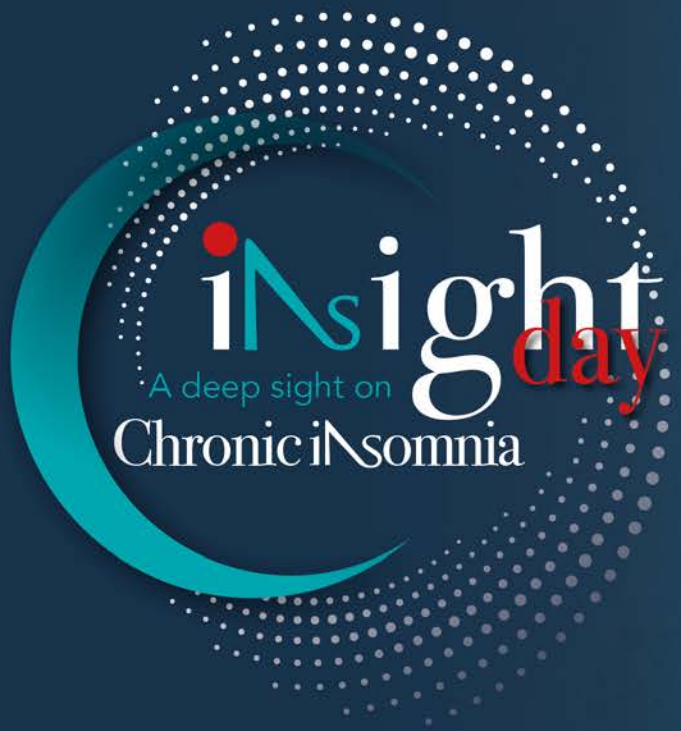


Napoli

24 novembre 2022

Hotel San Francesco al Monte

11.00-11.30

IL RUOLO DEL SISTEMA DELLE OREXINE NELLA REGOLAZIONE DEL RITMO SONNO-VEGLIA

Raffaele Ferri

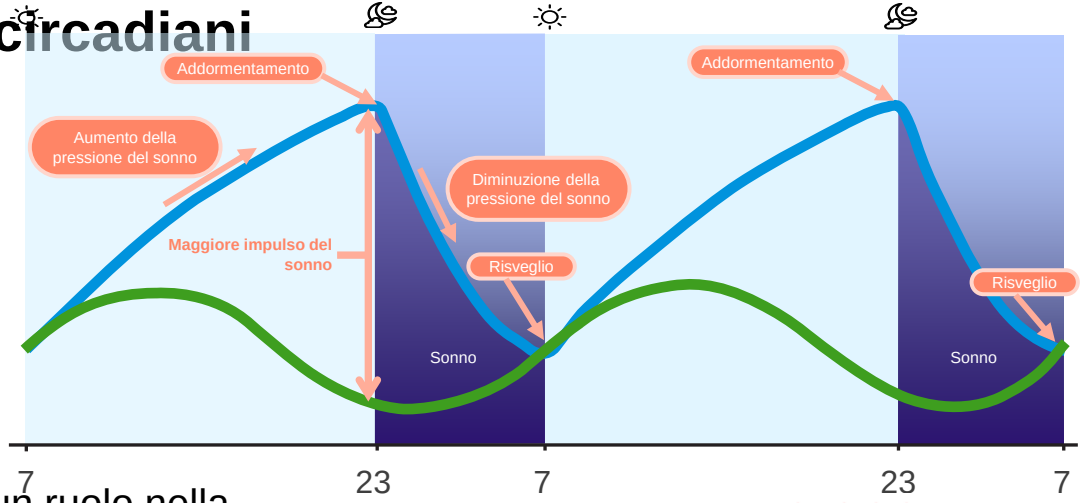
Troina (EN)

La regolazione del sonno può essere differenziata attraverso meccanismi omeostatici e circadiani

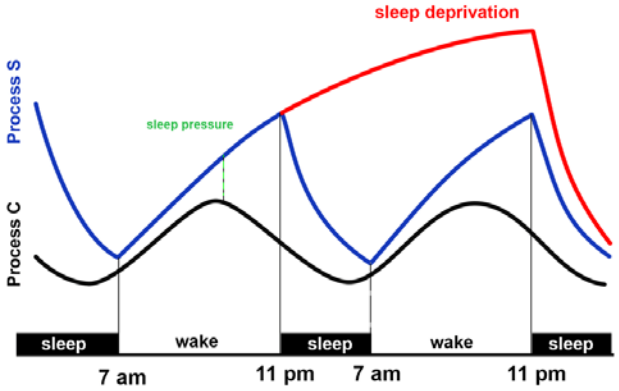
Figura adattata da della Monica C, *et al. Physiol News* 2018.[3]

Stimolo omeostatico > sonno

Stimolo circadiano > veglia



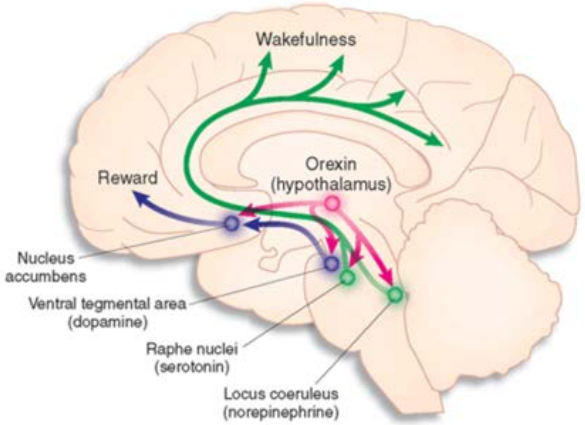
- **Processo circadiano** ("Processo C") ha un ruolo nella regolazione temporale dei cicli sonno-veglia[1]
  - L'**orexina** è regolata principalmente dal processo **circadiano**[1]
- **Processo omeostatico** ("Processo S") in funzione della durata della veglia[2]
  - Il GABA è il neurotrasmettitore inibitorio più diffuso, regolato principalmente dal processo **omeostatico**[1]

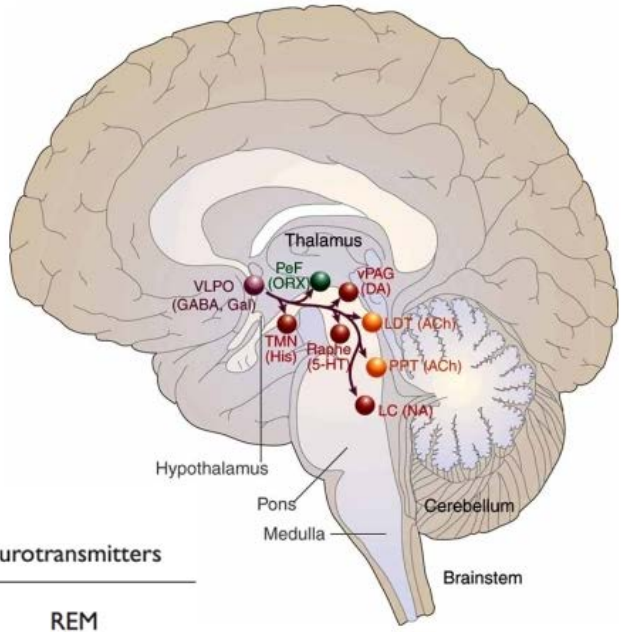


GABA, acido γ-amminobutirrico.

1. Schwartz JR, Roth T. *Curr Neuropharmacol* 2008;6:367-78; 2. Centers for Disease Control and Prevention. Pressione del sonno: guida omeostatica del sonno. Aggiornato al 31 marzo 2020. Disponibile su: https://www.cdc.gov/niosh/work-hour-training-for-nurses/longhours/mod2/11.html (accesso a settembre 2022); 3. della Monica C, *et al. Physiol News* 2018;113:36-39.

