

CME



CAST

EPISODE 2

Navigating the Neurophysiology of Sleep and Cataplexy: The Significance of Select Neurotransmitters

*Supported by an educational grant from
Harmony Biosciences*



Michael J. Thorpy, MD

Professor of Neurology

Albert Einstein College of Medicine

Director, Sleep-Wake Disorders Center

Department of Neurology

Montefiore Medical Center

Bronx, NY

President, New York State Society of Sleep Medicine

Past President of the Sleep Section, Academy of Neurology



Phyllis Zee, MD, PhD

Professor of Neurology

Chief, Division of Sleep Medicine in Department of Neurology

Director, Center for Circadian and Sleep Medicine

Northwestern University

Feinberg School of Medicine

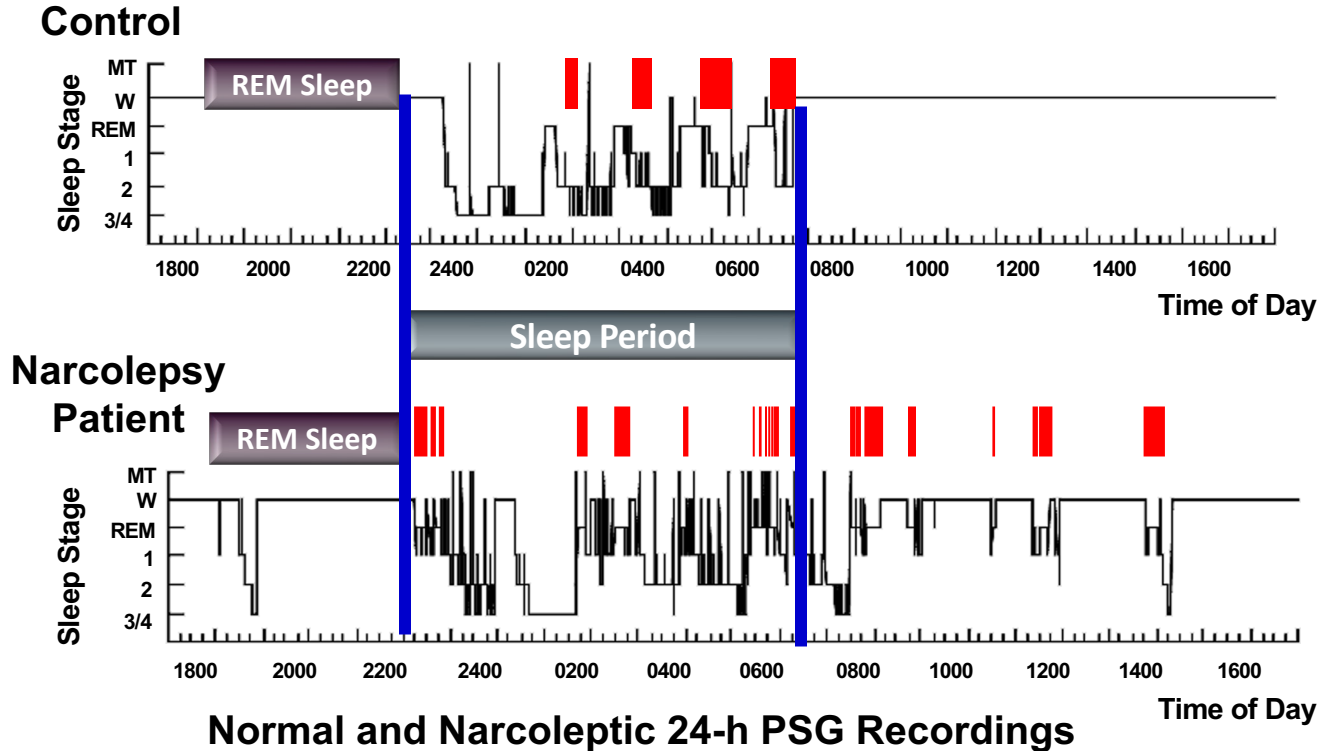
Chicago, IL



Learning Objective

Differentiate the neurotransmitters involved in cataplexy and the sleep-wake cycle, including their differential impact on wakefulness.

