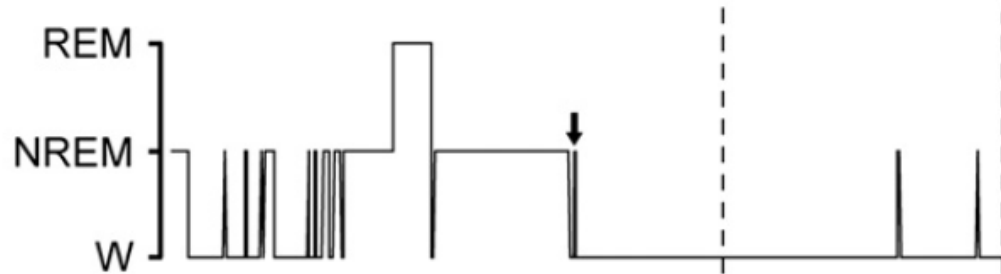
Doble inmunohistoquímica para hipocretina-2 y Fos



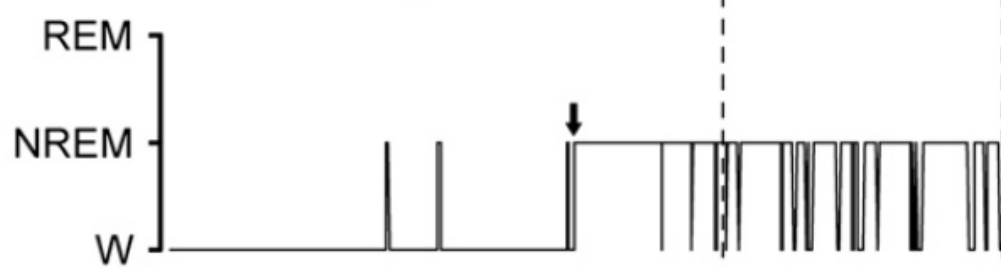
1. Vigilia tranquila
2. Vigilia alerta
3. Vigilia activa con actividad motora-exploratoria
4. Sueño lento
5. Sueño REM (Inducido por microinyecciones de carbacol en el NPO)