Gli stati di veglia e sonno sono regolati da sistemi di segnalazione diversi ma strettamente interagenti tra di loro nel sistema nervoso centrale





Wake-promoting neurotransmitters
Glutamate
Acetylcholine
Dopamine
Norepinephrine
Serotonin
Histamine
Orexin/hypocretin

Sleep-promoting neurotransmitters	
NREM	REM
GABA	Acetylcholine
Galanin	Glutamate
Adenosine	GABA
Melatonin	Glycine (muscle atonia)

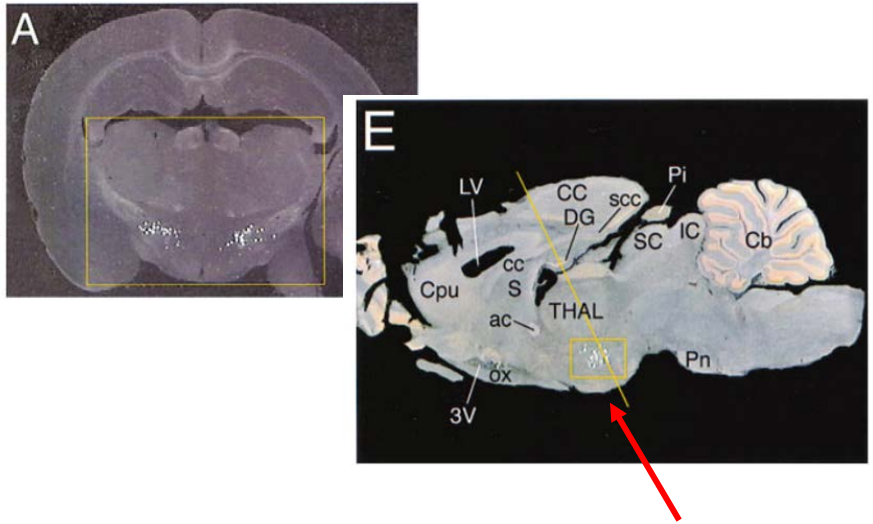
ARAS, sistema reticolare attivatore ascendente; BF, proencefalo basale; LC, locus coeruleus; LDT, nucleo tegmentale laterodorsale; LHA, area ipotalamica laterale; MnPN, nucleo preottico mediano; NREM, non associato a movimenti oculari rapidi; PPT, nucleo tegmentale peduncolopontino; REM, movimenti oculari rapidi; TMN, nucleo tuberomammillare; VLPO, aera preottica ventrolaterale; vPAG, grigio periacqueduttale ventrolaterale; VTA, area tegmentale ventrale.

1. Schwartz JR, Roth T. *Curr Neuropharmacol* 2008;6:367-78; 2. Riemann D, et al. *Lancet Neurol* 2015;14:547-58; 3. McGinty D e Szymusiak R. In: Kryger MH, et al., editors. *Principi e pratica della medicina del sonno*. 6a ed. Philadelphia, PA: Elsevier, 2017:62-77, e1-e5; 4. Brown RE, et al. *Physiol Rev* 2012;92:1087-187; 5. Mahoney CE, et al. *Nat Rev Neurosci* 2019;20:83-93; 6. Saper CB, et al. *Neuron* 2010;68:1023-42.

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]



PRE-PROOREXINA

OXA 33 aa

OXB 28 aa

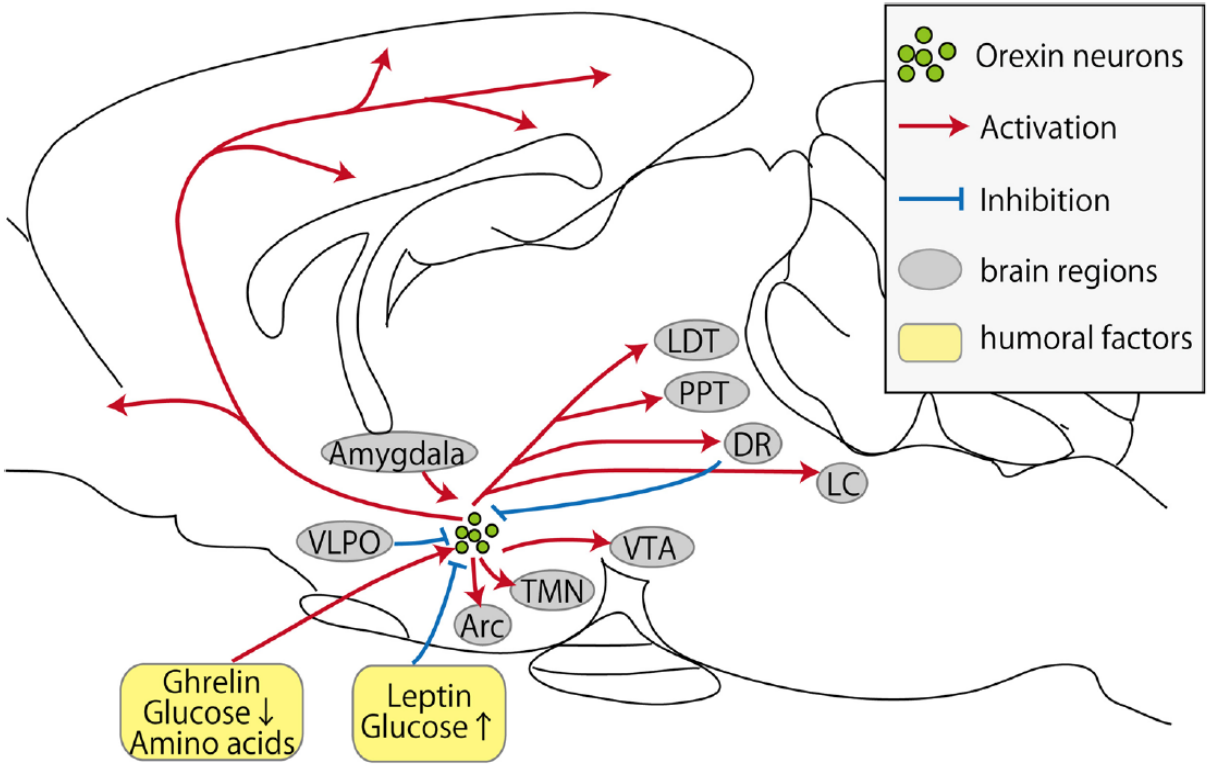


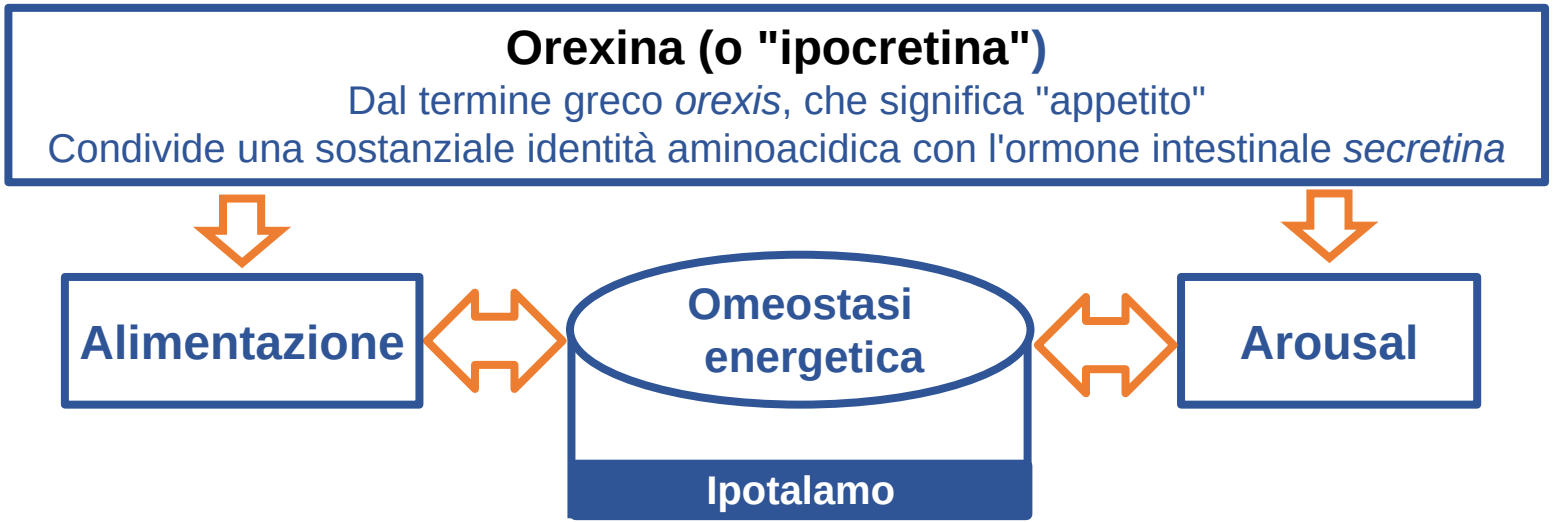
FIGURE 1 | Schematic representation of inputs and outputs of orexin neurons. Orexin neurons are found only in the lateral hypothalamic area but project throughout the entire central nervous system. Red arrows show excitatory projections, while blue lines show inhibitory projections.