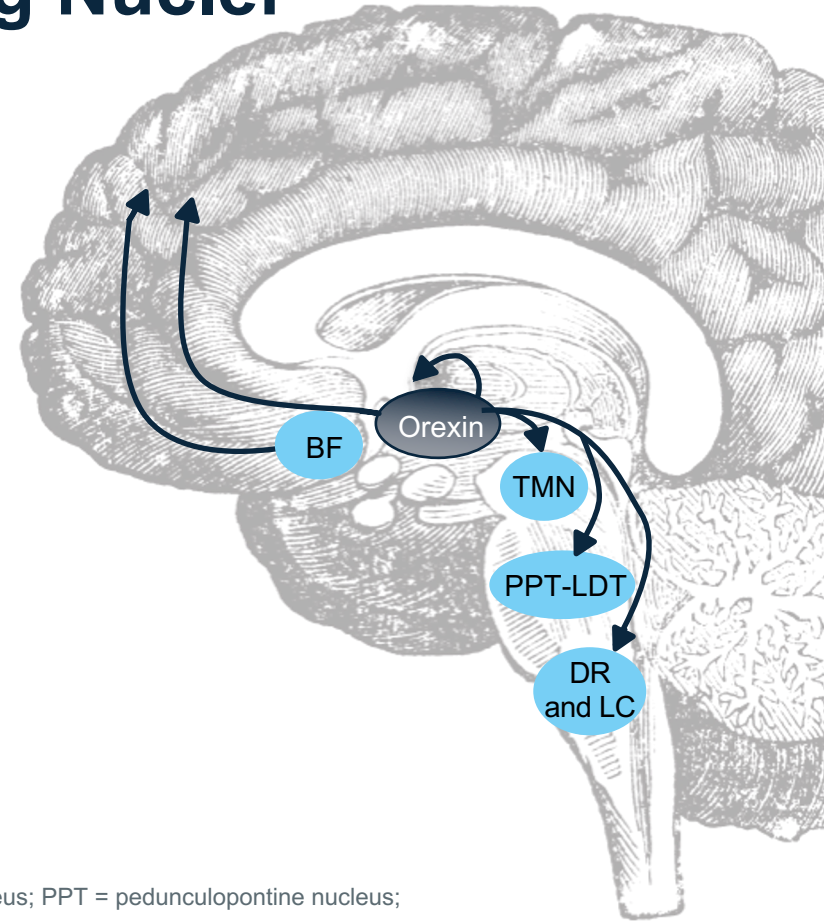
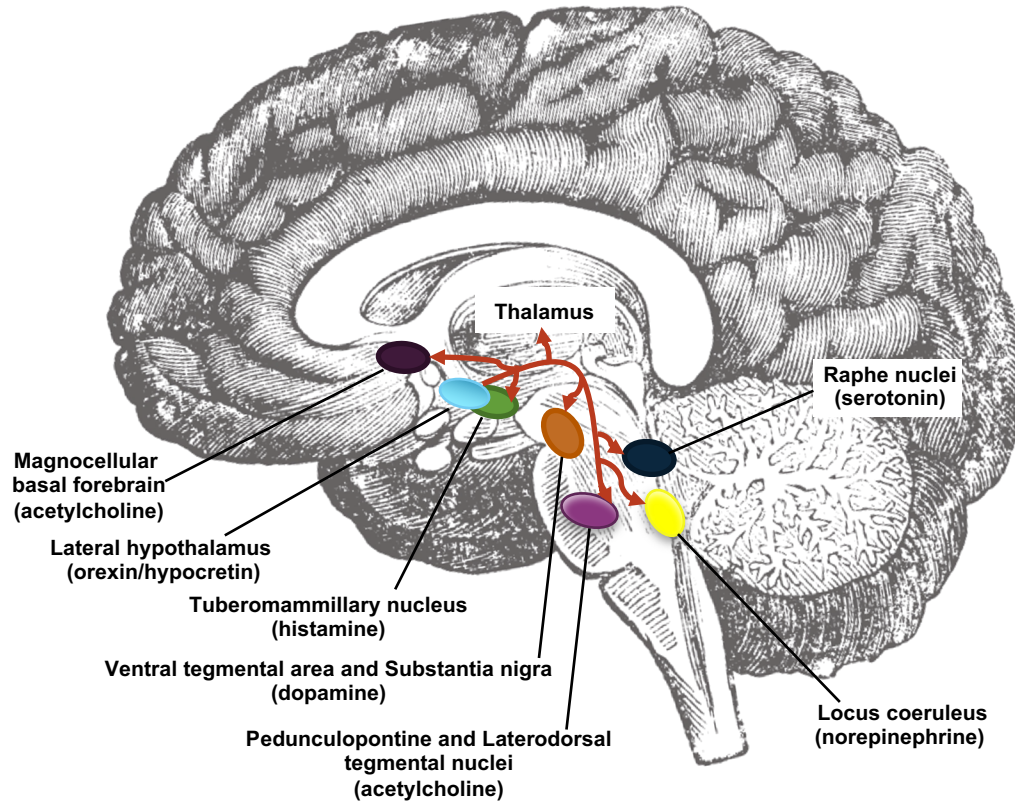
Dynamic Cycles of Wake and Sleep