- Locomoción

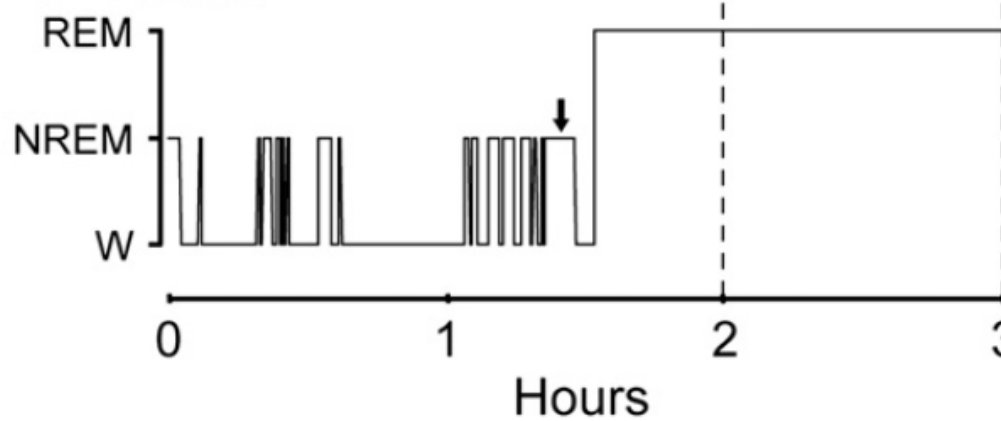
A Wakefulness



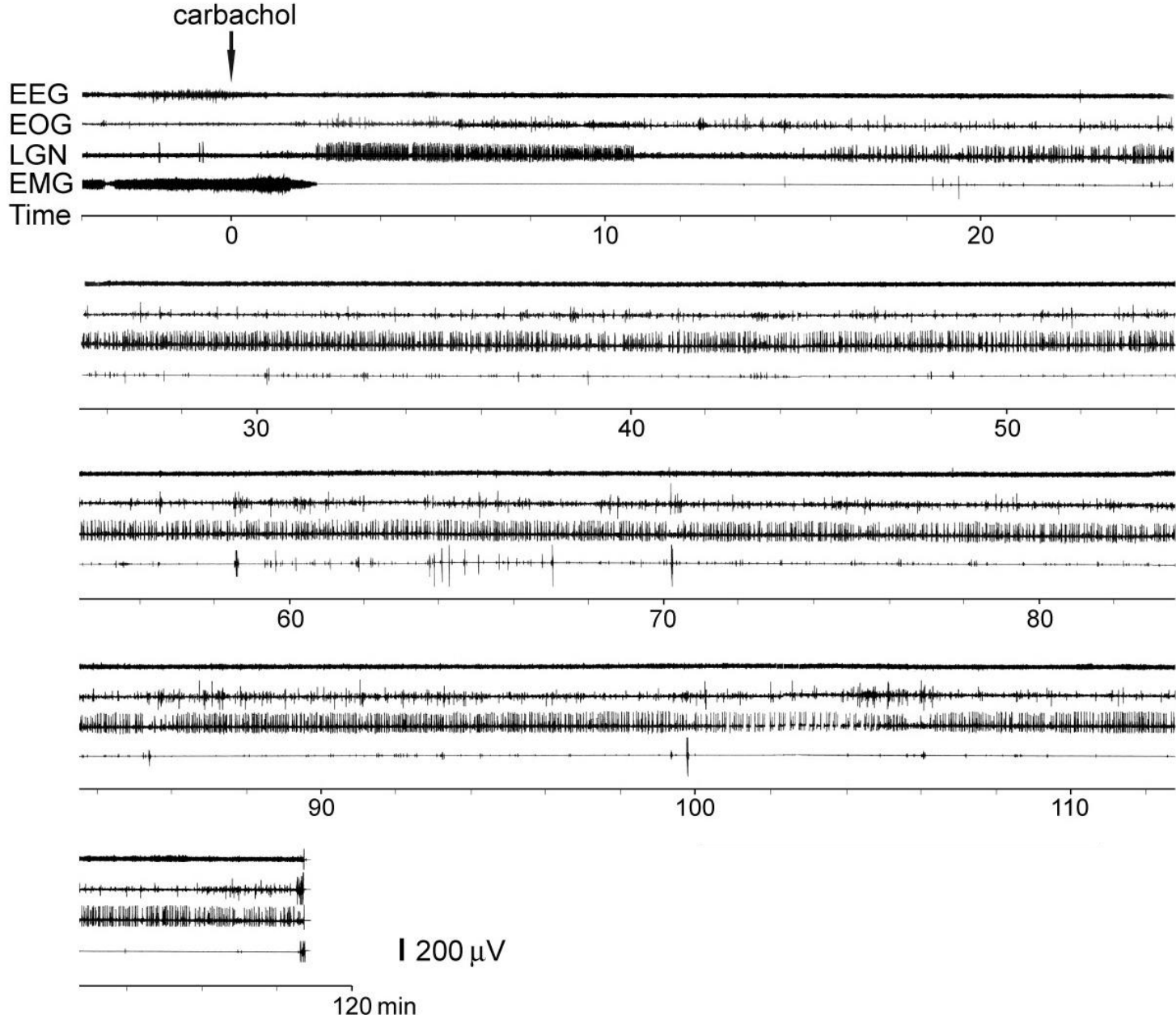
B NREM Sleep



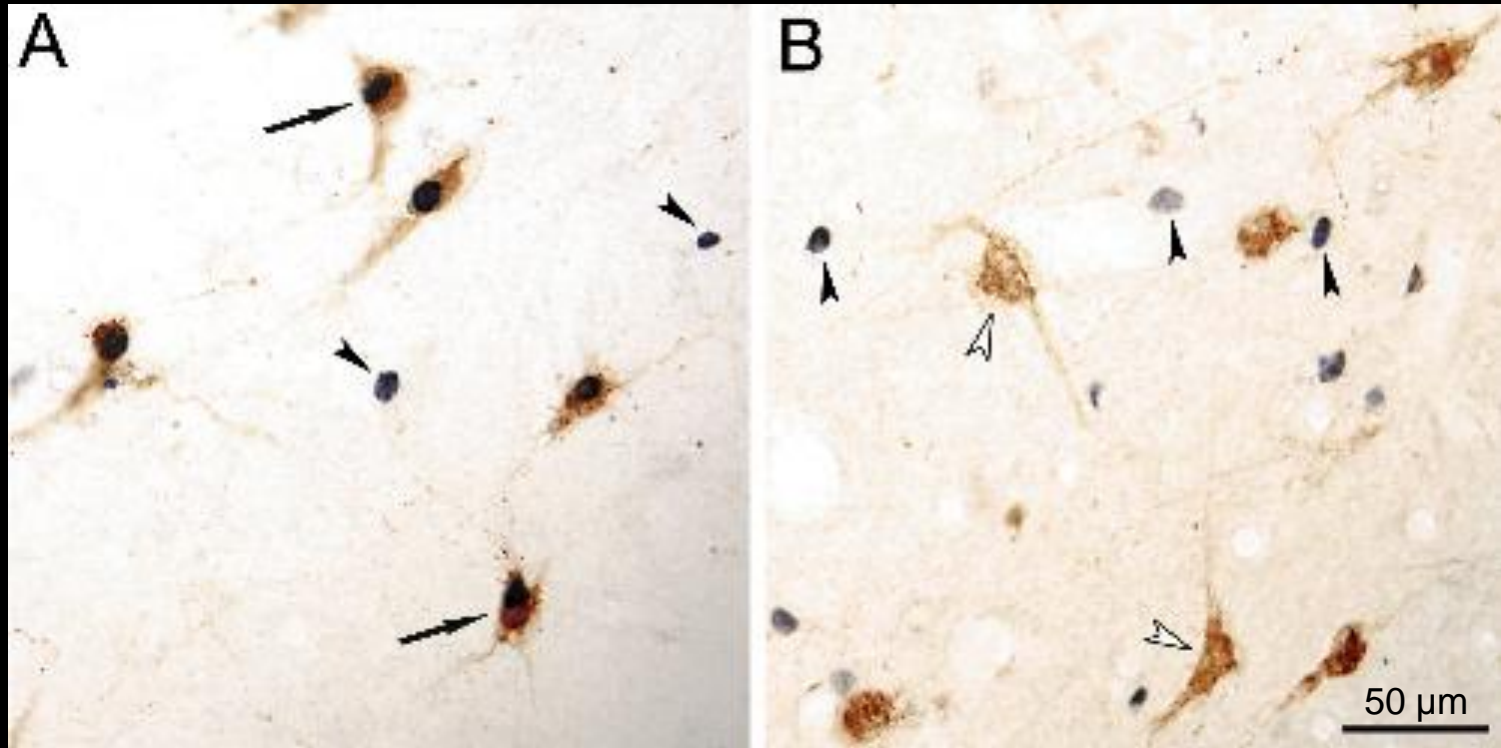
C REMc



Sueño REM inducido por microinyecciones de carbacol en el NPO



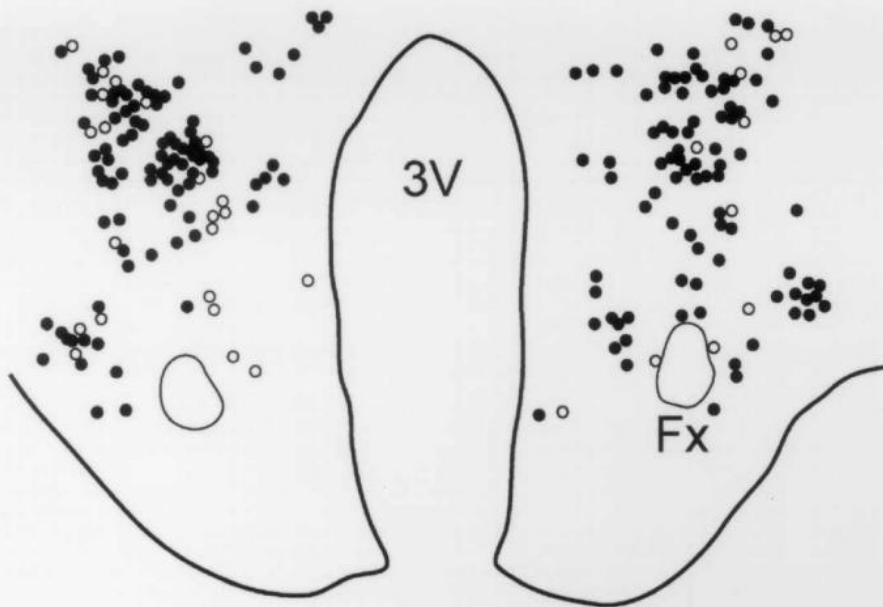
Las neuronas hipocretinérgicas están activas durante la vigilia con actividad motora exploratoria



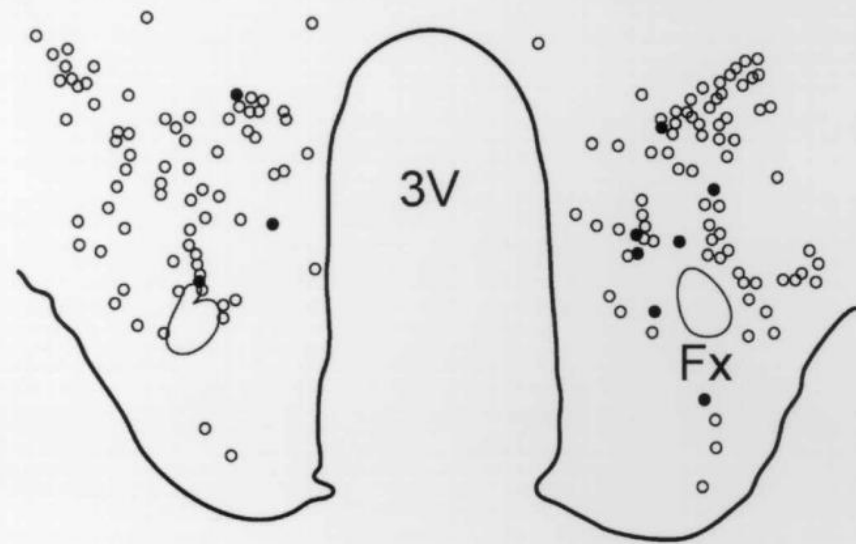
Vigilia con actividad-motora
exploratoria