Abbreviations: Arc, arcuate nucleus; DR, dorsal raphe nucleus; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; PPT, pedunculopontine tegmental nucleus; TMN, tuberomammillary nucleus; VTA, ventral tegmental area; VLPO, ventrolateral preoptic nucleus.

Inutsuka and Yamanaka, 2013

Sistema orexina/ipocretina

Famiglia di neuropeptidi ipotalamici e recettori accoppiati a proteine G che regolano il comportamento alimentare, il sonno, il bilancio energetico, funzioni cardiovascolari, ecc.



Convenzione sull'uso dei termini "orexine" (orexins) e "ipocretine" (hypocretins):

- ✓ "**orexine**" per designare i **peptidi e i loro recettori**
- ✓ "**ipocretine**" per designare i **rispettivi geni e mRNA**

1. Sakurai T, et al. *Cell* 1998;92:573-85; 2. De Lecea L, et al. *Proc Natl Acad Sci U S A* 1998;95:322-7.

Le Orexine

I peptidi orexinici sono prodotti da un numero discreto di neuroni nell'ipotalamo laterale

- Il sistema dell'orexina svolge un ruolo specifico nel sistema sonno-veglia[1–3]
  - Neuroni contenenti orexina della LHA : attivi durante la veglia; inattivi durante il sonno NREM e REM
    - Importante per il mantenimento di lunghi periodi di veglia
- I neuropeptidi orexina-A e orexina-B sono sintetizzati nella LHA[4–7]
  - OX1R: maggiore affinità per l'orexina A rispetto alla B
  - OX2R: lega entrambi i peptidi con uguale affinità

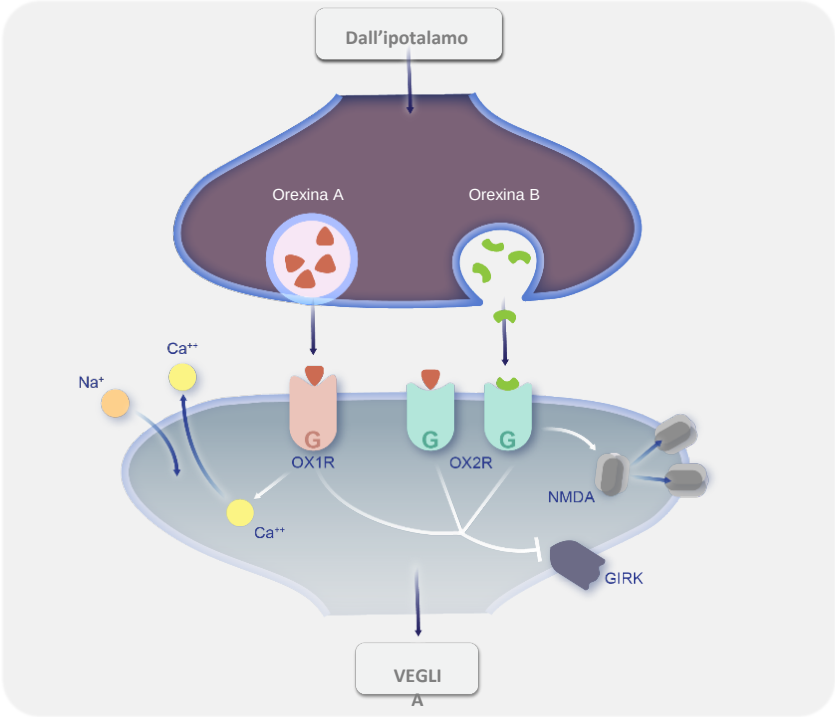


Figura adattata da Stahl SM. *CNS Spectr* 2016[7]
G, proteina G; GIRK, canali del potassio rettificanti verso l'interno regolati dalle proteine G; LHA, area ipotalamica laterale;
NMDA, acido N-metil-D-aspartico; NREM, non associato a movimenti oculari rapidi; OX1R, recettore dell'orexina 1; OX2R, recettore dell'orexina 2; REM, movimenti oculari rapidi.

1. Schwartz JR, Roth T. *Curr Neuropharmacol* 2008;6:367-78; 2. McGinty D e Szymusiak R. In: Kryger MH, et al., editors. *Principi e pratica della medicina del sonno*. 6a ed. Philadelphia, PA: Elsevier, 2017:62-77, e1-e5; 3. Mahoney CE, et al. *Nat Rev Neurosci* 2019;20:83-93; 4. de Lecea L, et al. *Proc Natl Acad Sci U S A* 1998;95:322-7; 5. Sakurai T, et al. *Cell* 1998;92:573-85; 6. Muehlan C, et al. *Expert Opin Drug Metab Toxicol* 2020;16:1063-78; 7. Stahl SM. *CNS Spectr* 2016;21:215-8.

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]

OXA
- 2 ponti S-S, pGLU N-terminale:
- > resistenza a peptidasi
- effetti a più lungo termine su OXR1 e OXR2

OXB
- peptide lineare:
- < resistenza a peptidasi
- effetti a più breve termine su OXR2

ELSEVIER

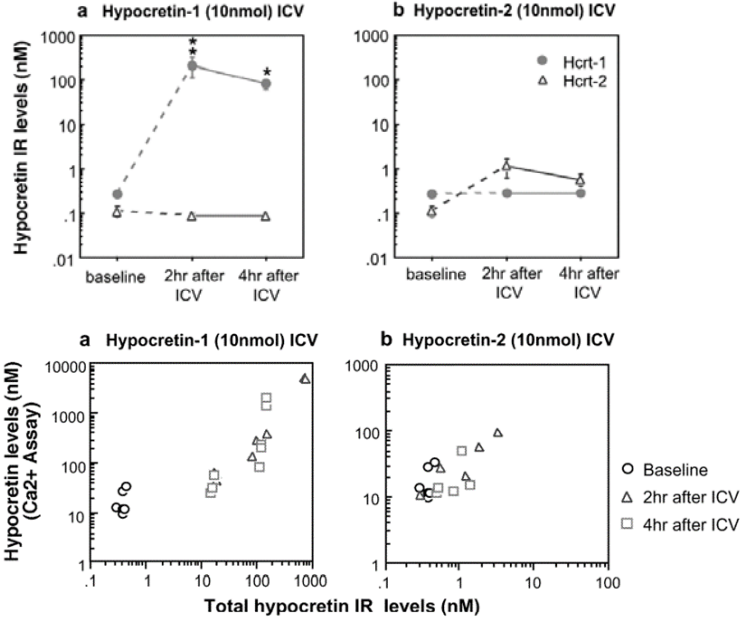
Neuroscience Letters 346 (2003) 182–186

Neuroscience Letters

www.elsevier.com/locate/neulet

Differential kinetics of hypocretins in the cerebrospinal fluid after intracerebroventricular administration in rats

