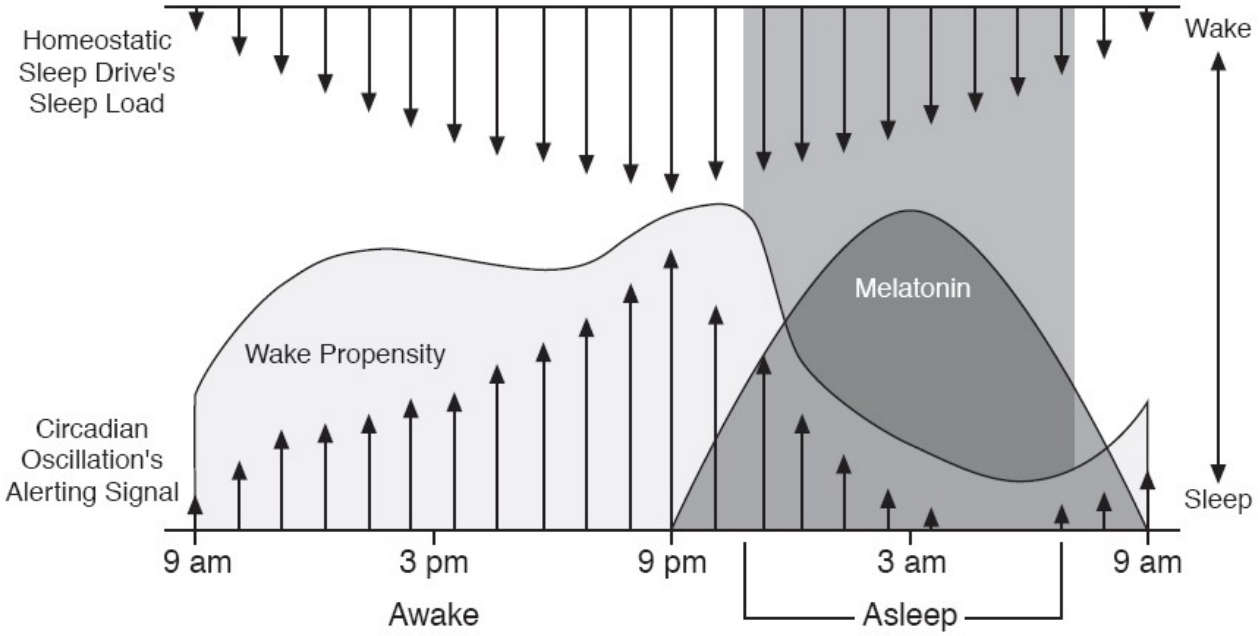
Il ruolo del sistema delle orexine nella regolazione del ritmo sonno-veglia

Dario Arnaldi, MD, PhD
Università di Genova

Fisiologia del sonno



[a]Adapted with permission from Kilduff and Kushida,[10] Edgar et al.,[11] and Dijk et al.[17]

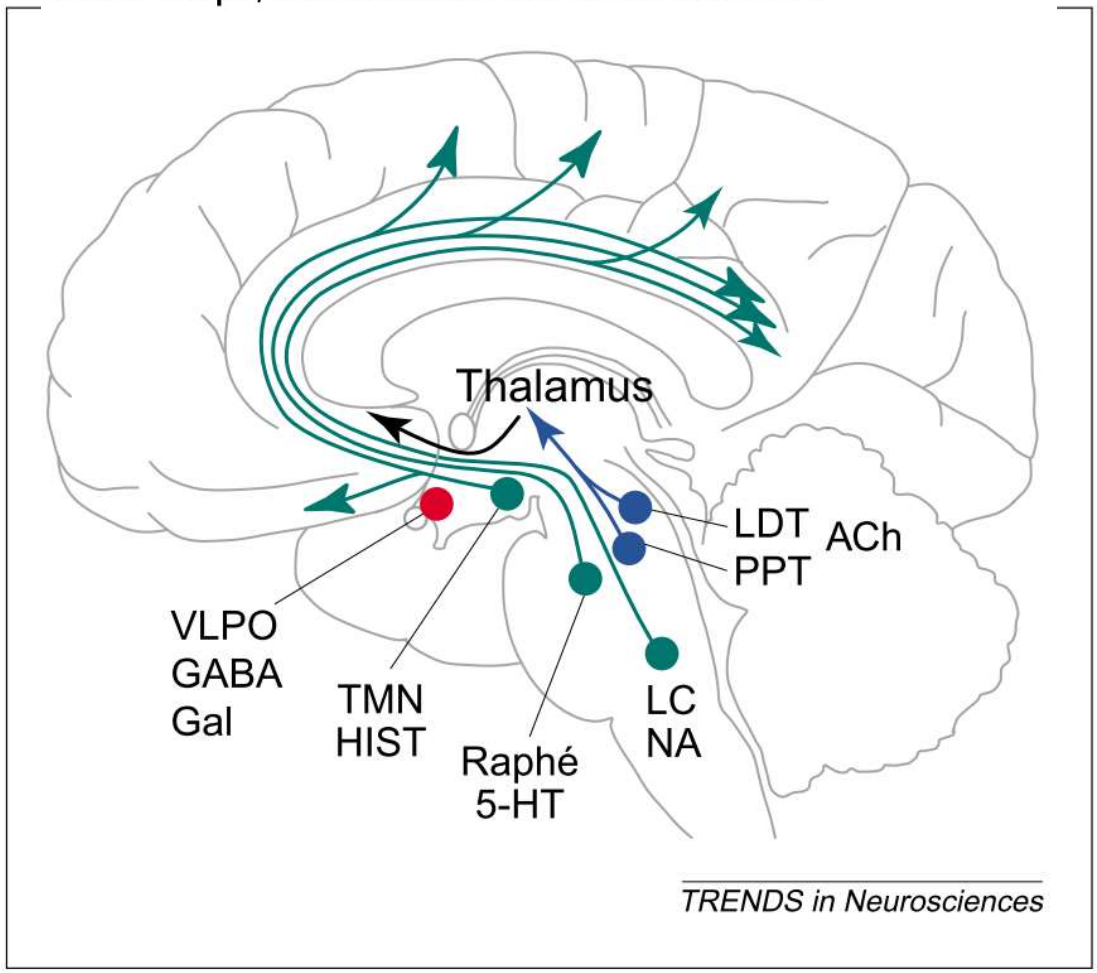
J Clin Psychiatry. 2005;66 Suppl 9:3-9; quiz 42-3.

The human circadian system in normal and disordered sleep.

Richardson GS.

The sleep switch: hypothalamic control of sleep and wakefulness

Clifford B. Saper, Thomas C. Chou and Thomas E. Scammell



TRENDS in Neurosciences Vol.24 No.12 December 2001

1° VIA:

Talamica

LDT: Nucleo laterodorsale
PPT: Nucleo peduncolopontino

Ach: acetilcolina

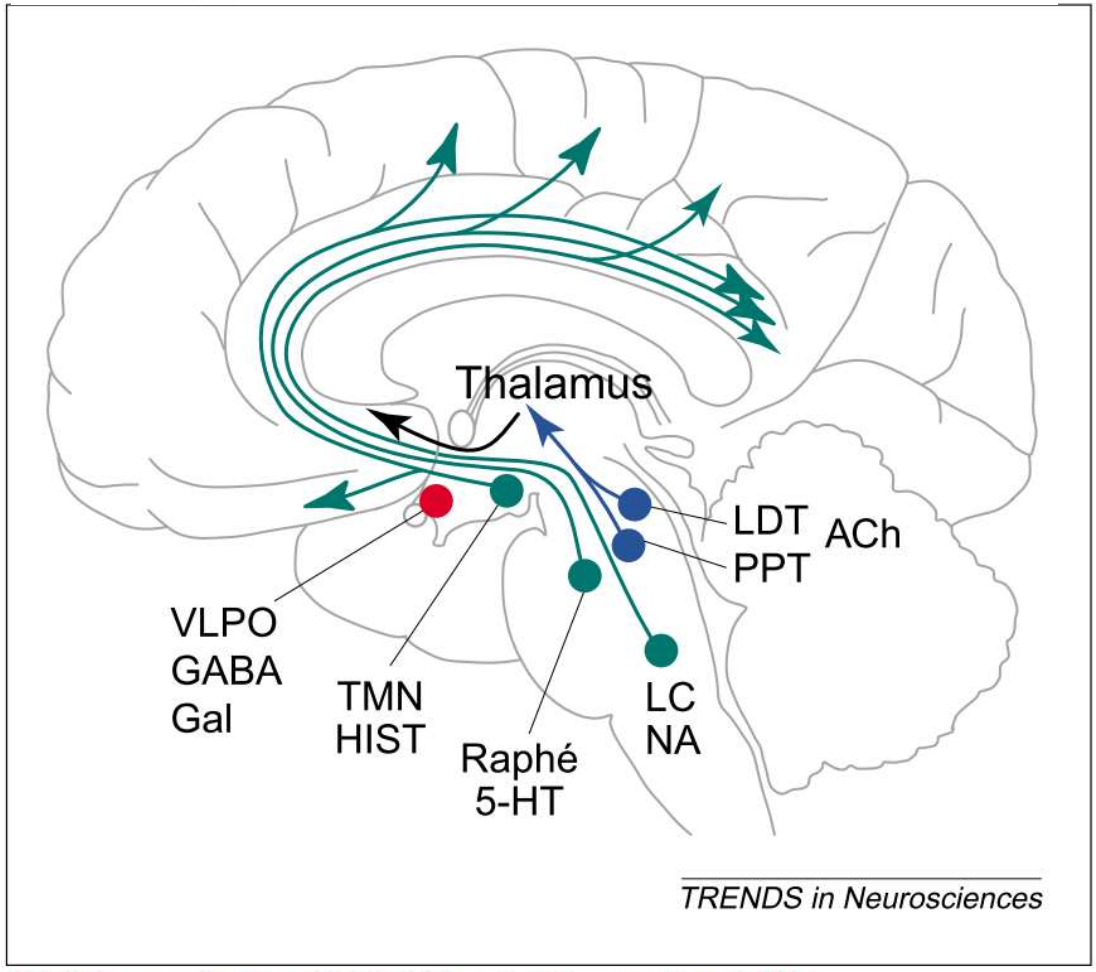
Talamo

Attivi in **VEGLIA** e **REM**

- Attività cerebrale
- In REM:
  - attivazione corticale
  - Atonia muscolare
  - active dreaming

The sleep switch: hypothalamic control of sleep and wakefulness

Clifford B. Saper, Thomas C. Chou and Thomas E. Scammell



TRENDS in Neurosciences Vol.24 No.12 December 2001

2° VIA:

Ipotalamica

Neuroni monoaminergici:

- Noradrenergici (LC)
- Serotoninergici (Raphé)
- Istaminergici (TMN)

Corteccia

- Molto attivi in **veglia**
- Diminuiscono in **NREM**
- Si fermano in **REM**

TRENDS in Neurosciences Vol.24 No.12 December 2001

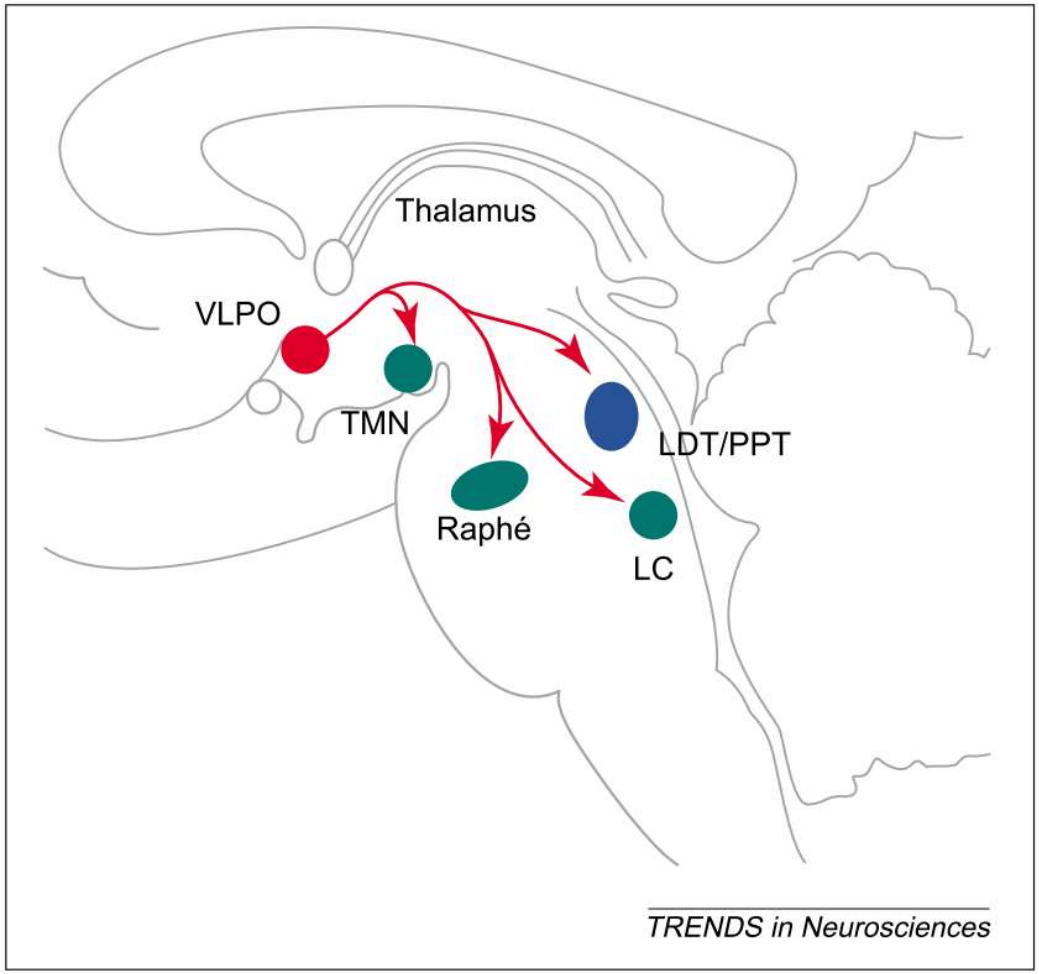
Il "firing" neuronale è stato dipendente

	Wakefulness	NREM sleep	REM sleep
EEG	Fast, low voltage	Slow, high voltage	Fast, low voltage
Eye movement	Vision related	Slow, infrequent	Rapid
Muscle tone	↑↑	↑	0
LDT/PPT	↑	0	↑↑
LC/DR/TMN	↑↑	↑	0
VLPO cluster	0	↑↑	↑?
VLPO extended	0	↑?	↑↑
Orexin/hyprocretin	↑↑	0?	0?

LDT: Nucleo laterodorsale **Acetilcolina**
PPT: Nucleo peduncolopontino **Acetilcolina**
LC: Locus Coeruleus **Noradrenalina**
DR: Raphé Dorsale **Serotonina**
TMN: Nucleo Tubero Mammillare **Istamina**