PSG = polysomnography; REM = rapid eye movement

Adapted from Rogers AE, et al. *Sleep*. 1994;17:590-587.

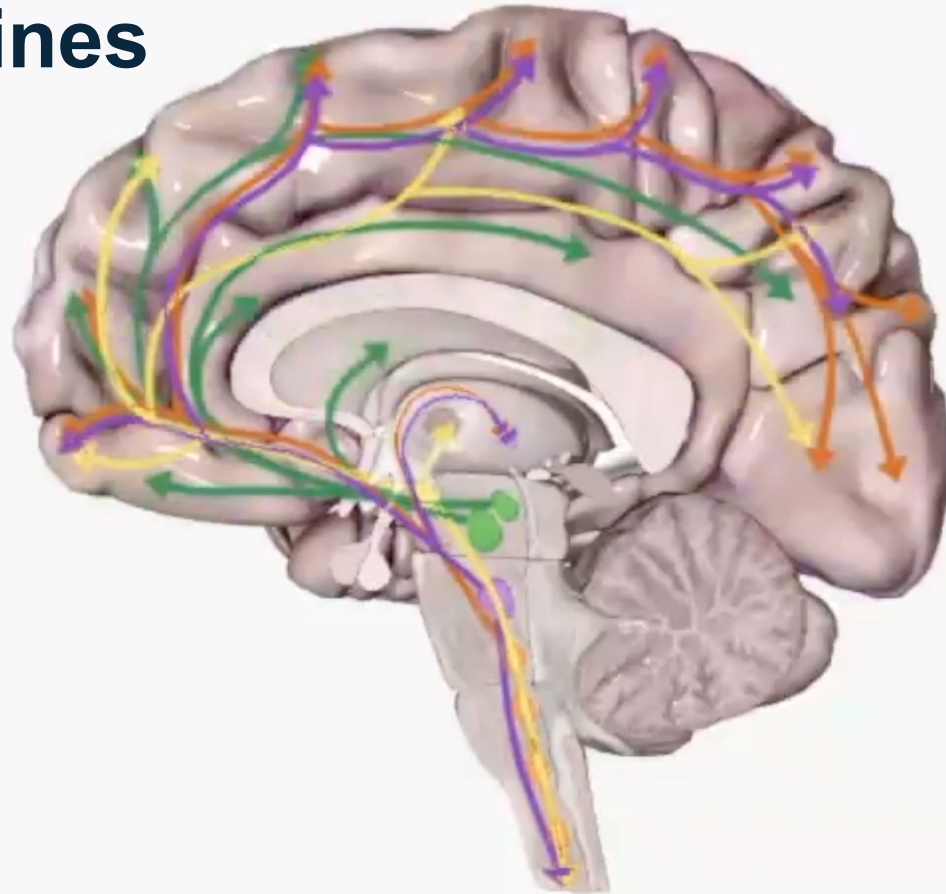
Wake Promoting Nuclei







BF = basal forebrain; DR = dorsal raphe; LC = locus coeruleus; LDT = laterodorsal tegmental nucleus; PPT = pedunculopontine nucleus; TMN = tuberomammillary nucleus