Yasushi Yoshida[a], Nobuhiro Fujiki[a], Richard A. Maki[b], David Schwarz[b], Seiji Nishino[a,*]



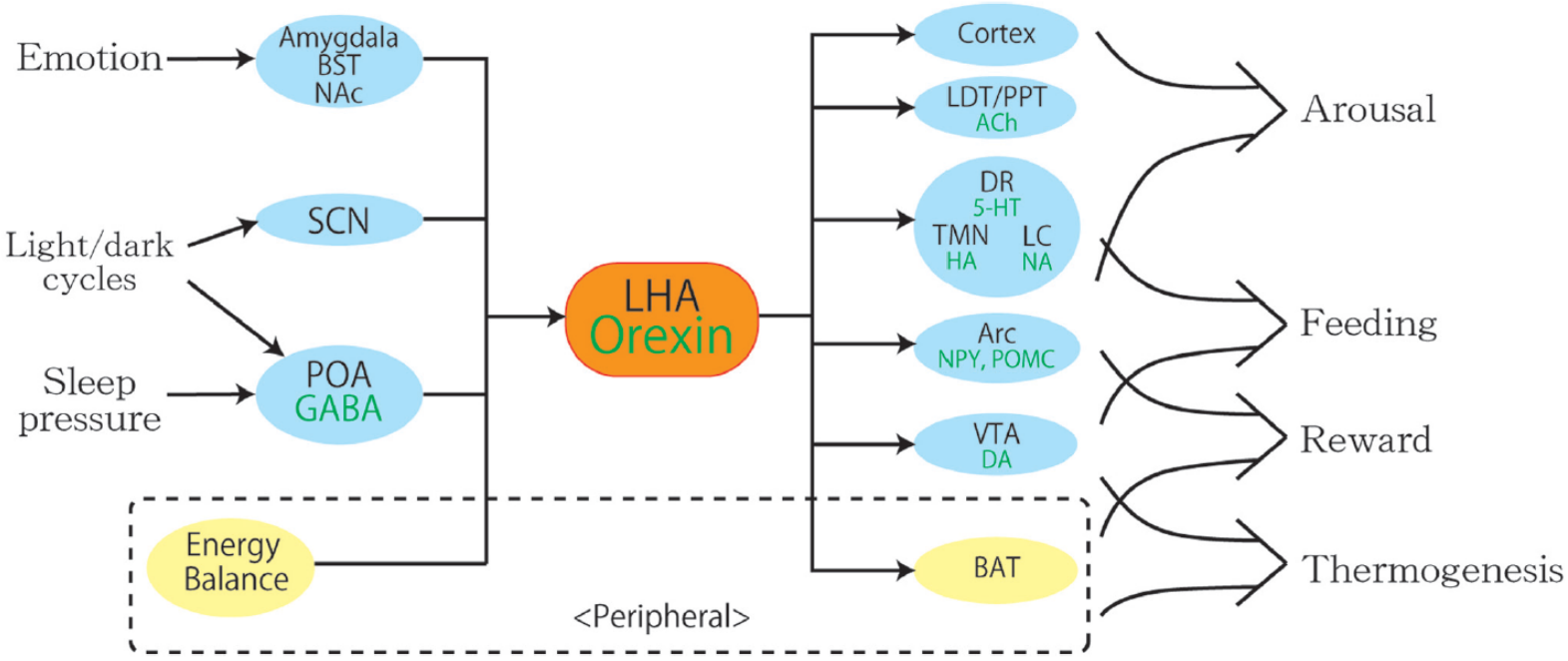


FIGURE 2 | A schematic diagram to illustrate the integrative physiological roles of orexin neurons. Orexin neurons regulate various physiological phenomena such as wakefulness, feeding, reward, and thermogenesis. The body energy level influences orexin neuronal activity to coordinate arousal and energy homeostasis. Inputs from the limbic system may be important to regulate the activity of orexin neurons to evoke emotional arousal or fear-related responses. Abbreviations: 5-HT, serotonin; ACh, acetylcholine; Arc, arcuate nucleus; BAT, brown adipose tissue; BST, bed nucleus of the stria terminalis; DA, dopamine; DR, dorsal raphe nucleus; GABA, gamma-aminobutyric acid; HA, histamine; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; LHA, lateral hypothalamic area; NA, noradrenalin; NAc, nucleus accumbens; NPY, neuropeptide Y; POA, preoptic area; POMC, proopiomelanocortin; PPT, pedunculopontine tegmental nucleus; SCN, suprachiasmatic nucleus; TMN, tuberomammillary nucleus; VTA, ventral tegmental area.

Inutsuka and Yamanaka, 2013

ARTICLE

https://doi.org/10.1038/s41467-021-25380-2 OPEN

Orexin receptors 1 and 2 in serotonergic neurons differentially regulate peripheral glucose metabolism in obesity

Xing Xiao[1,2,3], Gagik Yeghiazaryan[3,4], Simon Hess[3,4], Paul Klemm[1,2,3], Anna Sieben[1,2,3], André Kleinridders[1,2,3,5,10], Donald A. Morgan[6], F. Thomas Wunderlich[1,2,3], Kamal Rahmouni[6], Dong Kong[7,8], Thomas E. Scammell[9], Bradford B. Lowell[8], Peter Kloppenburg[3,4], Jens C. Brüning[1,2,3,5] & A. Christine Hausen[1,2,3]✉

OXR1 in neuroni 5'HT aumenta la sensibilità all'insulina, ma OXR2 la riduce

Sleep Medicine Reviews 58 (2021) 101440

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

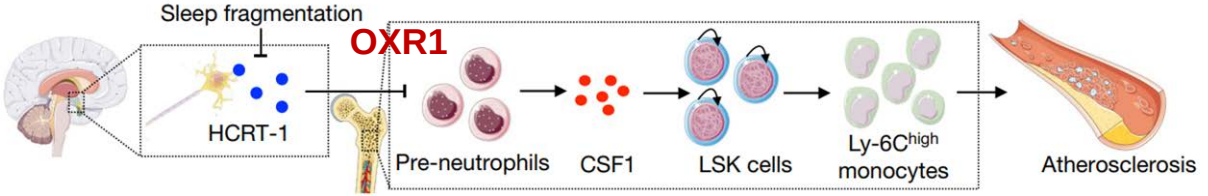
CLINICAL REVIEW

Cardiovascular disorders in narcolepsy: Review of associations and determinants

Poul Jørgen Jennum [a, *], Giuseppe Plazzi [b, c], Alessandro Silvani [d], Lee A. Surkin [e], Yves Dauvilliers [f, g]