The “off” switch

TRENDS in Neurosciences Vol.24 No.12 December 2001



VLPO, N preottico ventrolaterale

-GABA
-Galanina

TMN, Raphé, LC

VLPO Cluster

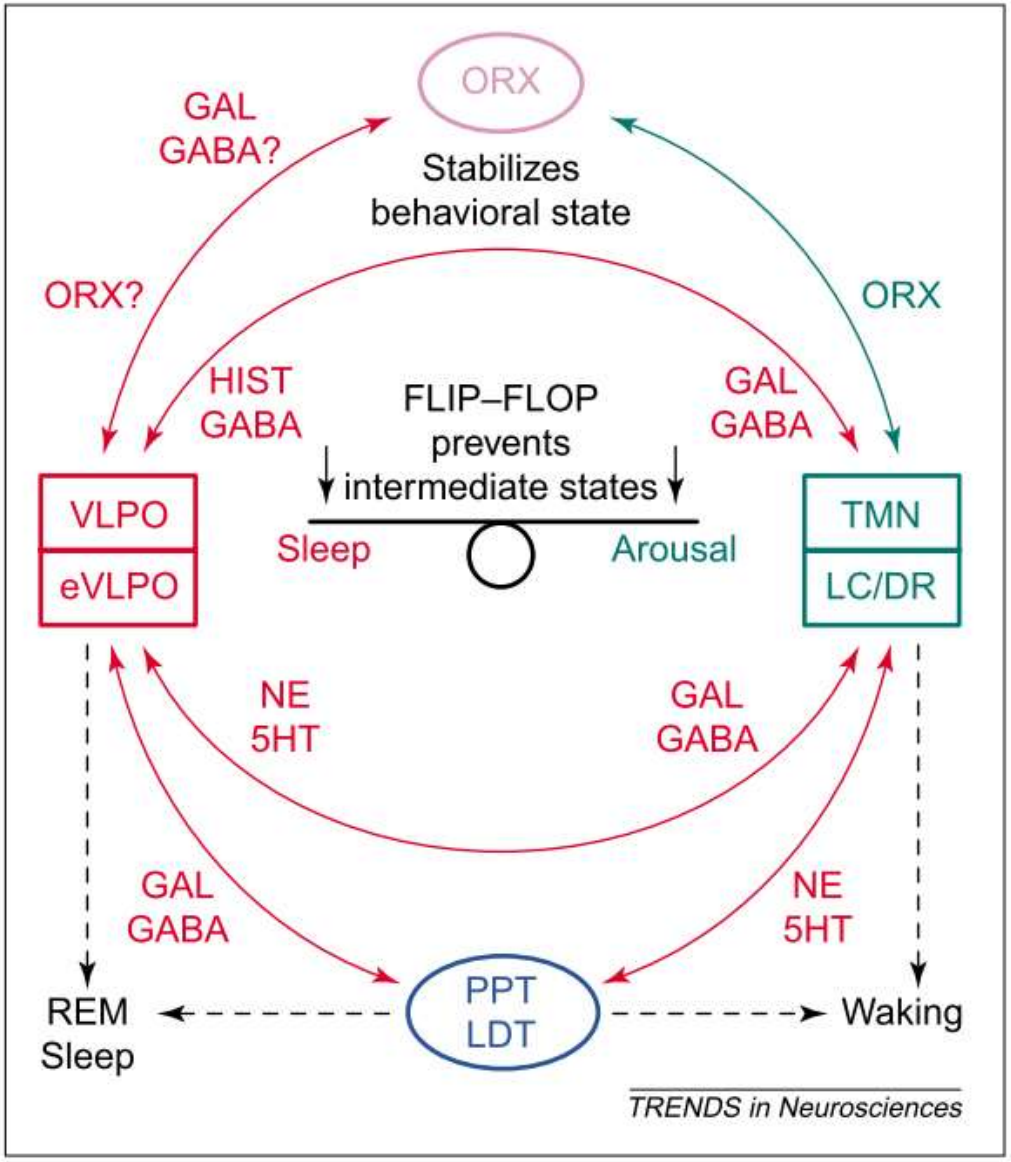
TMN

Transizione sonno-veglia

VLPO extended

LC; Raphè

REM



Flip-Flop

Instabile?

Orexina

Cell, Vol. 92, 573–585, February 20, 1998, Copyright ©1998 by Cell Press

Orexins and Orexin Receptors: A Family of Hypothalamic Neuropeptides and G Protein-Coupled Receptors that Regulate Feeding Behavior

Takeshi Sakurai,[1,8] Akira Amemiya,[1,9] Makoto Ishii,[1] Ichiyo Matsuzaki,[1,10] Richard M. Chemelli,[1,2] Hirokazu Tanaka,[1] S. Clay Williams,[1] James A. Richardson,[3] Gerald P. Kozlowski,[4] Shelagh Wilson,[5] Jonathan R. S. Arch,[5] Robin E. Buckingham,[5] Andrea C. Haynes,[5] Steven A. Carr,[6] Roland S. Annan,[6] Dean E. McNulty,[6] Wu-Schyong Liu,[6] Jonathan A. Terrett,[5] Nabil A. Elshourbagy,[6] Derk J. Bergsma,[6] and Masashi Yanagisawa[1,7]

[1]Howard Hughes Medical Institute
Department of Molecular Genetics
[2]Department of Pediatrics
[3]Department of Pathology
[4]Department of Physiology
University of Texas Southwestern
Medical Center at Dallas
Dallas, Texas 75235–9050
[5]SmithKline Beecham Pharmaceuticals
Harlow, Essex CM19 5AD
United Kingdom
[6]SmithKline Beecham Pharmaceuticals
King of Prussia, Pennsylvania 19406

lipids, peptides, and proteases. Ligand binding initiates intracellular signal transduction through the activation of heterotrimeric G proteins. All of the known small regulatory peptides (small peptide hormones and neuropeptides) exert their biological actions by acting on GPCRs. Recent efforts in genomics research have identified a large number of cDNA sequences that encode "orphan" GPCRs, i.e., putative GPCRs without known cognate ligands. Many of these orphan GPCRs are likely to be receptors for heretofore unidentified signaling molecules, including new peptide hormones and neuropeptides. GPCRs already represent the largest class of target molecules for drugs available in the clinic (Hardman et al., 1996). The orphan GPCRs therefore represent a fruitful resource for drug discovery (Stadel et al., 1997).

To approach these possibilities, we undertook a systematic biochemical search for endogenous peptide ligands for multiple orphan GPCRs, using a cell-based reporter system. These screening experiments led to the identification of a novel family of neuropeptides that bind to two closely related orphan GPCRs. We call these peptide ligands "orexins," after the Greek word orexis, which means appetite. The mRNA for the precursor of these peptides is abundantly and specifically expressed

Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 322–327, January 1998
Neurobiology

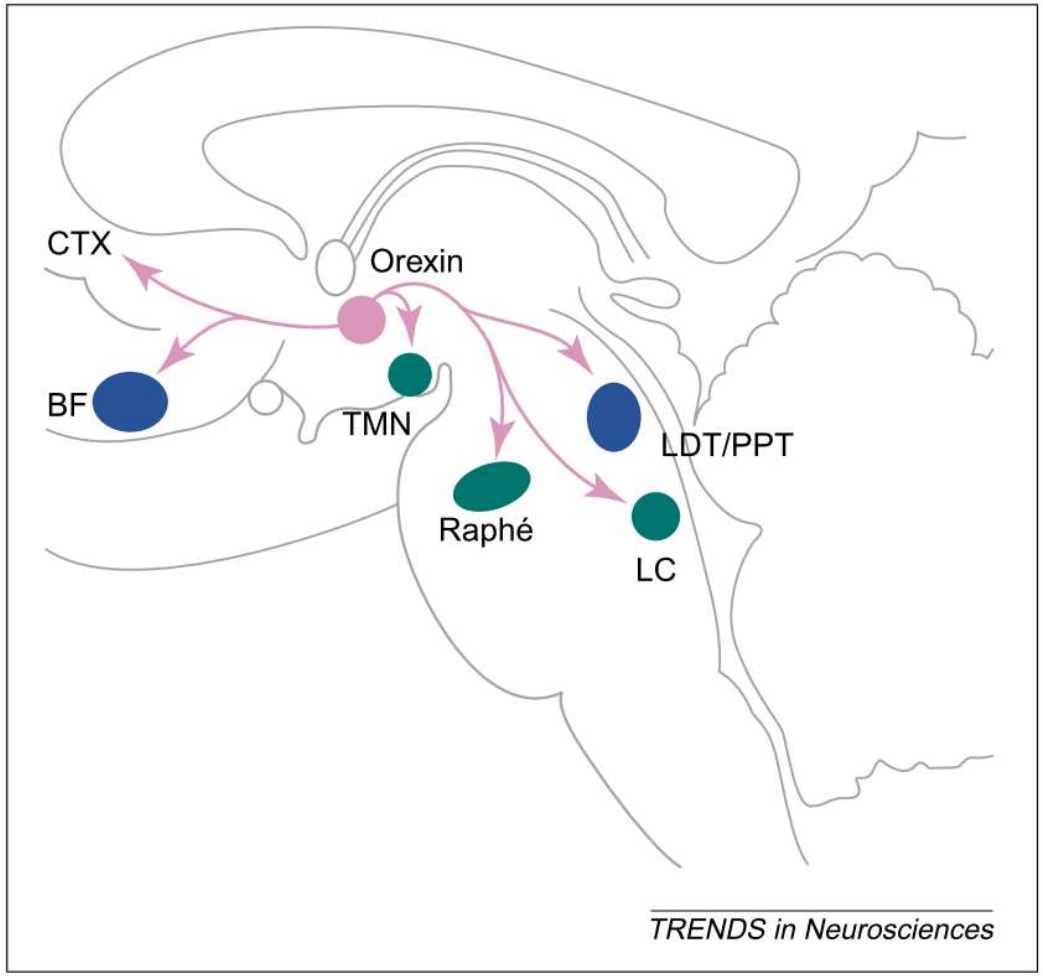
The hypocretins: Hypothalamus-specific peptides with neuroexcitatory activity