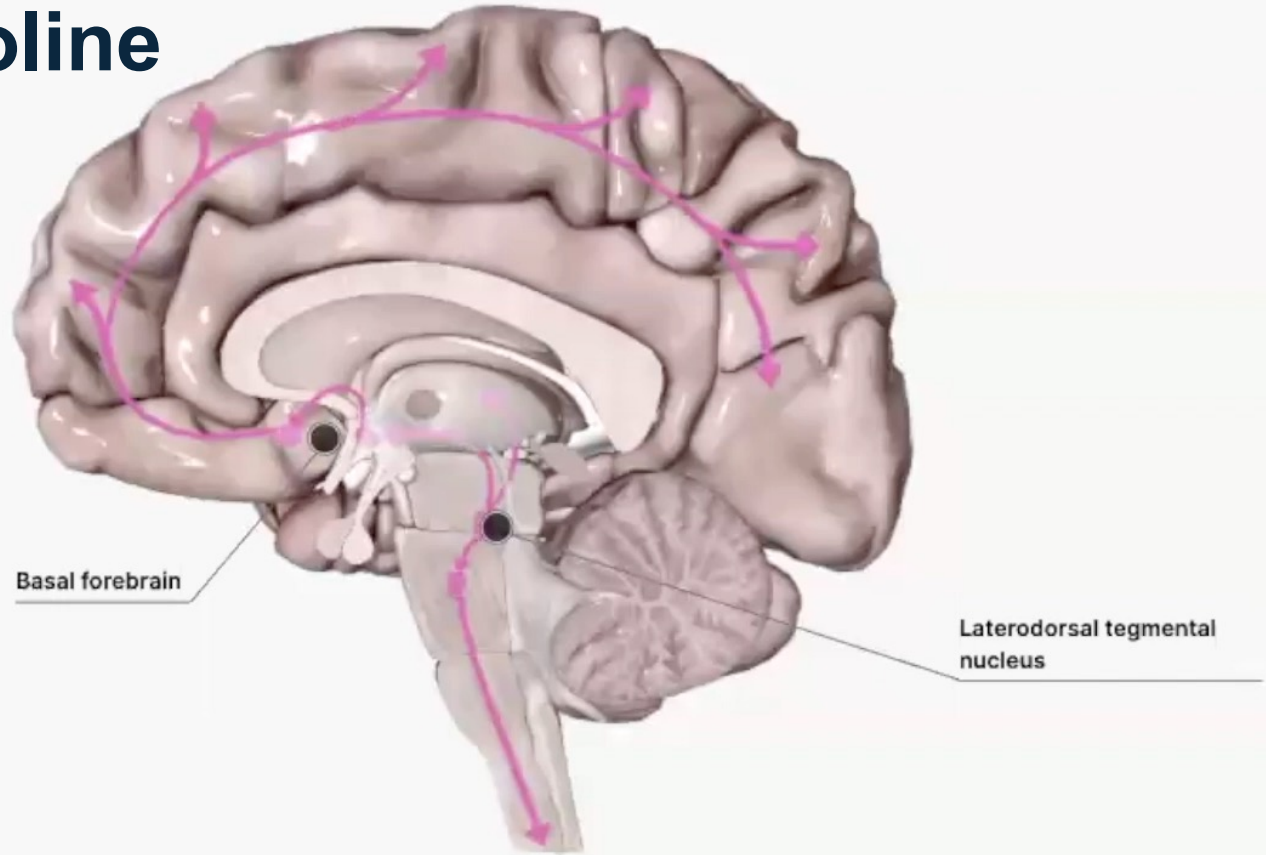
Silber MH, et al. *Neurology*. 2001;56:1616-1618. Mahoney CE, et al. *Nat Rev Neurosci*. 2019; 20(2):83-93.