Sleep modulates haematopoiesis and protects against atherosclerosis

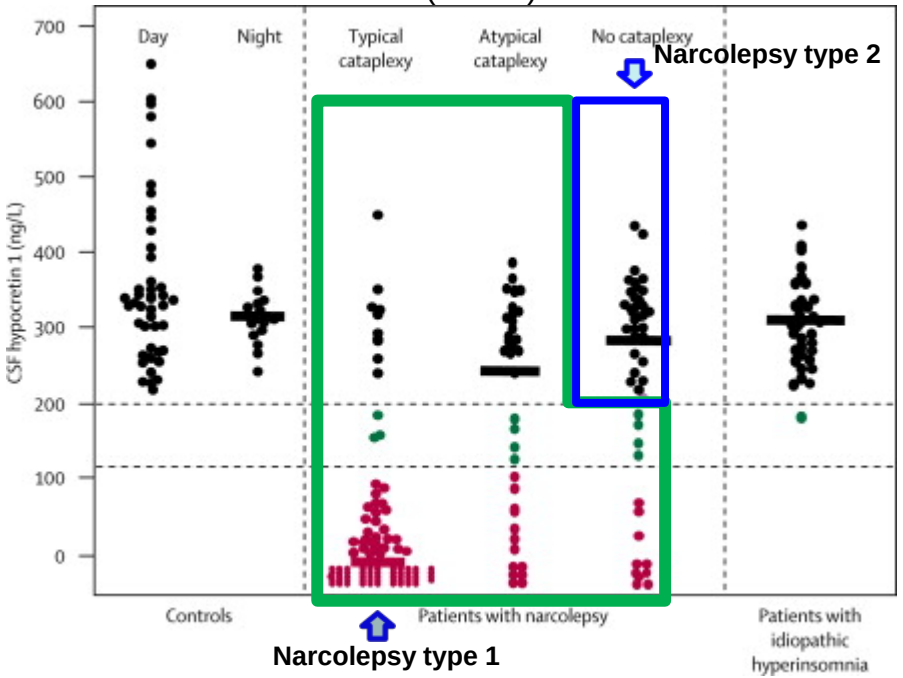
Cameron S. McAlpine[1], Máté G. Kiss[1,2,3], Sara Rattik[1], Shun He[1], Anne Vassalli[4], Colin Valet[1], Atsushi Anzai[1], Christopher T. Chan[1], John E. Mindur[1], Florian Kahles[1], Wolfram C. Poller[1], Vanessa Frodermann[1], Ashley M. Fenn[1], Annemijn F. Gregory[1], Lennard Halle[1], Yoshiko Iwamoto[1], Friedrich F. Hoyer[1], Christoph J. Binder[2,3], Peter Libby[5], Mehdi Tafti[4], Thomas E. Scammell[6], Matthias Nahrendorf[1,7] & Filip K. Swirski[1,7]*



Orexin deficiency in sporadic, HLA positive narcolepsy cases

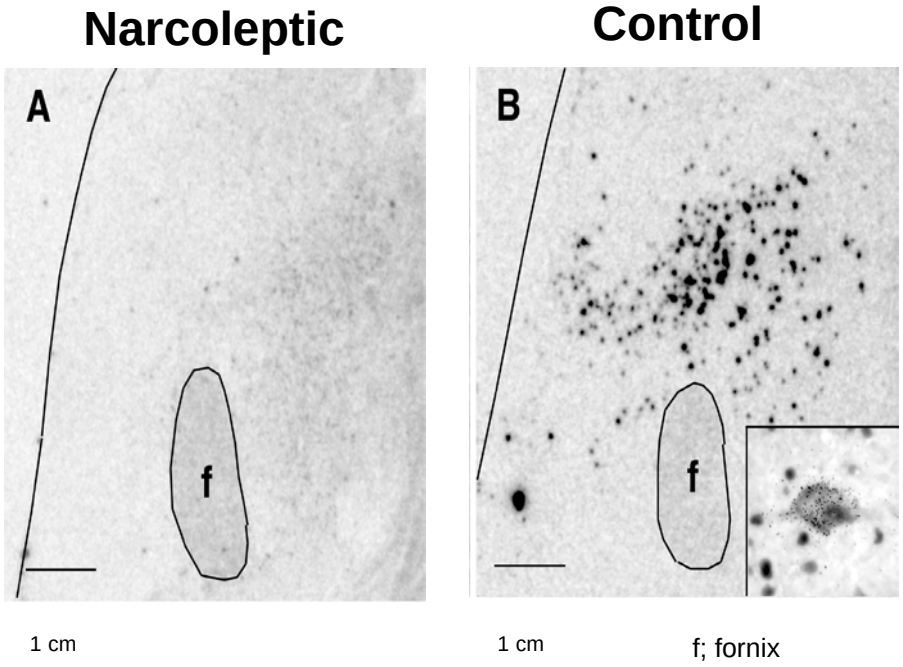
Cerebrospinal fluid

OXA (ELISA)



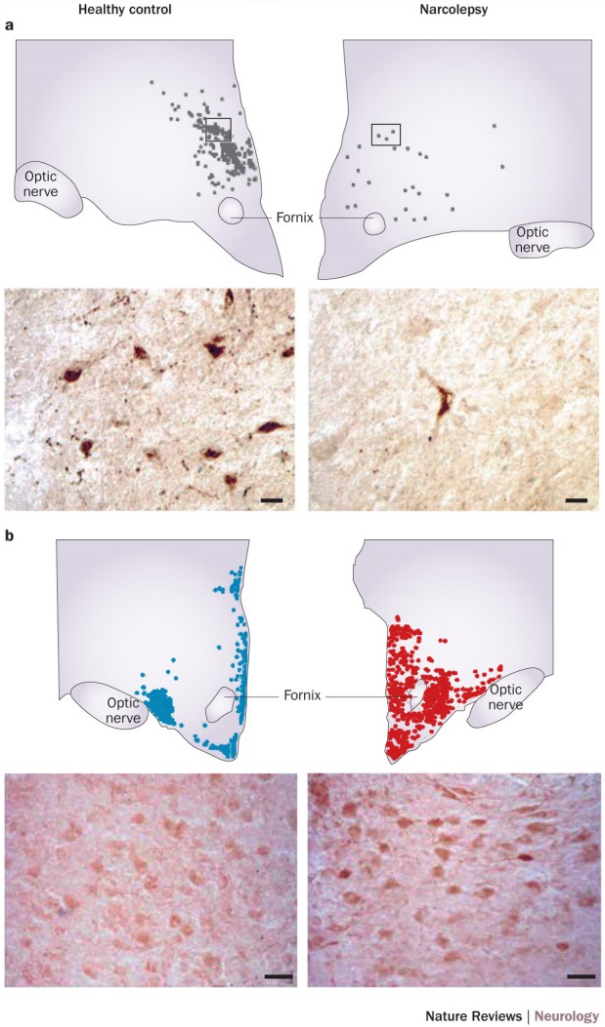
Lateral hypothalamus

mRNA in situ Hybridization



Adapted from Nishino et al. *Ann Neurol* 2001;50:381; Peyron et al. *Nat Med* 2000;6:991; Dauvilliers et al. *Lancet* 2007;369:499..

Loss of hypothalamic orexin neurons and increase in histamine neurons in narcolepsy



Shan, L. *et al.* (2015) Interactions of the histamine and hypocretin systems in CNS disorders
Nat. Rev. Neurol. oi:10.1038/nrneurol.2015.99

ACS Medicinal Chemistry Letters

pubs.acs.org/acsmedchemlett Letter

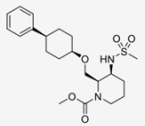
Discovery of TAK-925 as a Potent, Selective, and Brain-Penetrant Orexin 2 Receptor Agonist

Tatsuhiko Fujimoto, Kentaro Rikimaru, Koichiro Fukuda, Hiromichi Sugimoto, Kei Masuda, Norio Ohyabu, Yoshihiro Banno, Norihito Tokunaga,* Tetsuji Kawamoto, Yoshihide Tomata, Yasumi Kumagai, Motoo Iida, Yoichi Nagano, Mariko Yoneyama-Hirozane, Yuji Shimizu, Katsunori Sasa, Takashi Ishikawa, Hiroshi Yukitake, Mitsuhiro Ito, Kazunobu Aoyama, and Takahiro Matsumoto

Cite This: ACS Med. Chem. Lett. 2022, 13, 457−462 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: TAK-925, a potent, selective, and brain-penetrant orexin 2 receptor (OX2R) agonist, [methyl (2R,3S)-3-((methylsulfonyl)amino)-2-(((*cis*-4-phenylcyclohexyl)oxy)methyl)piperidine-1-carboxylate, **16**], was identified through the optimization of compound **2**, which was discovered by a high throughput screening (HTS) campaign. Subcutaneous administration of compound **16** produced wake-promoting effects in mice during the sleep phase. Compound **16** (TAK-925) is being developed for the treatment of narcolepsy and other related disorders.