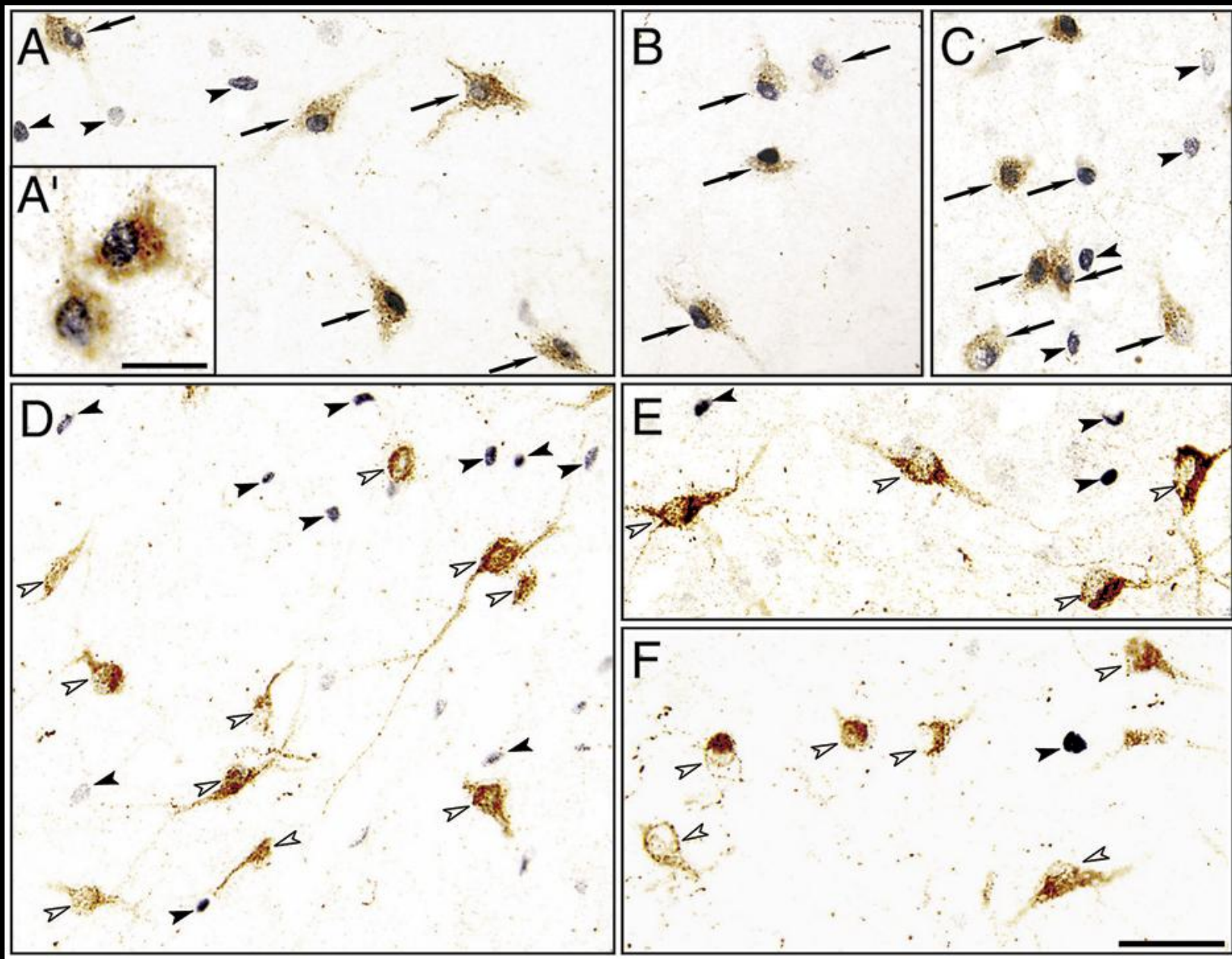
Vigilia tranquila

A. Active Wakefulness

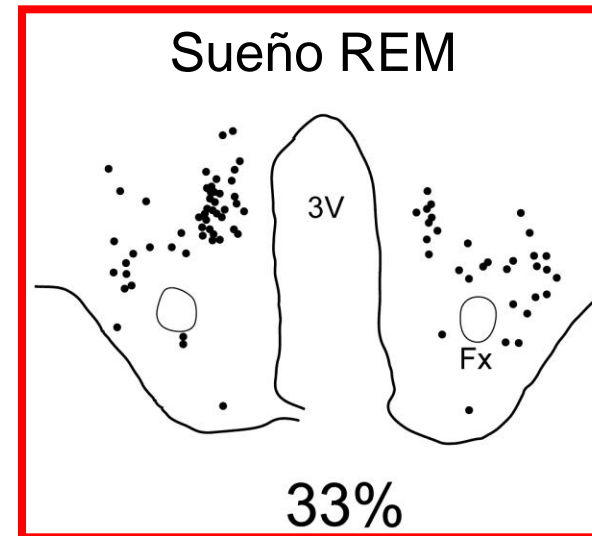
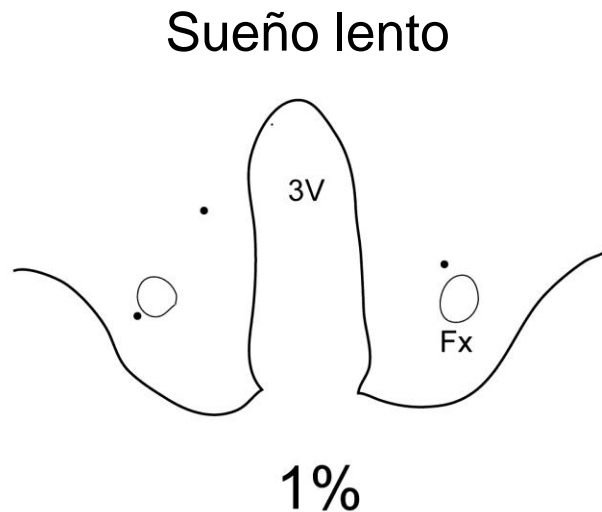
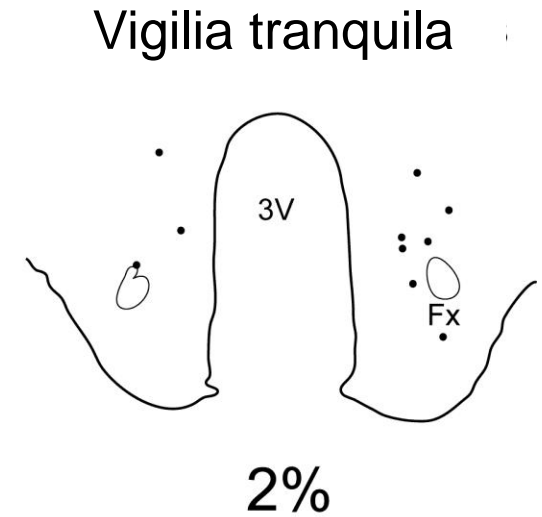
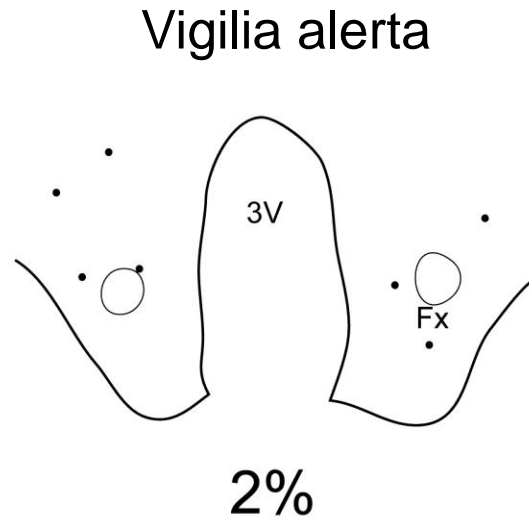
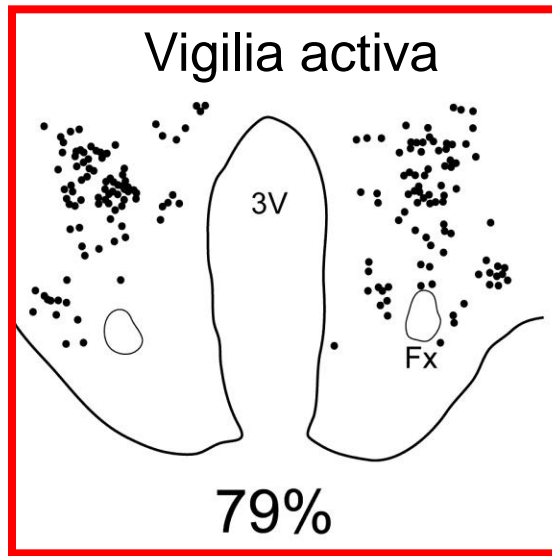