L. DE LECEA*†, T. S. KILDUFF*†‡, C. PEYRON‡, X.-B. GAO§, P. E. FOYE*, P. E. DANIELSON*, C. FUKUHARA*‡, E. L. F. BATTENBERG¶, V. T. GAUTVIK*‖, F. S. BARTLETT II**, W. N. FRANKEL**, A. N. VAN DEN POL‡§, F. E. BLOOM¶, K. M. GAUTVIK*‖, AND J. G. SUTCLIFFE*

Departments of *Molecular Biology and ¶Neuropharmacology, The Scripps Research Institute, La Jolla, CA 92037; ‡Center for Sleep and Circadian Neurobiology, Stanford University, Stanford, CA 94305; §Department of Neurosurgery, Yale University, New Haven, CT 06520; ‖Institute of Basic Medical Sciences, Department of Biochemistry, University of Oslo, P.O. Box 1112, Blindern, N-0317 Oslo, Norway; and **The Jackson Laboratory, Bar Harbor, ME 04609

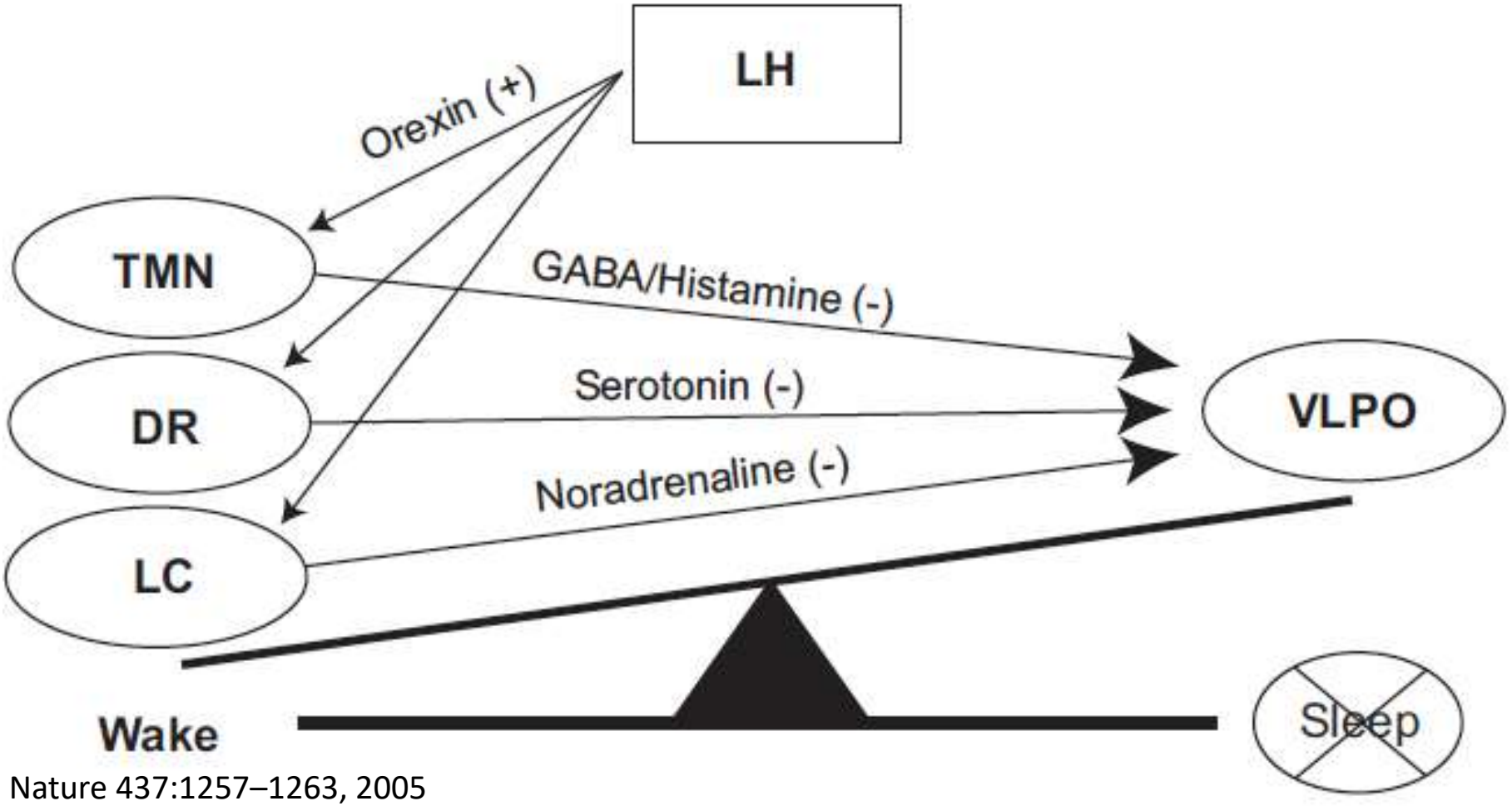
LA SCOPERTA DEL SISTEMA OREXINERGICO

Sistema Orexinergico



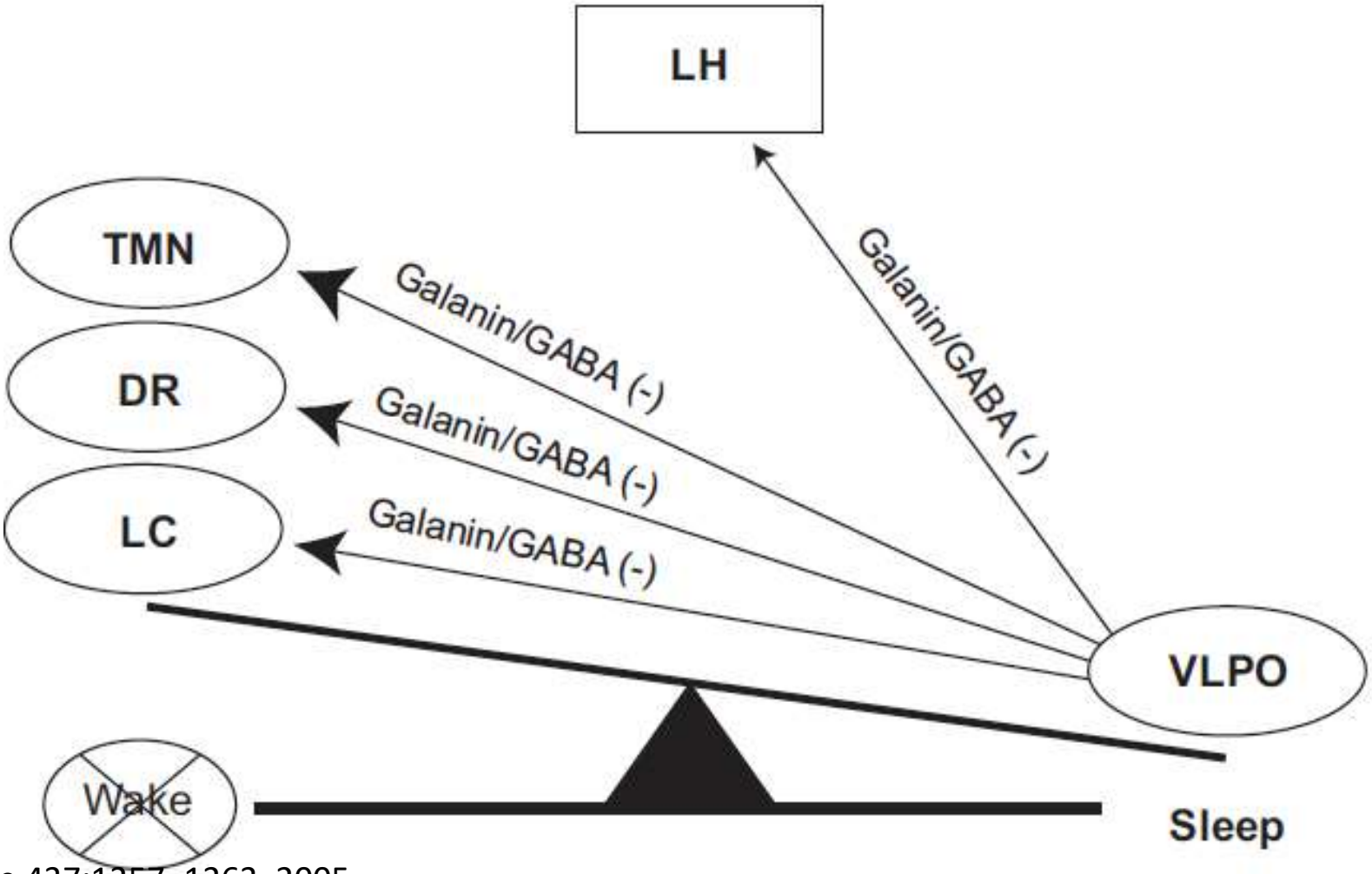
Innerva tutti i componenti del sistema ascendente dell'arousal, così come la corteccia cerebrale