Wake-Promoting Neurotransmitters - Monoamines

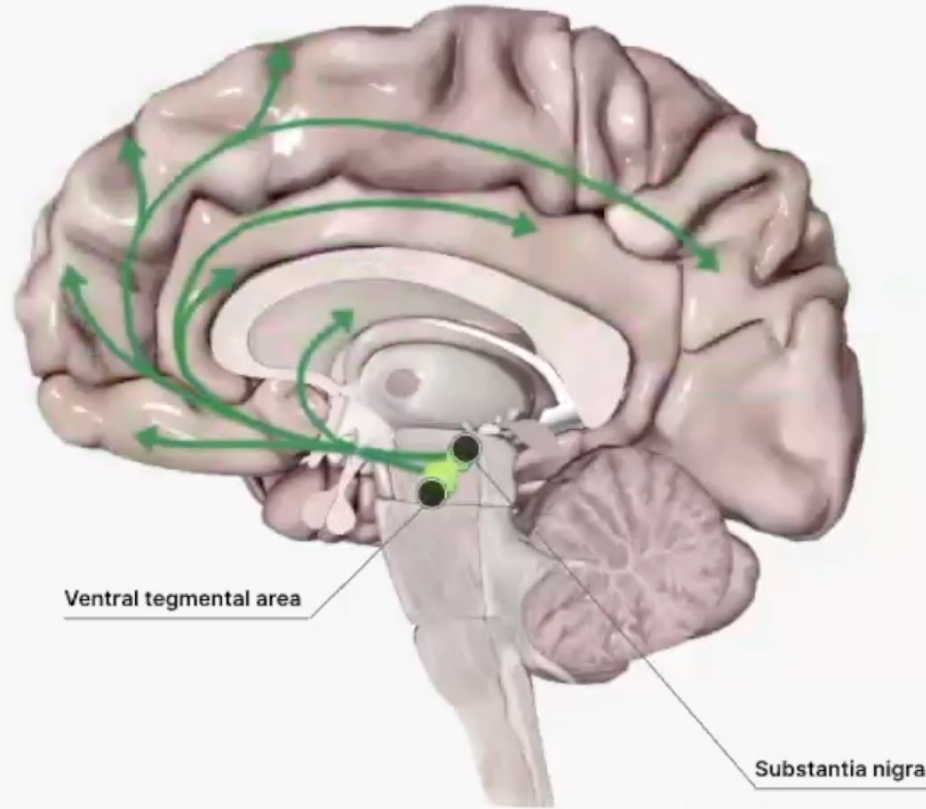


-  = Dopamine
-  = Histamine
-  = Norepinephrine
-  = Serotonin

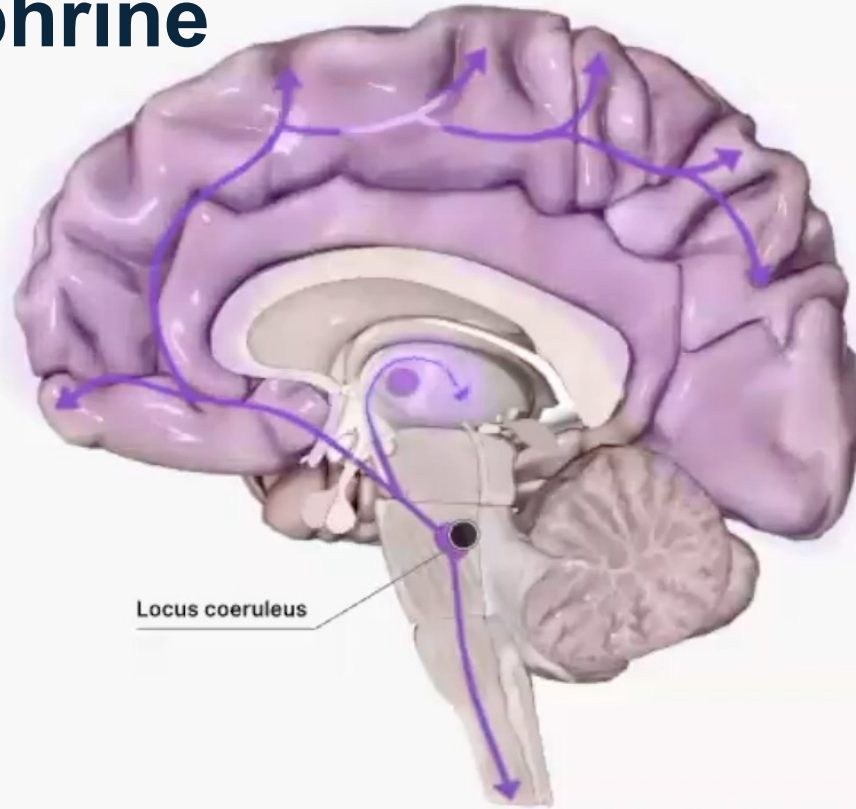
Wake-Promoting Neurotransmitters - Acetylcholine