B. Quiet Wakefulness

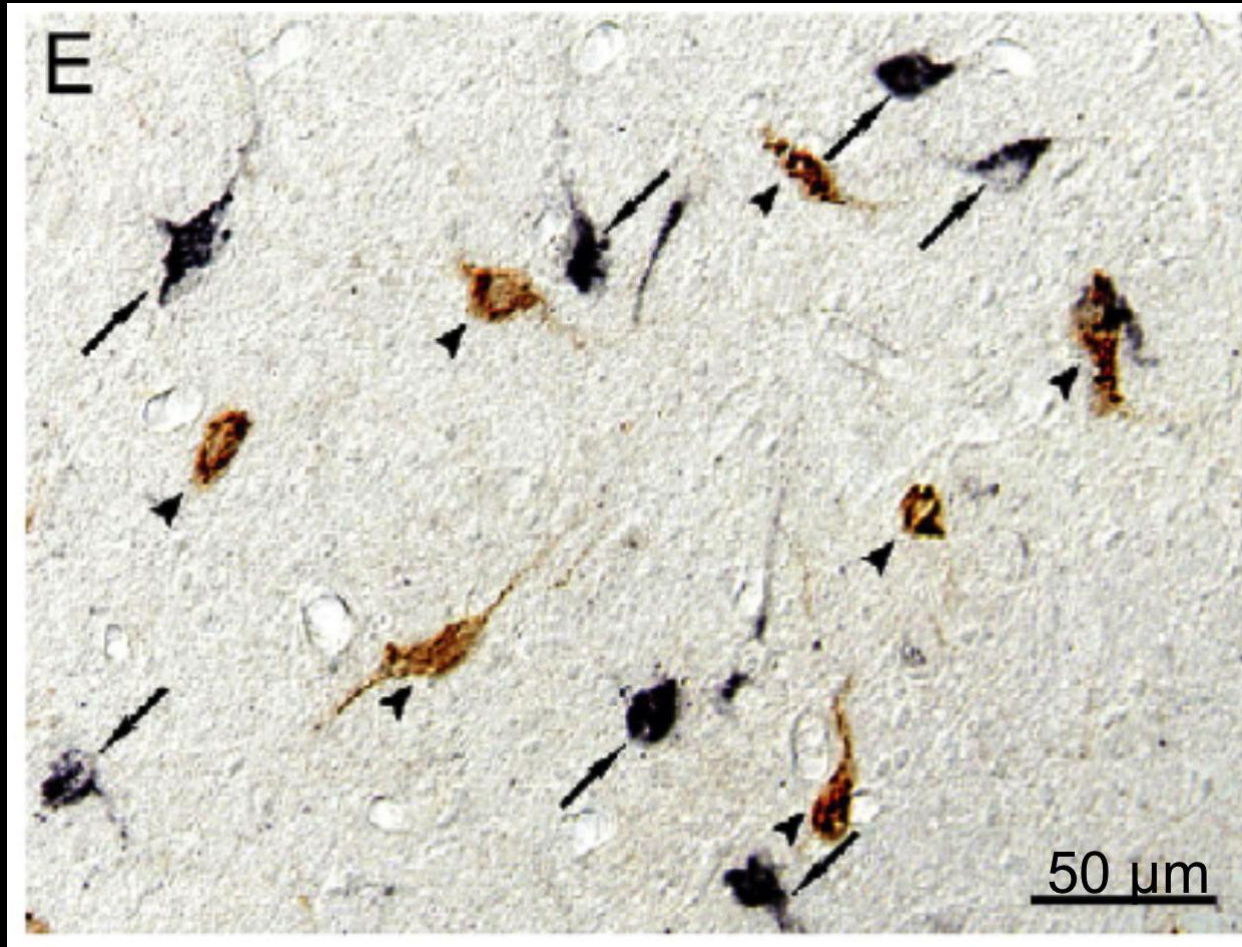




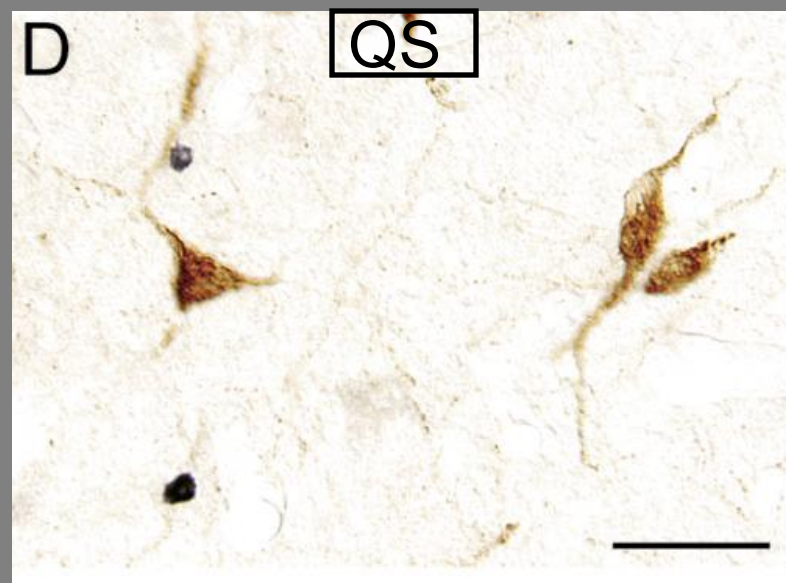
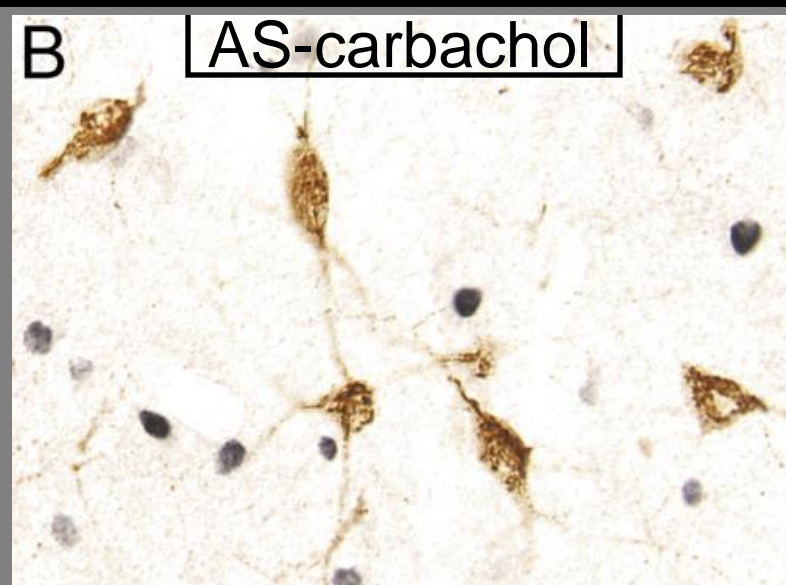
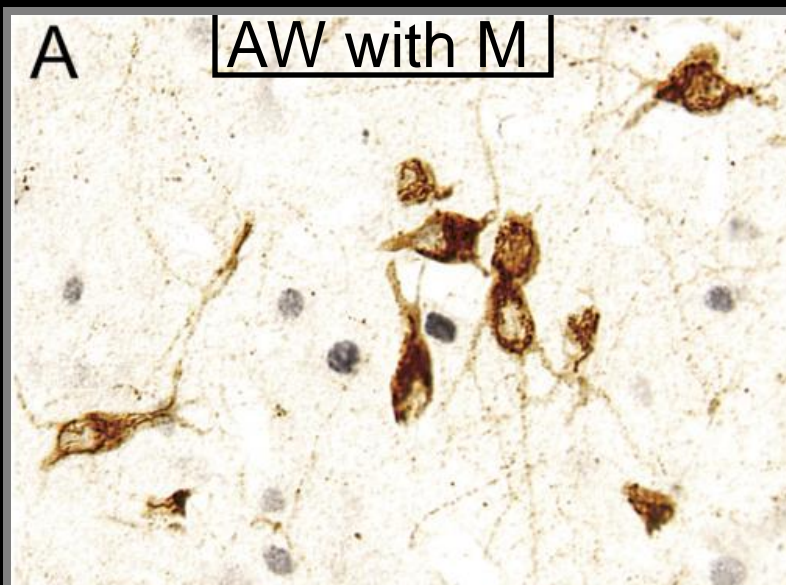
Las neuronas hipocretinérgicas expresan Fos en vigilia con actividad motora y en sueño REM