L’orexina Rinforza LC, TMN e Raphè che inibiscono VLPO



Saper et al. Nature 437:1257–1263, 2005

In sonno VLPO inibisce ORX e monoamine



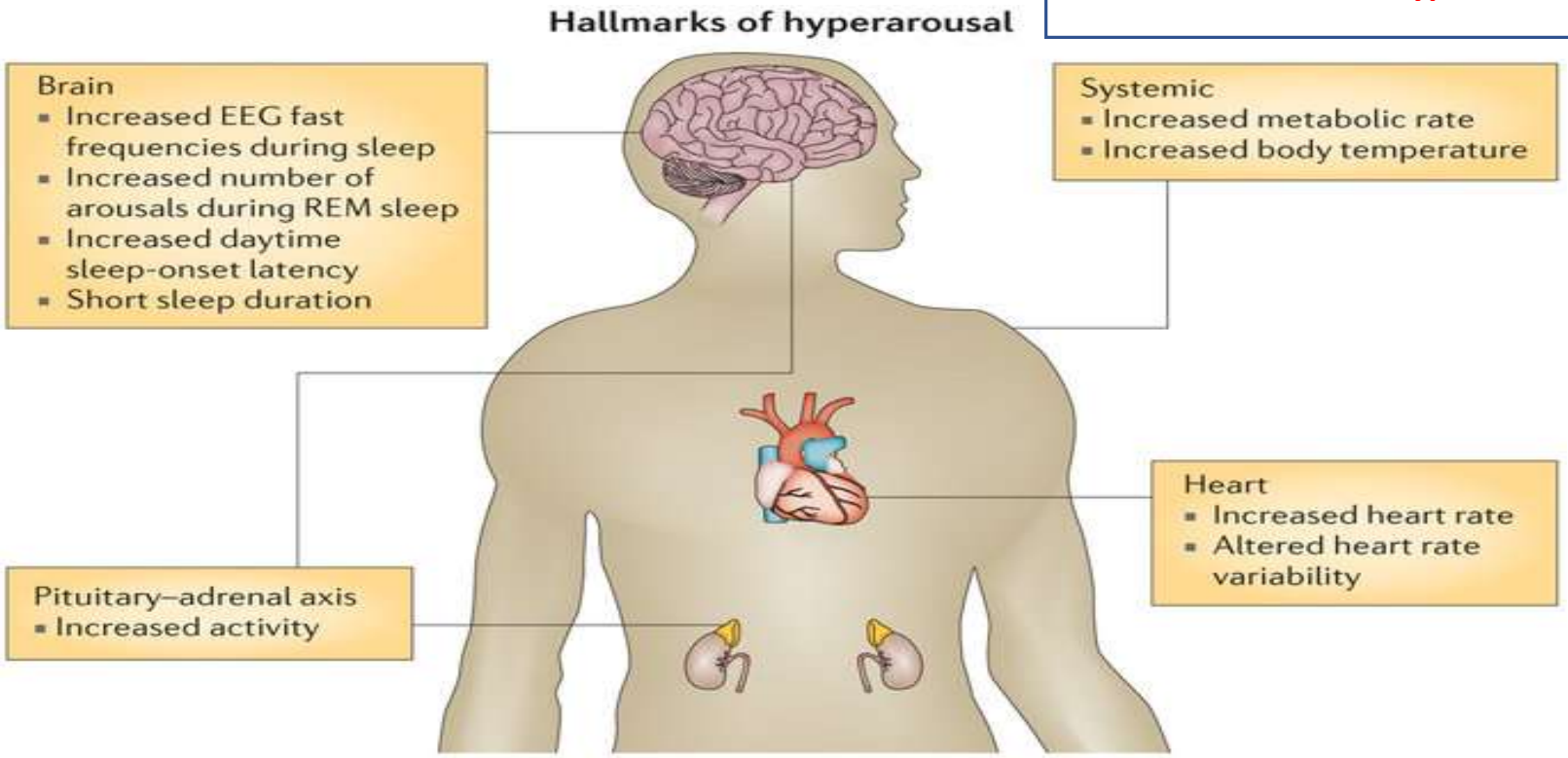
Saper et al. Nature 437:1257–1263, 2005

Fisiopatologia dell'insonnia

Insomnia disorder

Charles M. Morin[1], Christopher L. Drake[2], Allison G. Harvey[3], Andrew D. Krystal[4], Rachel Manber[5], Dieter Riemann[6] and Kai Spiegelhalder[6]

l'iperattivazione del sistema dello stress è il meccanismo psicofisiologico alla base dell'insonnia cronica-hyperarousal

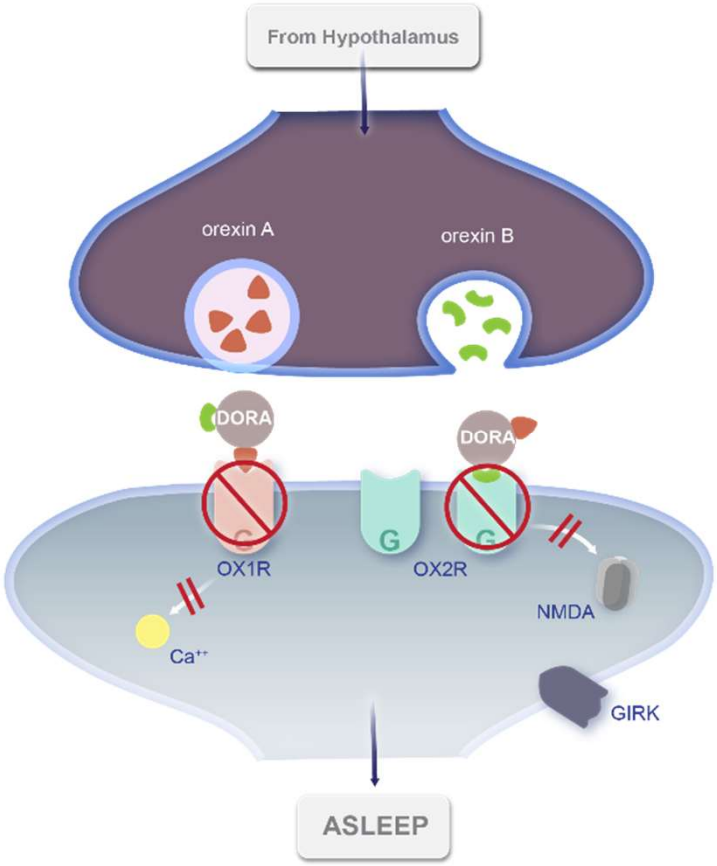


Nature Reviews | Disease Primers 2015

Daridorexant è un antagonista selettivo e ad alta affinità di entrambi i recettori dell'orexina (OX1R e OX2R)

- Il sistema dell'orexina **promuove la veglia** → l'antagonismo dei recettori dell'orexina consente il sonno[1-3]
- Daridorexant è un antagonista selettivo di OX1R e OX2R[4]
  - Profilo PK/PD ottimale
    - **Rapido assorbimento** per un rapido inizio del sonno[5]
    - Emivita appropriata che consente **il mantenimento del sonno senza sonnolenza nel mattino successivo**[5-7]