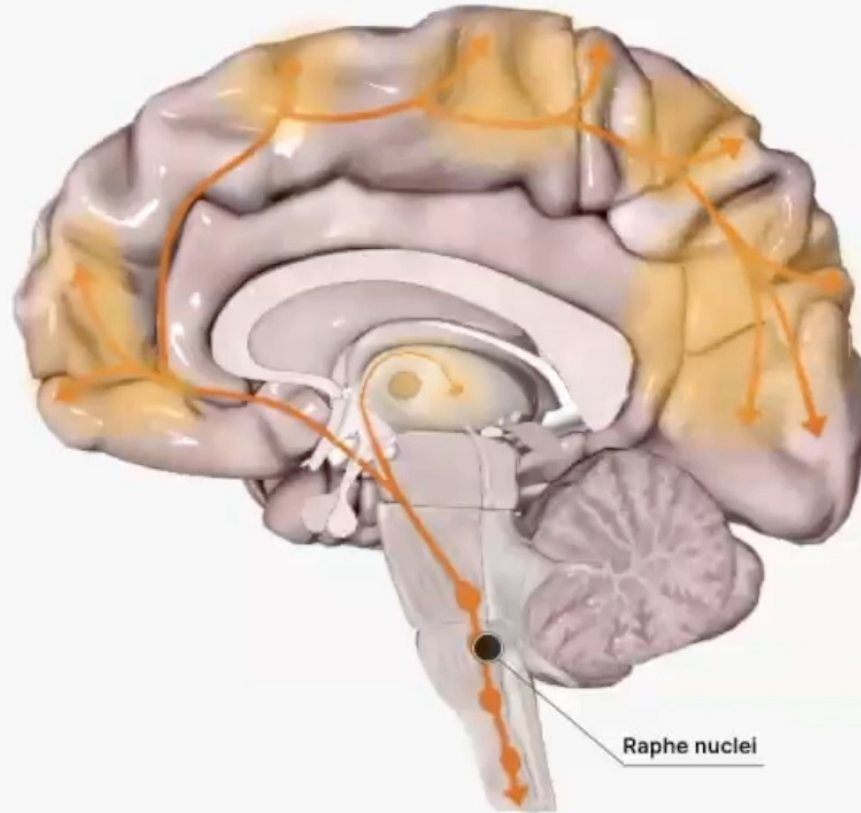
Wake-Promoting Neurotransmitters - Dopamine



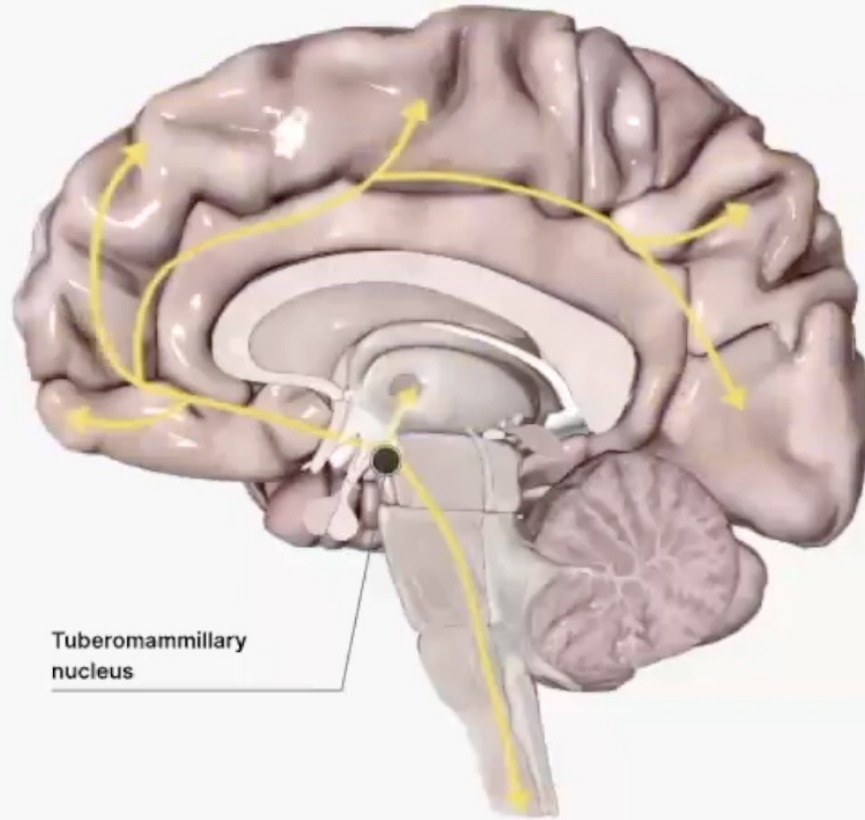
Wake-Promoting Neurotransmitters - Norepinephrine