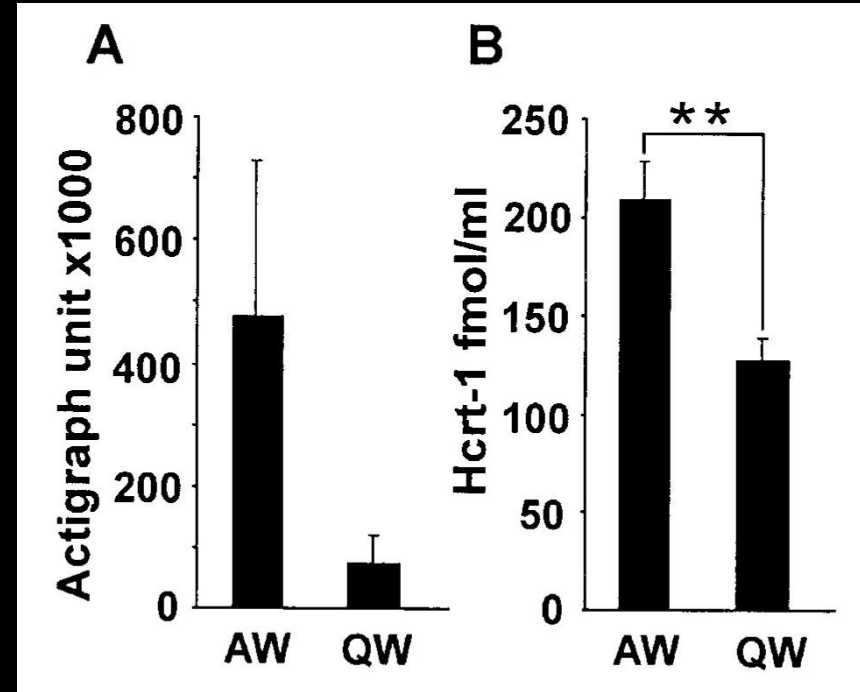
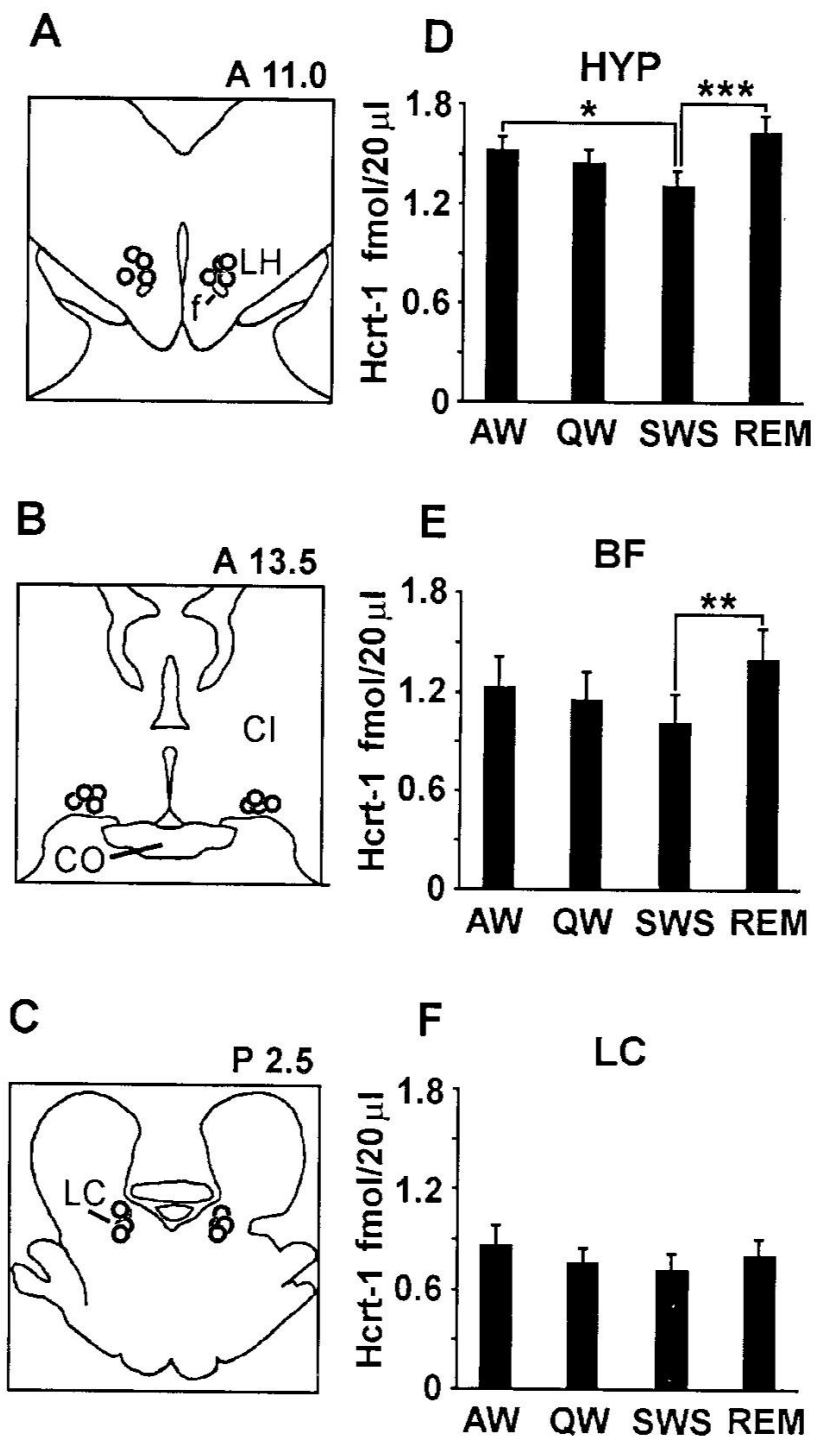
Las neuronas MCHérgicas e hipocretinérgicas están localizadas en la misma región del hipotálamo

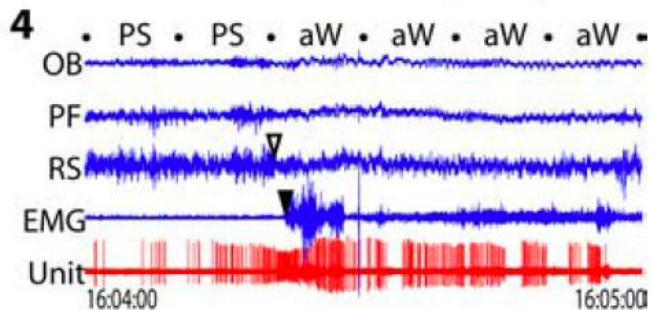
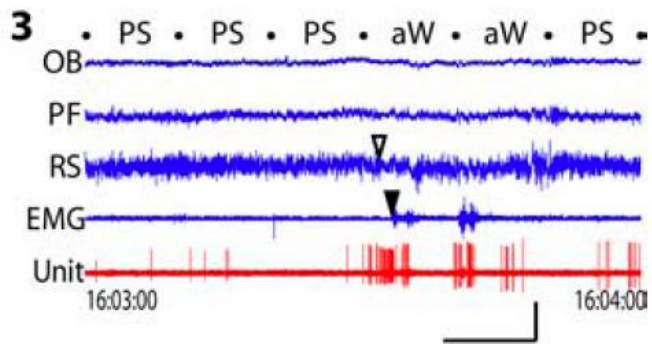
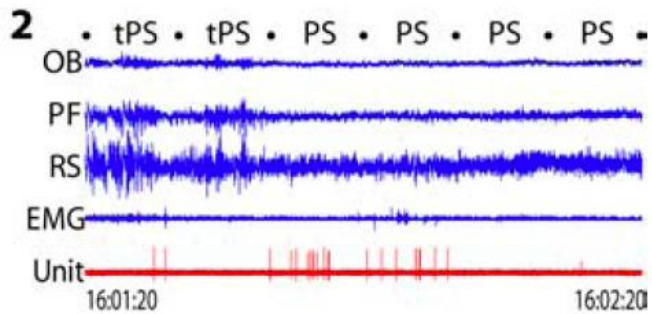
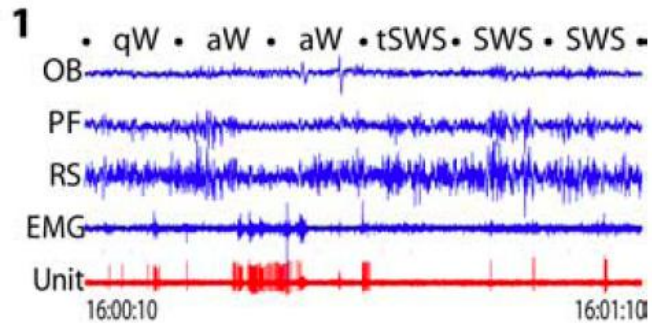