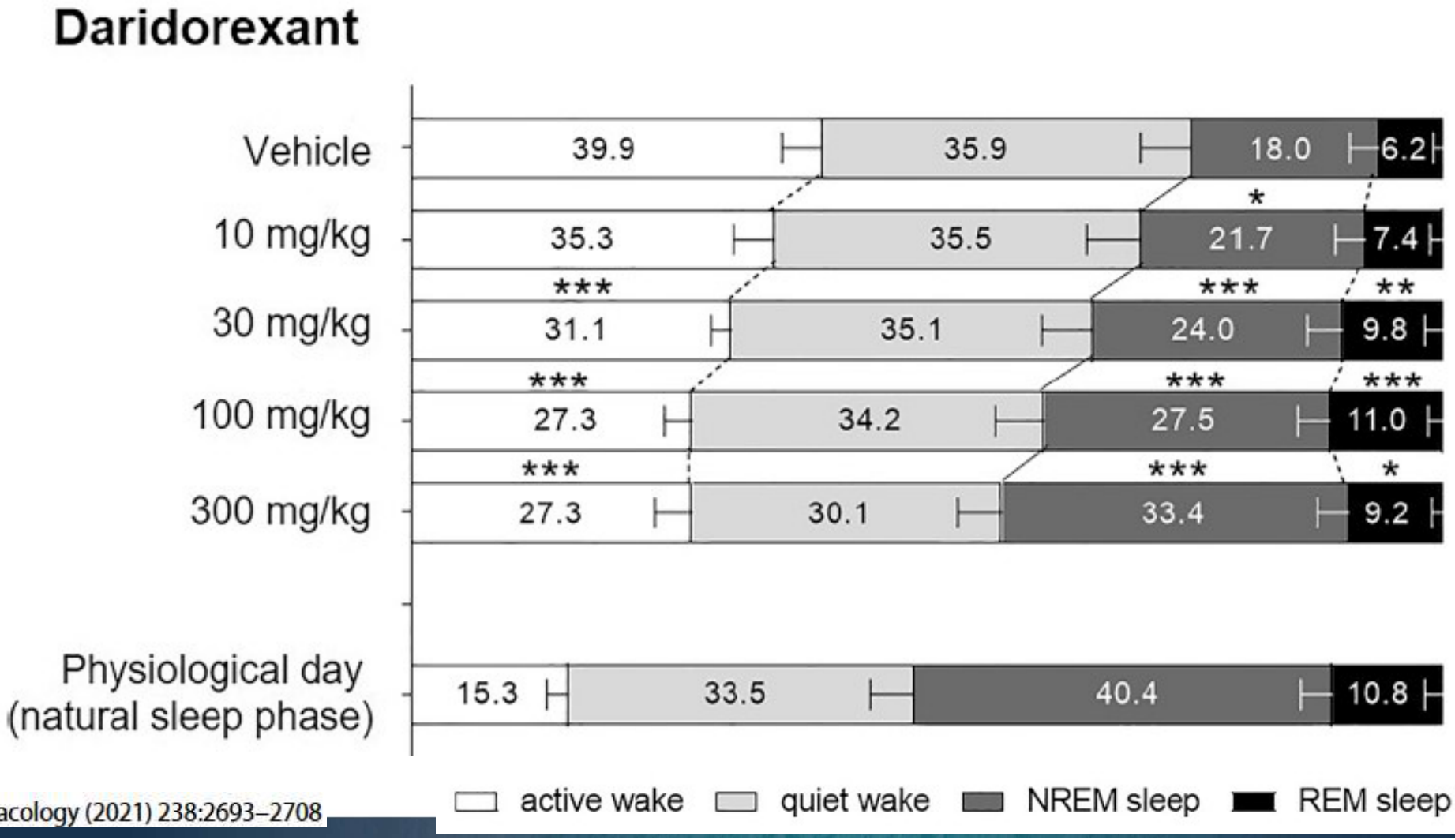
Daridorexant risponde al bisogno insoddisfatto di un farmaco per il trattamento dei sintomi di insorgenza e di mantenimento del sonno senza effetti residui nel mattino successivo e per il miglioramento del funzionamento diurno[7-9]



OX1R = recettore dell'orexina di tipo 1; OX2R = recettore dell'orexina di tipo 2; PK = farmacocinetica; PD = farmacodinamica; DORA = antatonista doppio del recettore dell'orexina; NMDA = N-metil-D-aspartato; Ca^{++} = ione calcio; GIRK = G protein-coupled inwardly rectifying potassium.

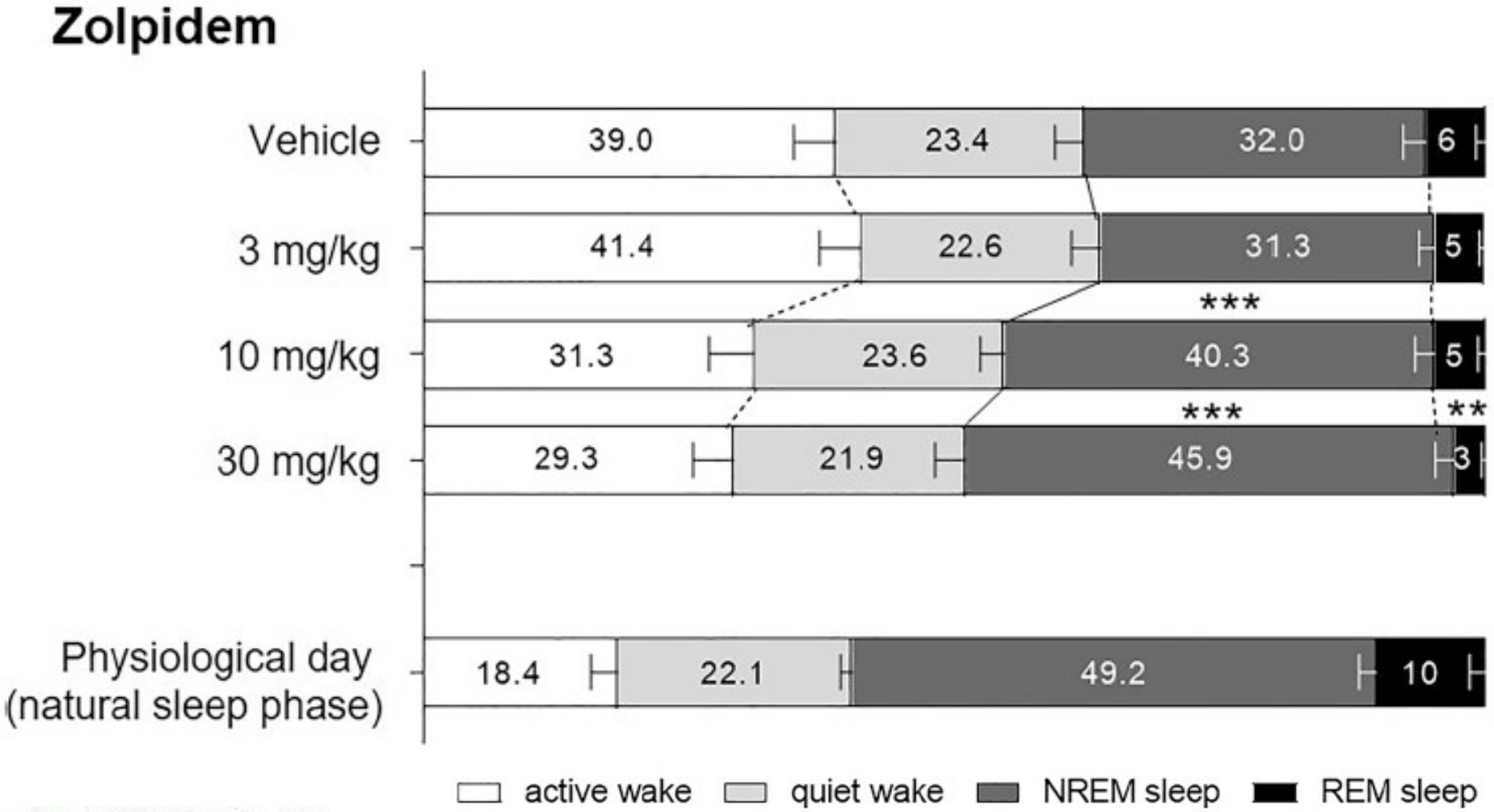
1. Muehlan C, et al. *J Clin Psychopharmacol*. 2020;40(2):157-166; 2. Scammell TE, et al. *Neuron*. 2017;93(4):747-765; 3. Wang C, et al. *Front Mol Neurosci*. 2018;11:220; 4. Treiber A, et al. *J Pharmacol Exp Ther*. 2017;362(3):489-503; 5. Muehlan C, et al. *Clin Pharmacol Ther*. 2018;104(5):1022-1029; 6. Muehlan C, et al. *Eur Neuropsychopharmacol*. 2019;29(7):847-857; 7. Muehlan C, et al. *J Psychopharmacol*. 2020;34(3):326-335; 8. Janto K, et al. *J Clin Sleep Med*. 2018;14(8):1399-1408; 9. Data on file – 17321 Trial 301 and 302 Key Results for IM and EM_Final. Investor Deck; 10. Stahl SM. *CNS Spectr*. 2016;21(3):215-218.