16 (TAK-925)

PNAS RESEARCH ARTICLE | MEDICAL SCIENCES OPEN ACCESS

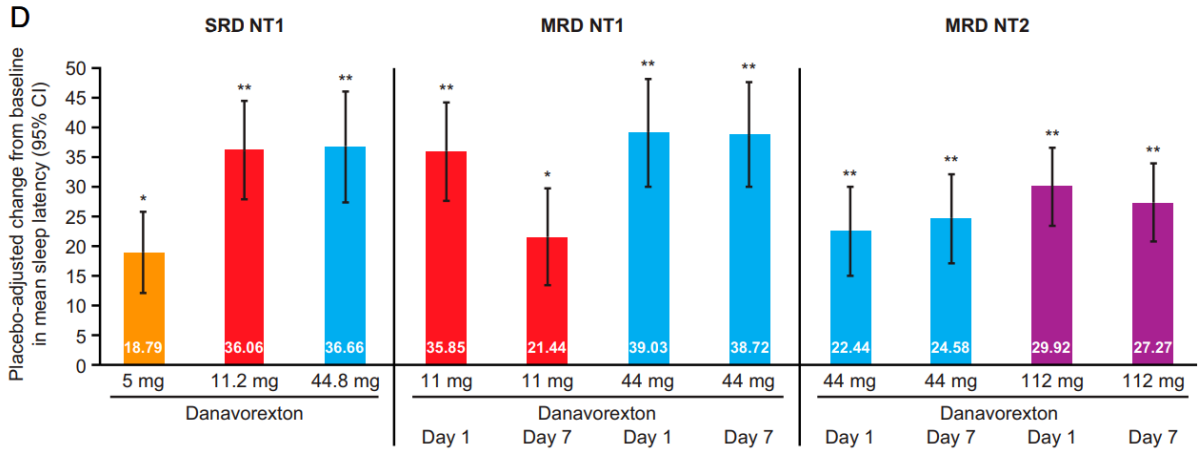
Orexin 2 receptor–selective agonist danavorexton improves narcolepsy phenotype in a mouse model and in human patients

Rebecca Evans[a,1,2], Haruhide Kimura[b,1], Robert Alexander[a,2], Ceri H. Davies[b], Hélène Faessel[a], Deborah S. Hartman[a,2], Takashi Ishikawa[b], Emiliangelo Ratti[a,2], Kohei Shimizu[c], Motohisa Suzuki[b], Shinichiro Tanaka[c], Hiroshi Yukitake[b], Yves Dauvilliers[d,3], and Emmanuel Mignot[e,3,4]

Infusione IV, 9 ore

Cataplexy. Prior to confinement at the clinical site in the MRD study, the mean numbers of cataplexy events during a time-matched 9-h baseline period from day −7 to day 1 were 2.3 (SD, 1.50), 5.8 (SD, 7.68), and 3.2 (SD, 2.59) for the placebo, danavorexton 11 mg, and danavorexton 44 mg groups, respectively. One individual in the danavorexton 11 mg cohort reported 17 cataplexy events during the baseline period, resulting in a higher baseline mean in that group.

Over the 7-d treatment period in the MRD study, the mean number of cataplexy episodes in individuals with NT1 during IV infusion decreased to zero in both danavorexton groups but not in the placebo group. Participants reported no cataplexy episodes during infusion of danavorexton 11 mg or 44 mg over the 7-d study period, compared with a mean number of cataplexy episodes of 1.8 during placebo infusion.



L'attività dell'orexina stabilizza veglia e sonno

I livelli di orexina aumentano durante il giorno, contribuendo a contrastare la pressione omeostatica del sonno e a stabilizzare la veglia

Stato di veglia[1,2]

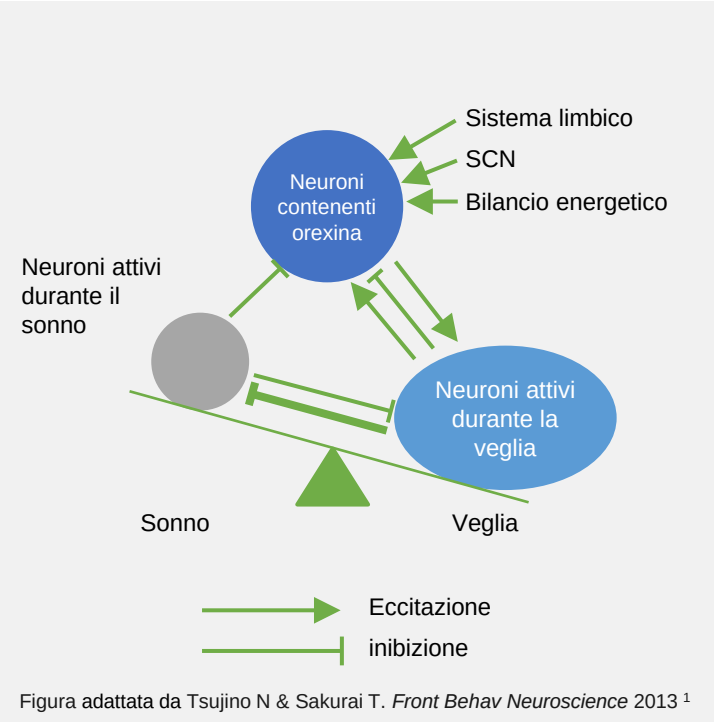
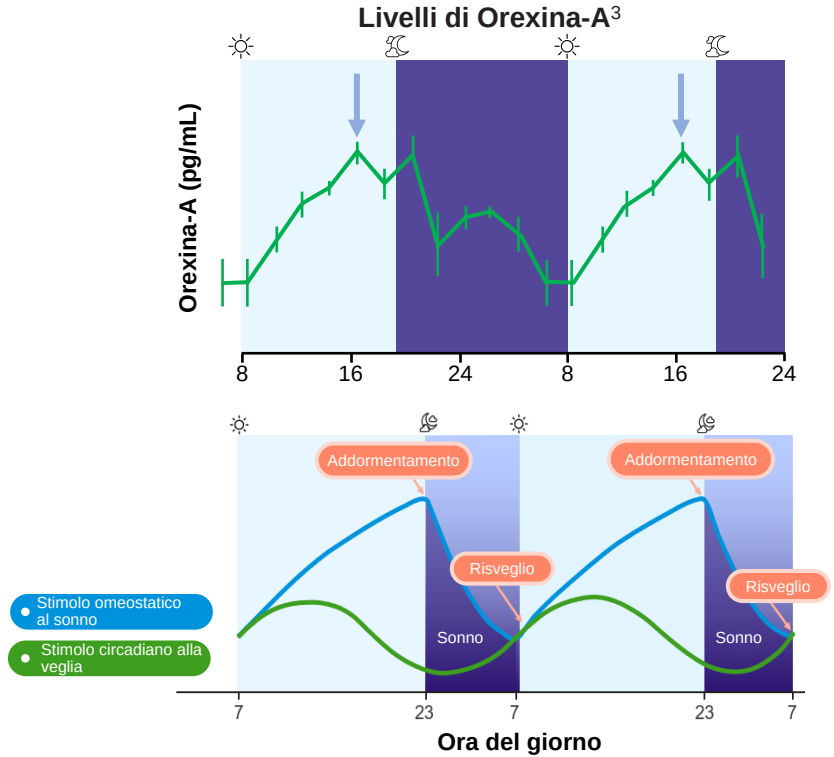


Figura adattata da Tsujino N & Sakurai T. *Front Behav Neuroscience* 2013 [1]

Livelli di Orexina-A[3]



Concentrazioni di Orexina-A valutate nel liquido cerebrospinale cisternale di scimmia scoiattolo, un primate che vive in America meridionale con pattern sonno-veglia simili all'uomo. SCN, nucleo soprachiasmatico. 1. Tsujino N, Sakurai T. *Front Behav Neurosci* 2013;7:28; 2. Saper CB, *et al. Nature* 2005;437:1257-63; 3. Zeitzer JM, *et al. J Neurosci* 2003;23:3555-60.