Las neuronas MCHérgicas no expresan Fos en los estados comportamentales analizados



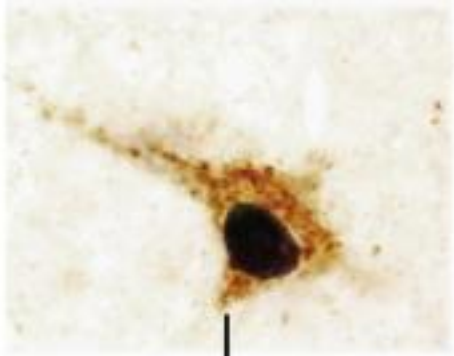
La liberación de hipocretinas aumenta en vigilia activa y sueño REM



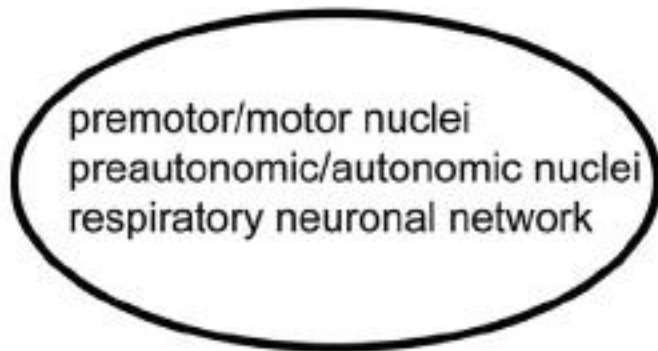
C

Neuronas hipocretinérgicas durante el sueño REM:

- Inhibición durante el Sueño REM-Tónico
- Activación durante el Sueño REM-Fásico



The activity of the hypocretinergic neurons increases in correlation with the “phasic” components of REM sleep



Hypocretinergic neurons project and activate areas involved in the generation of the “phasic” components of REM sleep.

Hypocretinergic neurons induce the “phasic” components of REM sleep

LETTERS

Neural substrates of awakening probed with optogenetic control of hypocretin neurons

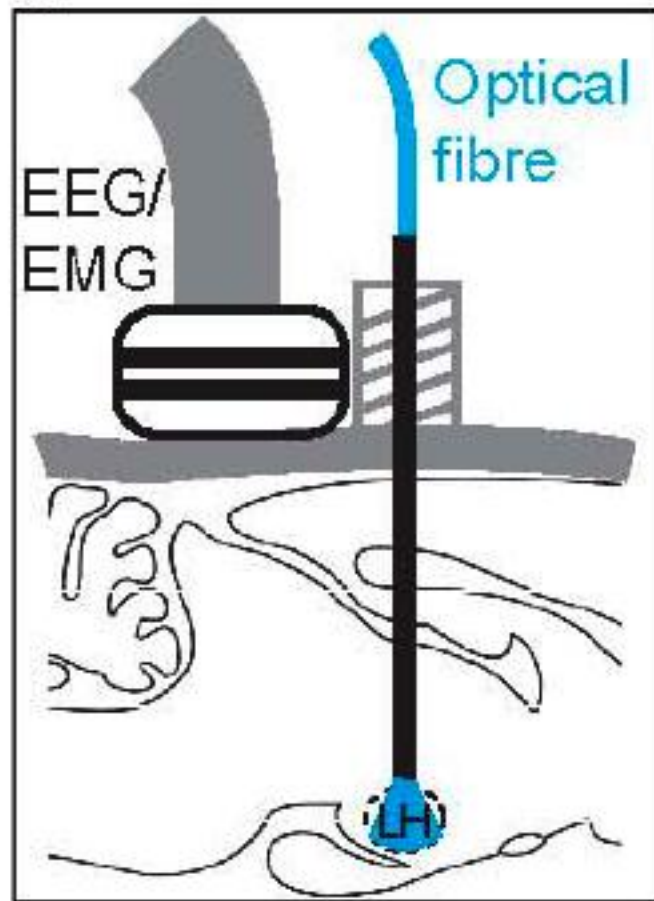
Antoine R. Adamantidis^{1*}, Feng Zhang^{2*}, Alexander M. Aravanis², Karl Deisseroth^{1,2} & Luis de Lecea¹

The neural underpinnings of sleep involve interactions between sleep-promoting areas such as the anterior hypothalamus, and arousal systems located in the posterior hypothalamus, the basal forebrain and the brainstem^{1,2}. Hypocretin³ (Hcrt, also known as orexin⁴)-producing neurons in the lateral hypothalamus⁵ are important for arousal stability², and loss of Hcrt function has been linked to narcolepsy^{6–9}. However, it is unknown whether electrical activity arising from Hcrt neurons is sufficient to drive awakening from sleep states or is simply correlated with it. Here we directly probed the impact of Hcrt neuron activity on sleep state transitions with *in vivo* neural photostimulation^{10–18}, genetically targeting channelrhodopsin-2 to Hcrt cells and using an optical fibre to deliver light deep in the brain, directly into the lateral hypothalamus, of freely moving mice. We found that direct, selective, optogenetic photostimulation of Hcrt neurons increased the probability of transition to wakefulness from either slow wave sleep or rapid eye movement sleep. Notably, photostimulation using 5–30 Hz light pulse trains reduced latency to wakefulness, whereas 1 Hz trains did not. This study establishes a causal relationship between frequency-dependent activity of a genetically defined neural cell type and a specific mammalian behaviour central to clinical conditions and neurobehavioural physiology.

mCherry, continuous light illumination for 1 s evoked robust action potential trains under current-clamp conditions (Fig. 1e) with firing frequencies ranging from 8 to 25 Hz. Moreover, as in hippocampal neurons¹², 15-ms blue-light pulses were able to drive reliable action potential trains from 1 to 50 Hz under whole-cell current-clamp conditions (Fig. 1f), although reliability decreased slightly with increasing frequency (Fig. 1g). At 20 Hz, 100% of light pulses gave rise to action potentials, whereas at 50 Hz, $84 \pm 14\%$ of light pulses gave rise to action potentials ($n = 6$ cells; Fig. 1g). We found that basal properties including input resistance ($366 \pm 43 \text{ M}\Omega$, $n = 6$)²¹ and resting membrane potential were unaltered by ChR2-mCherry expression ($P > 0.05$; Fig. 1h). Together, these data show that lentivirus-mediated expression of ChR2-mCherry in Hcrt neurons is well tolerated, specific and sufficient to drive precise and reliable action potential firing across a range of frequencies.