Daridorexant migliora il sonno, preservandone l'architettura



Psychopharmacology (2021) 238:2693–2708

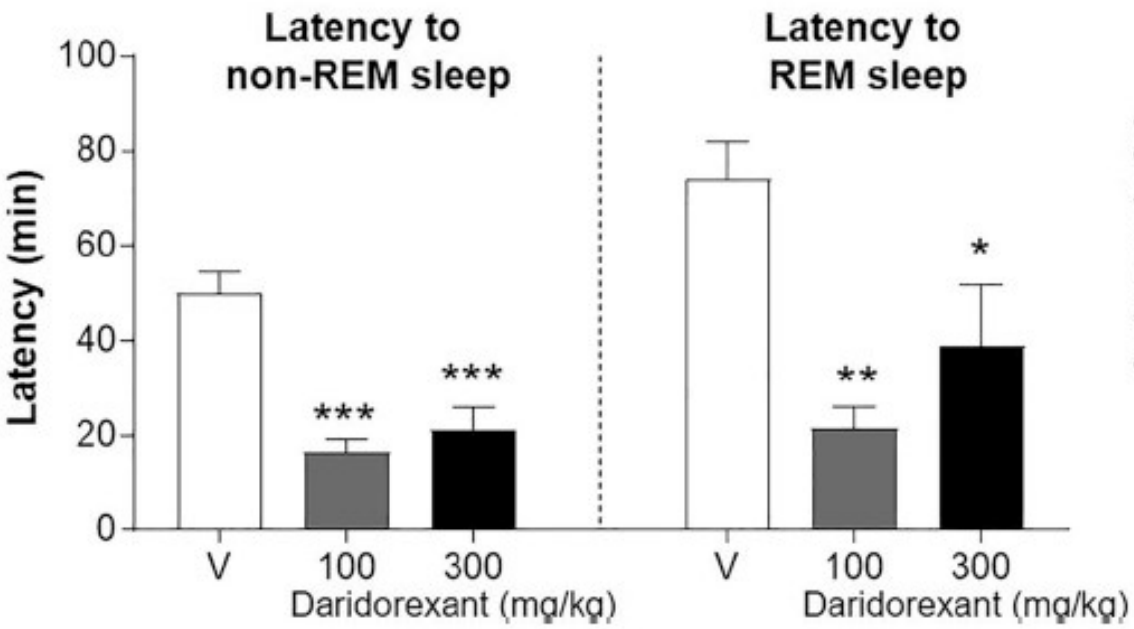
Daridorexant migliora il sonno, preservandone l'architettura



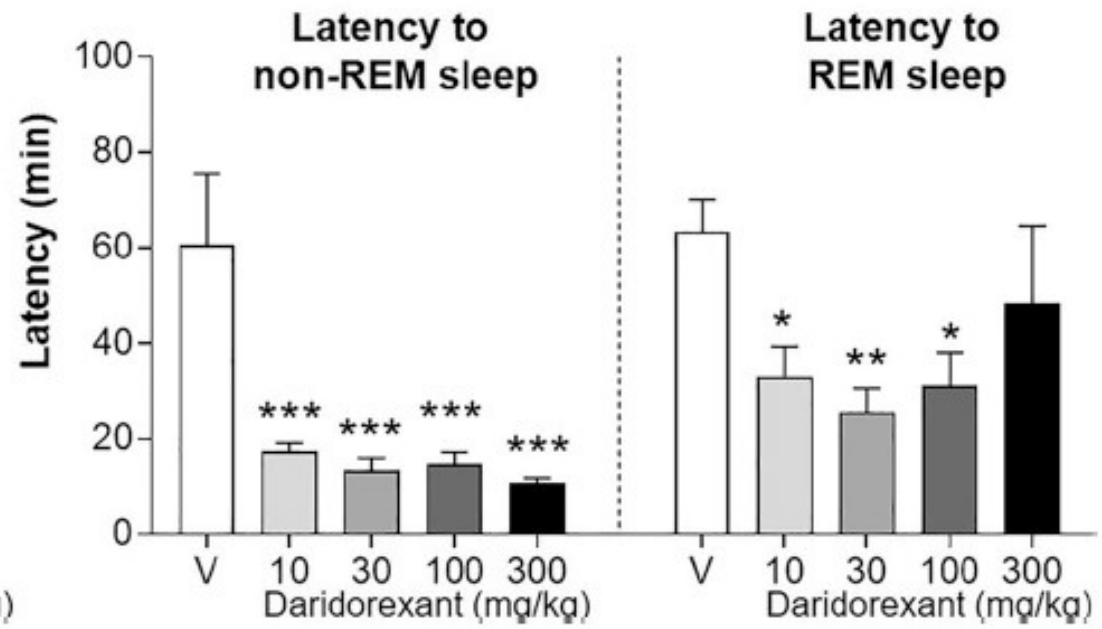
Psychopharmacology (2021) 238:2693–2708

Daridorexant riduce la latenza del sonno

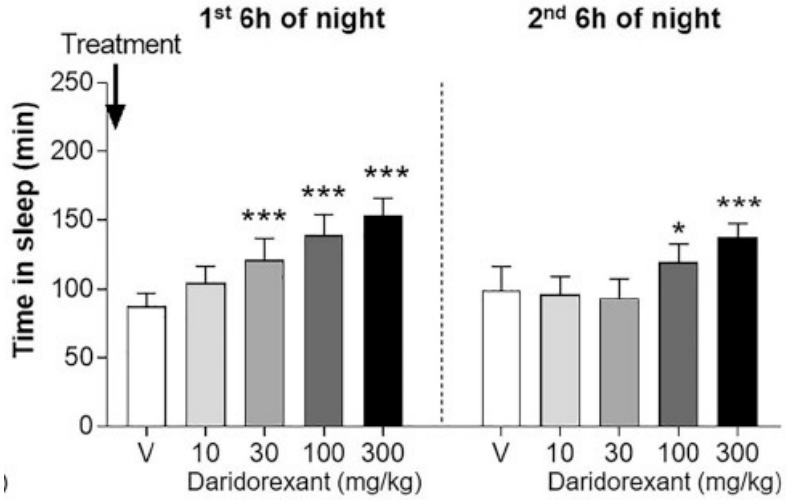
Fase 'inattiva' (Sonno)



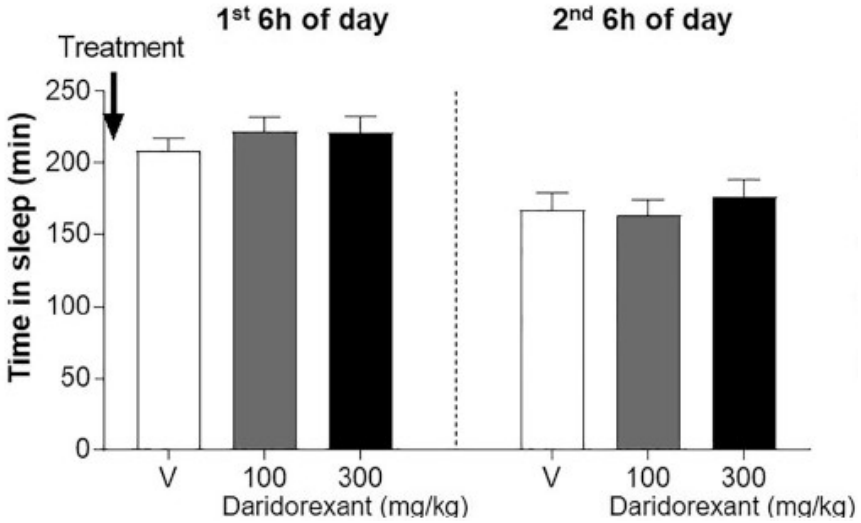
Fase 'attiva' (Veglia/Hyperausal)