L'attività dell'orexina stabilizza veglia e sonno

I livelli di orexina si abbassano durante la notte, quando diminuisce la pressione del sonno (durante il sonno)

Stato di sonno[1,2]

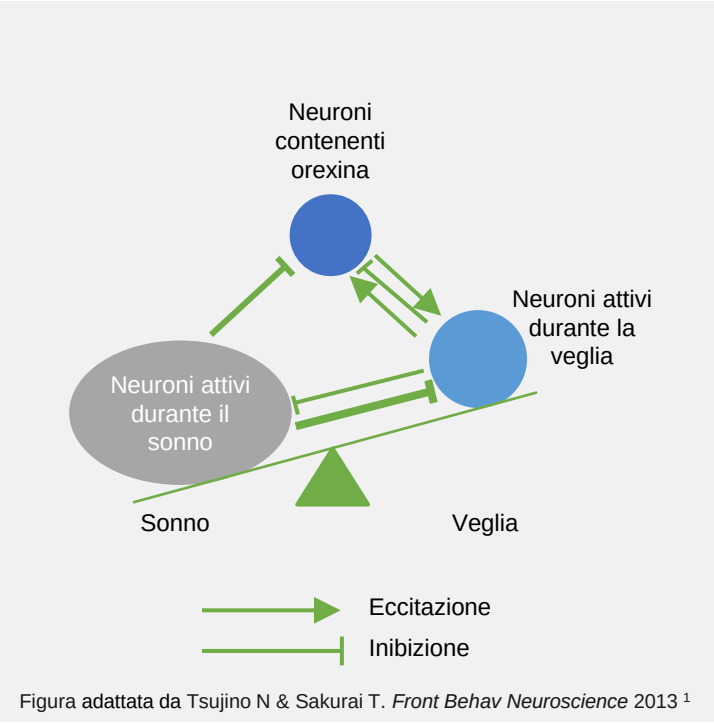
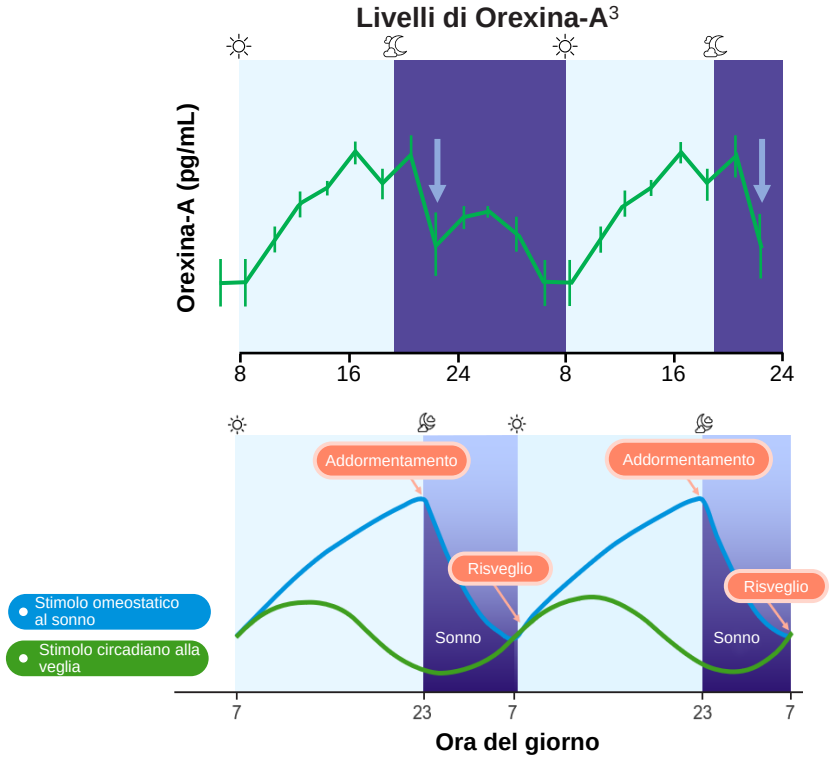


Figura adattata da Tsujino N & Sakurai T. *Front Behav Neuroscience* 2013 [1]

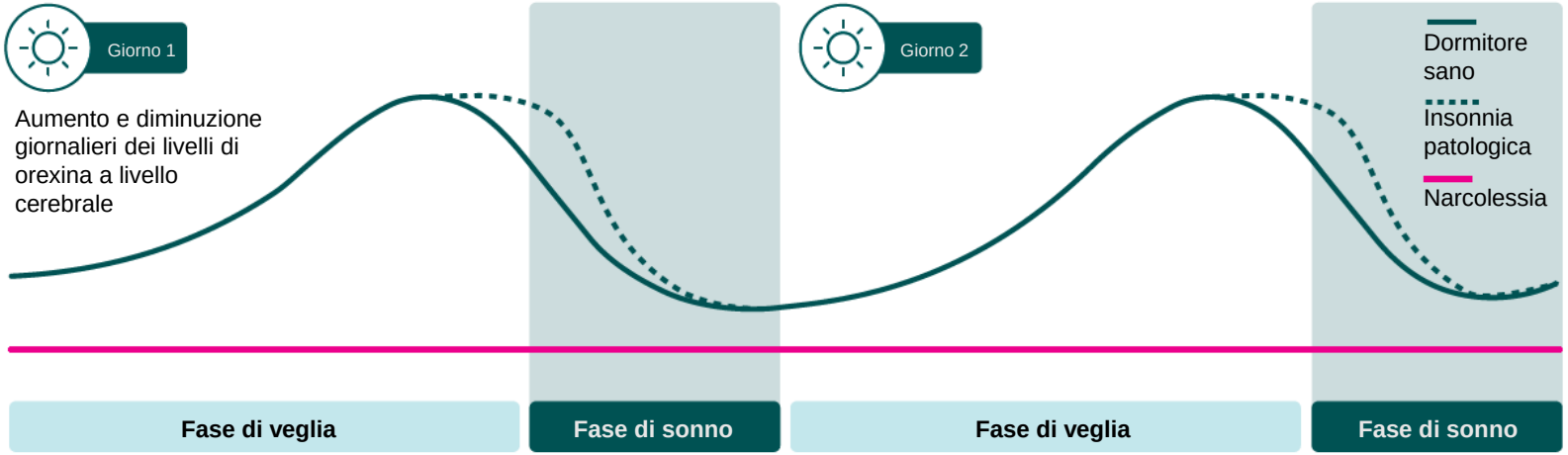
Livelli di Orexina-A[3]



Concentrazioni di Orexina-A valutate nel liquido cerebrospinale cisternale di scimmia scoiattolo, un primate che vive in America meridionale con pattern sonno-veglia simili all'uomo.

1. Tsujino N, Sakurai T. *Front Behav Neurosci* 2013;7:28; 2. Saper CB, *et al. Nature* 2005;437:1257-63; 3. Zeitzer JM, *et al. J Neurosci* 2003;23:3555-60.