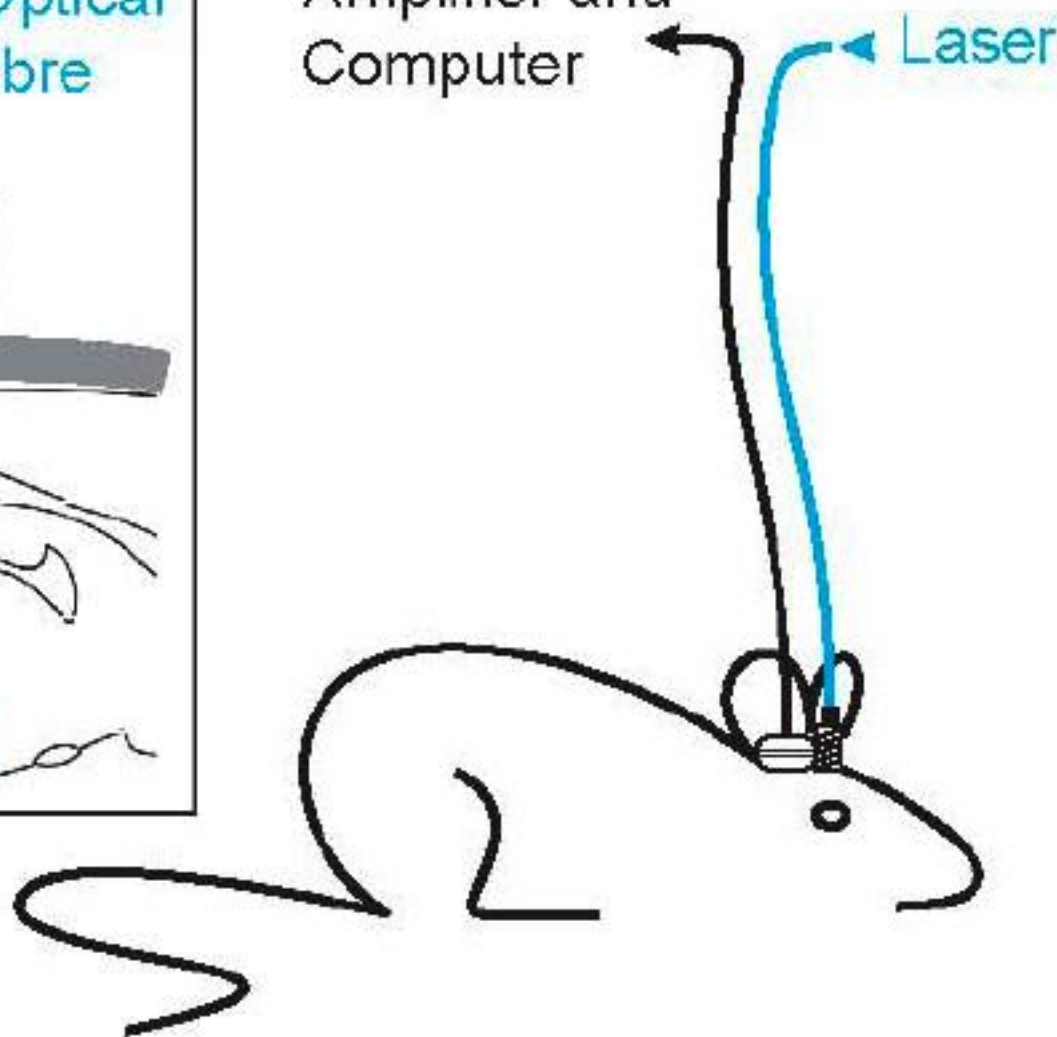
We next studied the effect of photostimulation of *Hcrt::ChR2-mCherry* neurons on the sleep-wake cycle of freely moving mice. *Hcrt::ChR2-mCherry* or *Hcrt::mCherry* (control) lentiviruses were stereotactically delivered to the lateral hypothalamus; to determine the behavioural consequences of Hcrt neuron activation, we quantitatively analysed sleep recordings of mice chronically implanted with electroencephalographic (EEG) and electromyographic (EMG) elec-

a



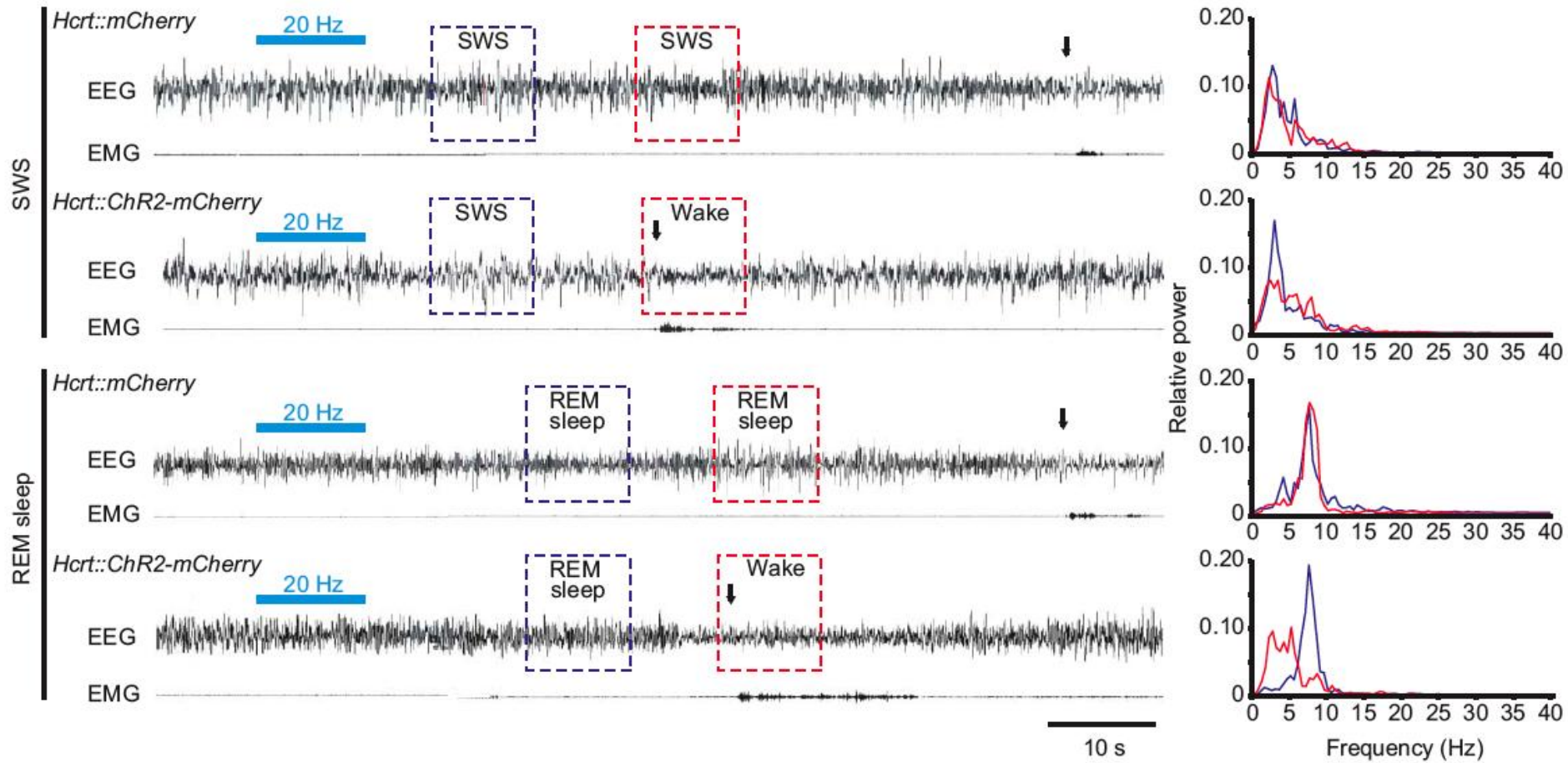
Amplifier and
Computer

Laser



La activación de las neuronas hipocretinérgicas aumenta las transiciones a la vigilia.