Psychopharmacology (2021) 238:2693–2708

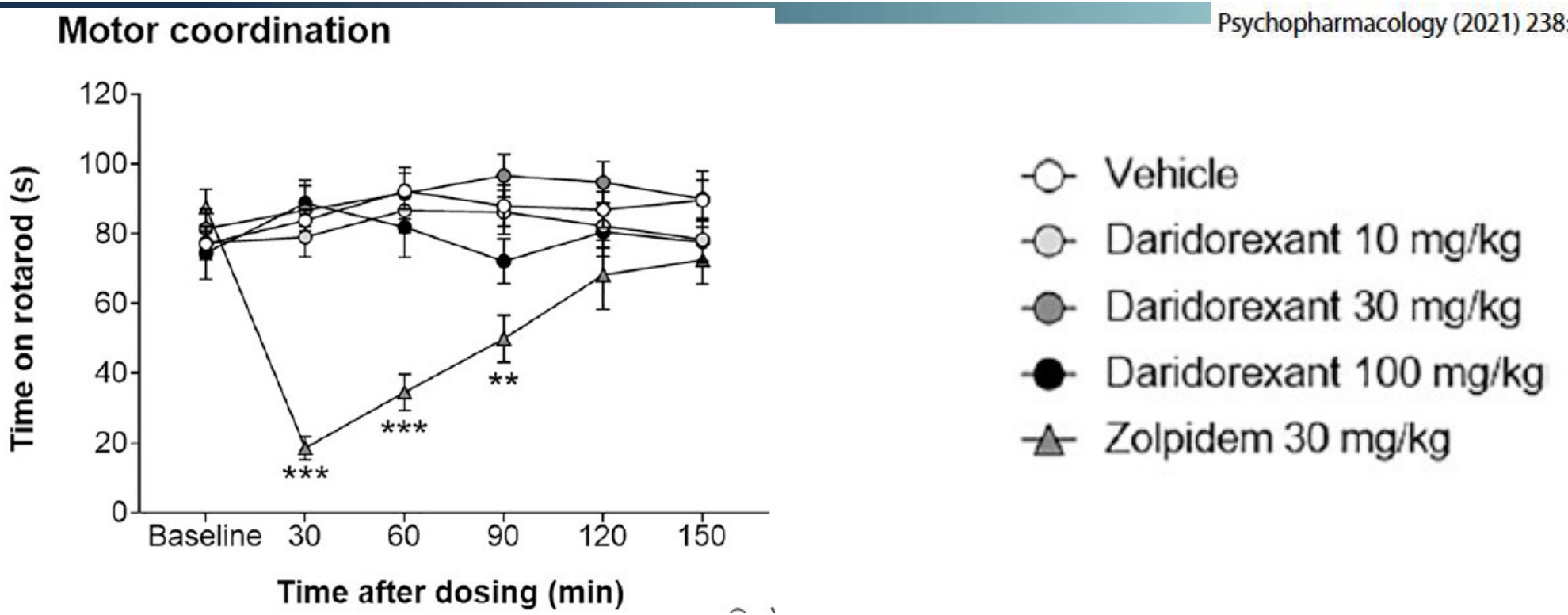


Daridorexant diminuisce la veglia (hyperausal), non modifica il sonno ‘per se’

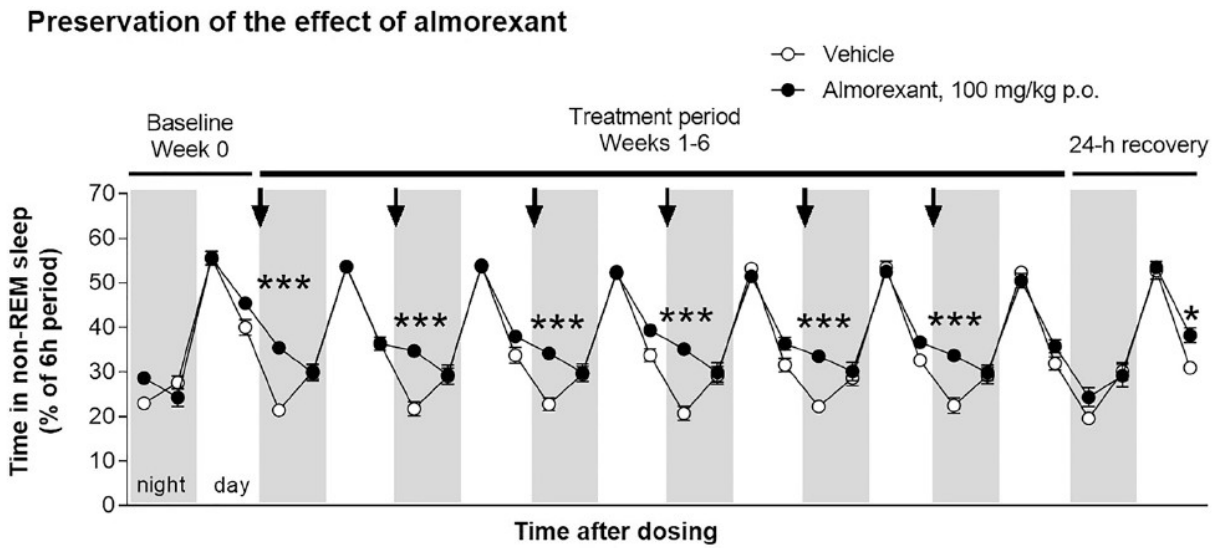


Daridorexant diminuisce la veglia (hyperausal), non modifica il sonno ‘per se’

Psychopharmacology (2021) 238:2693–2708

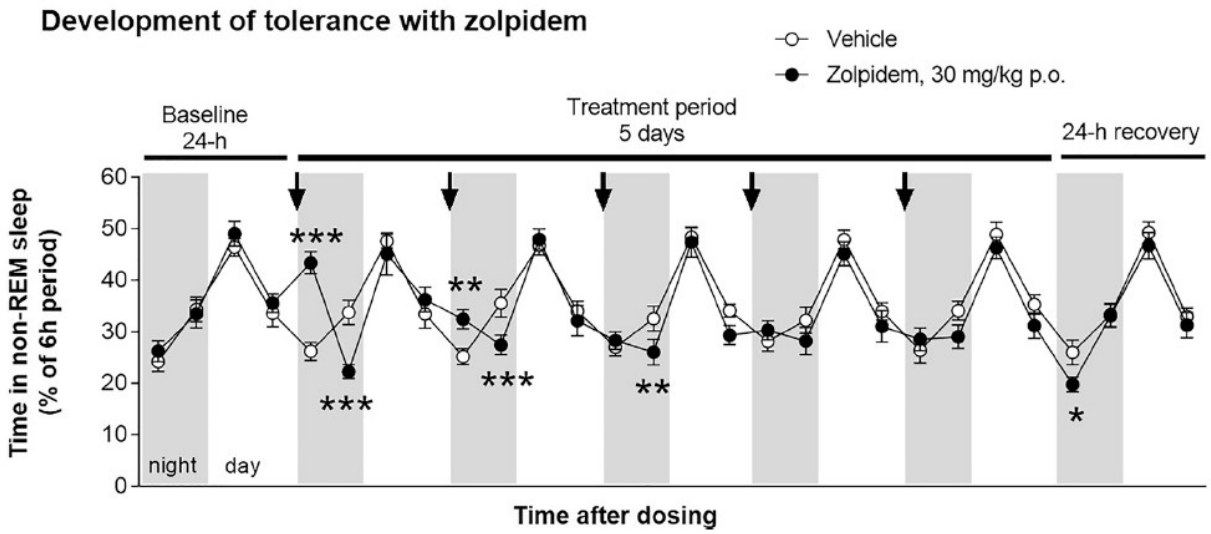


DARIDOREXANT NON INTERFERISCE CON LE ATTIVITÀ DIURNE



Effetto duraturo nel tempo, senza tolleranza

Psychopharmacology (2021) 238:2693–2708



Effetto duraturo nel tempo, senza tolleranza

De somno et vigilia. aristotele

- *Innanzitutto dunque questo certo (è) evidente, che per lo stesso essere vivente sussiste sia la veglia che il sonno; sono infatti opposti tra di loro, e il **sonno appare una privazione della veglia**; sempre infatti i fenomeni opposti sia sotto gli altri aspetti sia nelle cose naturali appaiono verificarsi nello stesso soggetto ed essere condizioni dello stesso soggetto, e intendo dire per esempio salute e malattia, e bellezza e bruttezza, e forza e debolezza, e vista e cecità, e udito e sordità.*