L'insonnia può derivare dal rilascio prolungato di orexina, che prolunga la veglia notturna[1] (iperarousal)



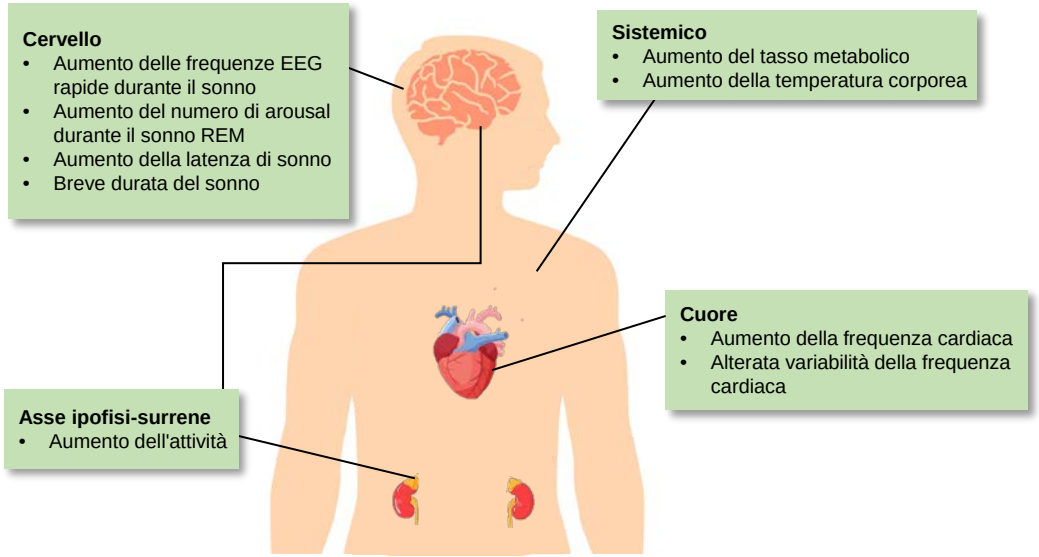
- L'**iperarousal** notturno può portare a disturbi del sonno e a compromissione del funzionamento diurno[2]

1. Sun Y, *et al. Front Neurol Neurosci* 2021;45:22-37; 2. Levenson JC, *et al. Chest* 2015;147:1179-92.

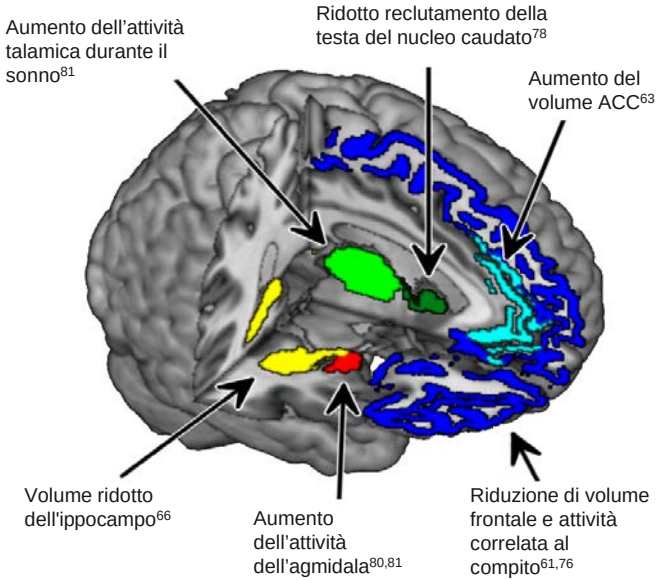
Il ciclo perpetuo dell'insonnia

Una spirale negativa di insufficiente adattamento notturno all'angoscia, con conseguente accumulo di iperarousal, che a sua volta ostacola un sonno ristoratore

Segni distintivi dell'iperarousal



Iperattivazione dello stress e dei sistemi infiammatori[1]



Neurobiologia dell'iperarousal[2]

Immagine ripresa da Lancet Neurology, Vol. 14, Riemann D, et al. The neurobiology, investigation, and treatment of chronic insomnia, 547-558. Copyright 2015, con il permesso di Elsevier. Ristampato da The Lancet, Vol 14, Riemann D, et al. The neurobiology, investigation, and treatment of chronic insomnia, 547-558. Copyright 2015, con autorizzazione di Elsevier.

Figura adattata da Morin CM, et al. *Nat Rev Dis Primers* 2015[1]

ACC,corteccia cingolata anteriore; EEG, elettroencefalogramma; REM, movimenti oculari rapidi.

1. Morin CM, et al. *Nat Rev Dis Primers* 2015;1:15026; 2. Riemann D, et al. *Lancet Neurol* 2015;14:547-58.

Promozione del sonno attraverso il sistema dell'orexina

“Discovery and development of orexin receptor antagonists and therapeutics for insomnia”

Winrow CJ e Renger JJ. Br J Pharmacol 2014

"L'identificazione dei neuropeptidi orexinici e del loro coinvolgimento nella regolazione degli stati sonno/veglia ha stimolato lo sviluppo farmaceutico di nuovi trattamenti mirati per l'insonnia. L'osservazione in modelli animali secondo cui la perdita funzionale dell'attività orexinergica era associata a un aumento della sonnolenza e a una veglia frammentata ha portato all'idea che il blocco farmacologico dei recettori dell'orexina potesse essere in grado di affrontare una causa sottostante dell'insonnia."

Winrow CJ, Renger JJ. *Br J Pharmacol* 2014;171:283-93.

Table 1. Brief profiles of the main orexin receptor antagonists.

Drug	Type	Half-life, hours	Side effects*	Approved	WASO	TST	Sleep latency
Almorexant	DORA	8	somnolence, dizziness, diplopia, attention deficit, fatigue	not approved, concerns on hepatic safety	↓	↑	↓
Suvorexant	DORA	12	somnolence, headache	USA, Japan	↓	↑	↓
Lemborexant	DORA	17-19	somnolence, fatigue, headache, abnormal dreams	USA, Canada, Australia, Japan	↓	↑	↓
Daridorexant	DORA	8	headache, somnolence, fatigue	USA, EU	↓	↑	↓
Vornorexant (TS-142)	DORA	1.3-3.3		not approved	↓	↑	↓
JNJ-48816274	OX2R SORA	1	somnolence, abnormal dreams	not approved	↓	↑	↓
Seltorexant (JNJ-42847922)	OX2R SORA	2-3	somnolence, fatigue, dizziness, headache, abdominal discomfort, and nightmares	not approved	↓	↑	↓

*Possible narcoleptic-like symptoms, potentially for all agents, at high doses. SORA = selective orexin receptor antagonist; DORA = dual orexin receptor antagonist; WASO = wakefulness after sleep onset; TST = total sleep time.

Mogavero et al. - Targeting Orexin Receptors for the Treatment of Insomnia – submitted

Table 2. Clinical practice recommendations.

- Considering that one of the major critical issues in the treatment of patients with insomnia is drug resistance, the orexin receptor antagonists seem to open up important therapeutic perspectives, as they do not seem to cause addiction or rebound effects and seem to balance the arousal system.
- DORA agents showed good tolerance, even in the long term, without alterations in the polysomnographic parameters, a fundamental fact in the treatment of a chronic disorder such as insomnia, often associated to other comorbid conditions.
- Some orexin receptor antagonists have shown good efficacy and tolerance in both sexes, in adults, elderly and adolescents, an important fact in consideration of the groups and categories of patients most affected by the disorder and the fragility of some of them.
- An important aspect in the management of patients with insomnia is the consideration of the different phenotypes of the disease; at the moment, some DORA have been shown to be particularly effective in postmenopausal women, many have shown that they do not negatively impact respiratory parameters (with positive implications in patients with comorbid insomnia and sleep apnea syndrome); this implies a potentially wide therapeutic field of utilization.

Table 3. Future research agenda.

- Further studies are needed for a better stratification of patients to be treated with certain types of DORA or SORA agents (insomnia in menopausal women, comorbidity with psychiatric disorders, headache, epilepsy, and neurodegenerative disorders or cancer).
- Further studies in patients with comorbid insomnia and sleep apnea syndrome are needed for a better definition of their interaction and the role of orexins.
- Considering the absence of rebound and addictive effects, the use of DORA and SORA agents should be defined in special protocols for detoxifying from other drug abuse in patients with insomnia.
- Further randomized controlled trials in children and adolescents should be encouraged.
- Additional clinical and laboratory data on the use of SORA agents are needed.
- Studies on interactions and comparison with other drugs used in the clinical practice for the treatment of insomnia are recommended.

Mogavero et al. - Targeting Orexin Receptors for the Treatment of Insomnia – submitted

iNsight day

A deep sight on

Chronic iNsomnia