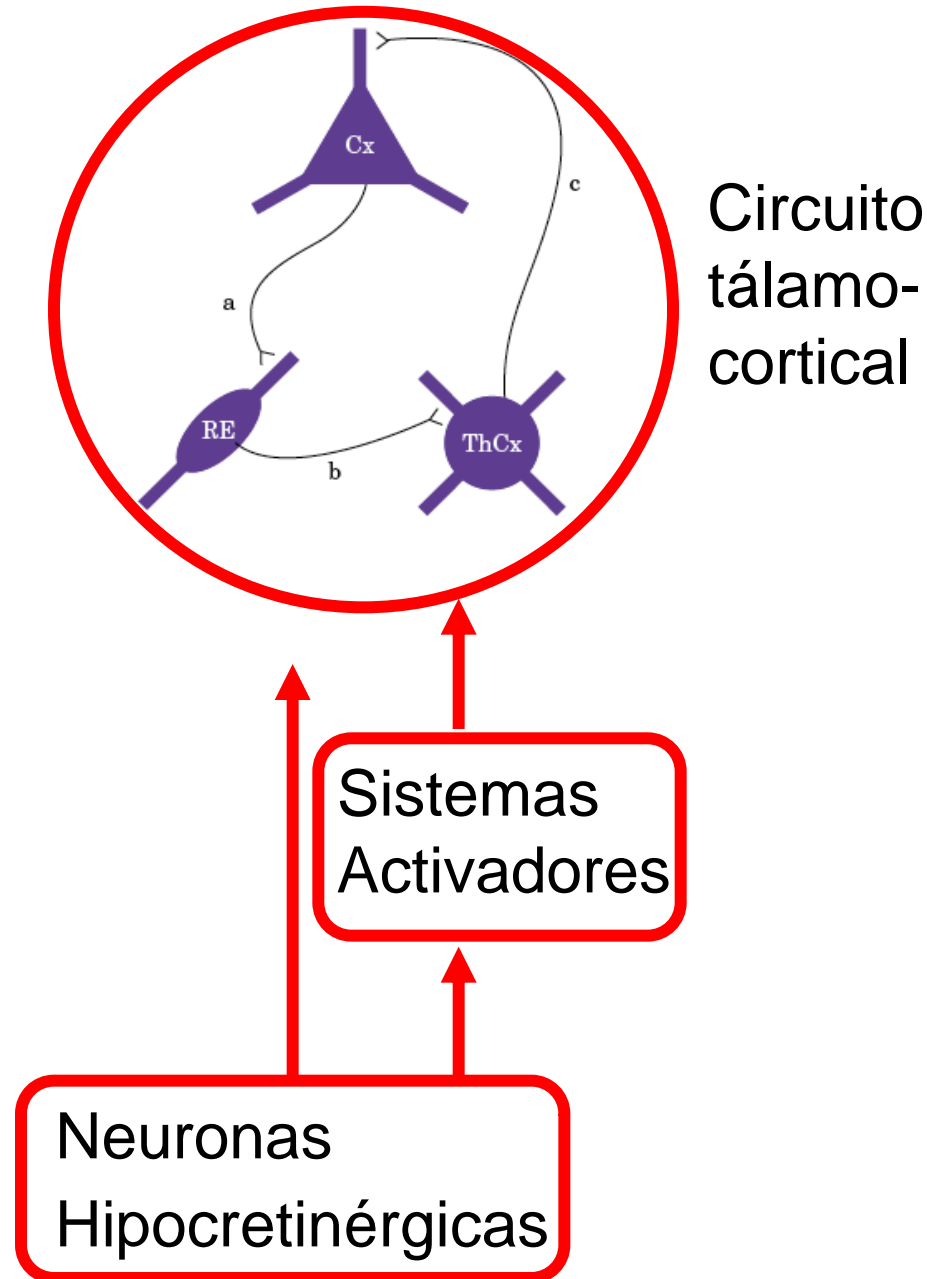
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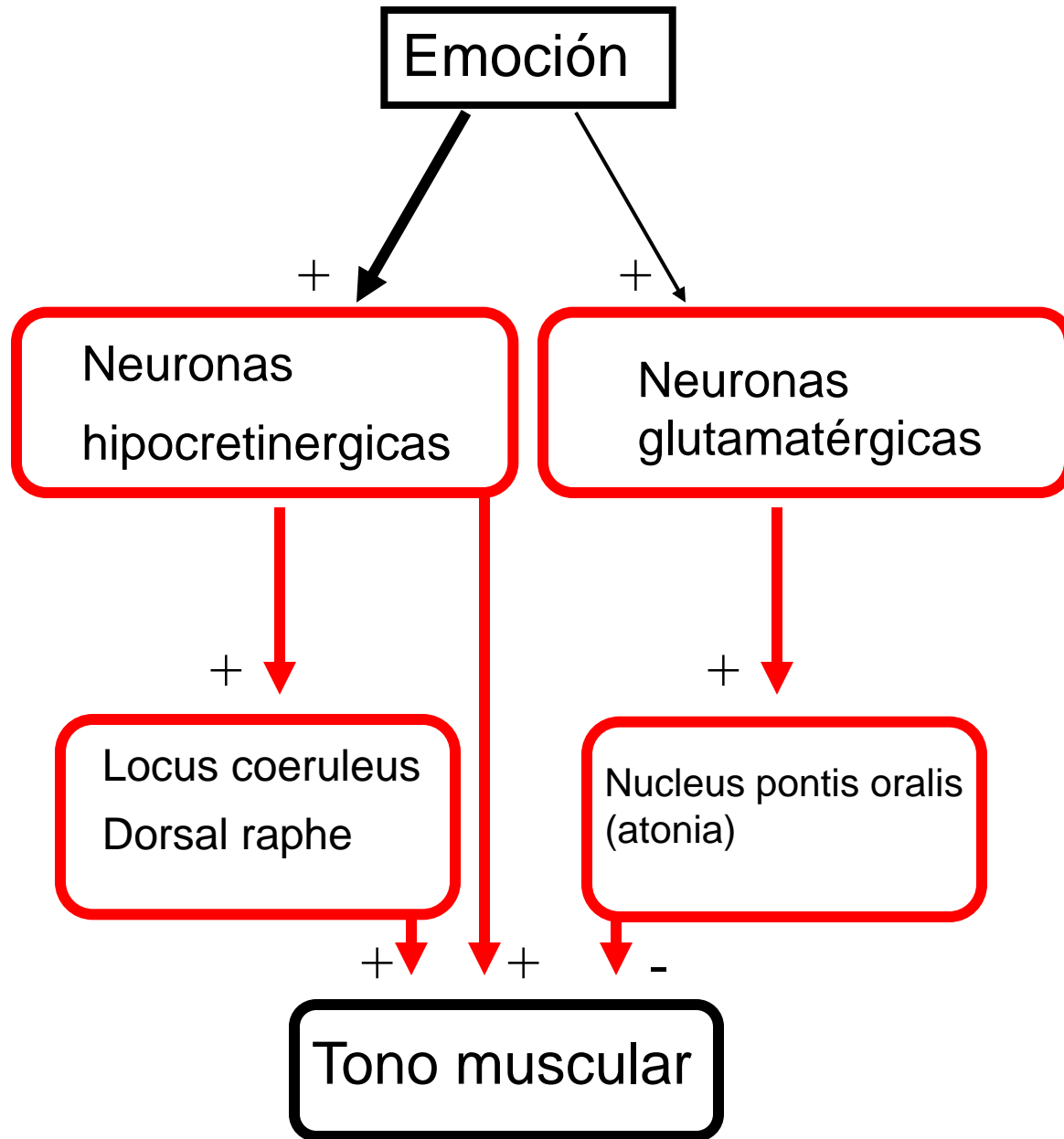


Las neuronas hipocretinergicas se activan durante la vigilia activa con actividad motora-exploratoria pero no durante vigilia tranquila, locomocion forzada o sueño lento.

Las neuronas hipocretinergicas se activan durante los componentes fásicos del sueño REM.

Neuronas hipocretinérgicas facilitan el estado de vigilia actuando directamente sobre el circuito tálamo-cortical y a través de otros sistemas activadores





Conclusiones

- Las neuronas hipocretinérgicas promueven la vigilia.
- Un déficit en el sistema hipocretinérgico es la base patogénica de la Narcolepsia.



"El sueño del escolar". Jean-Baptiste Greuze