Wake-Promoting Neurotransmitters - Serotonin

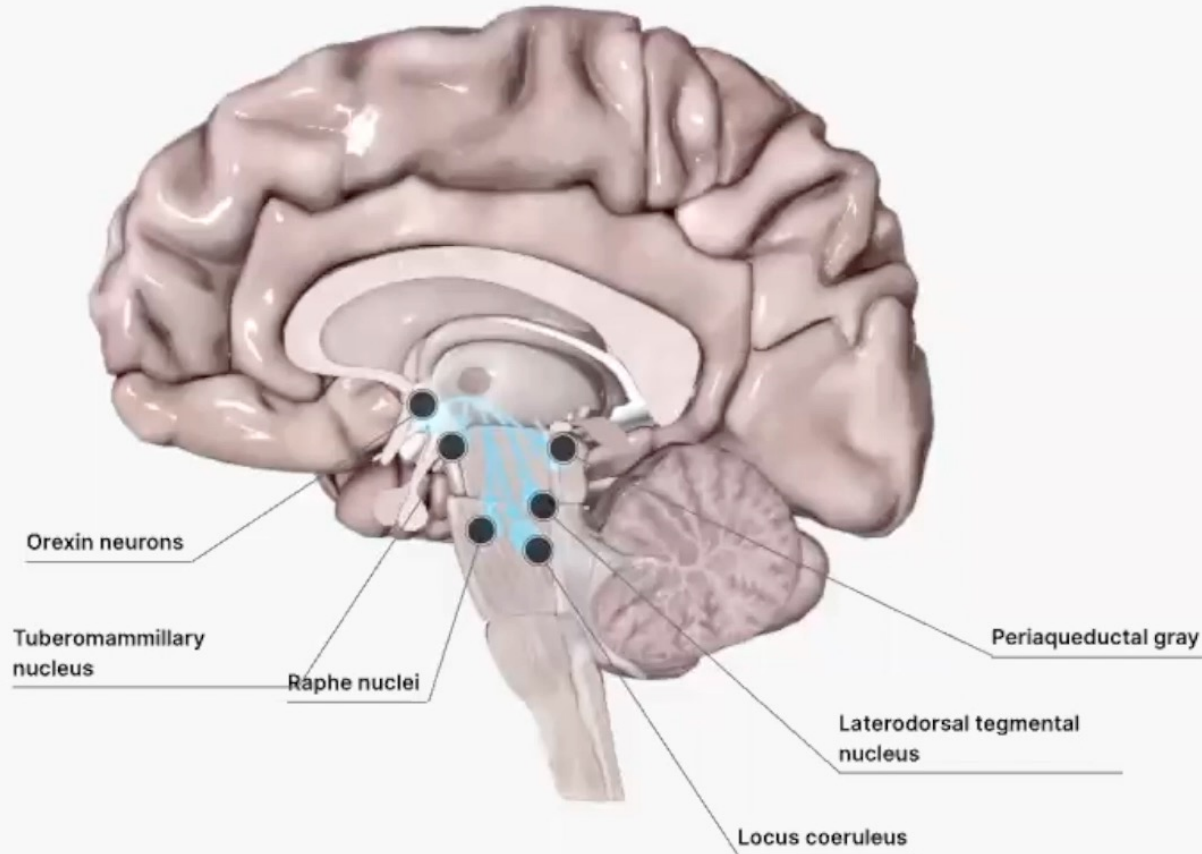


Wake-Promoting Neurotransmitters - Histamine



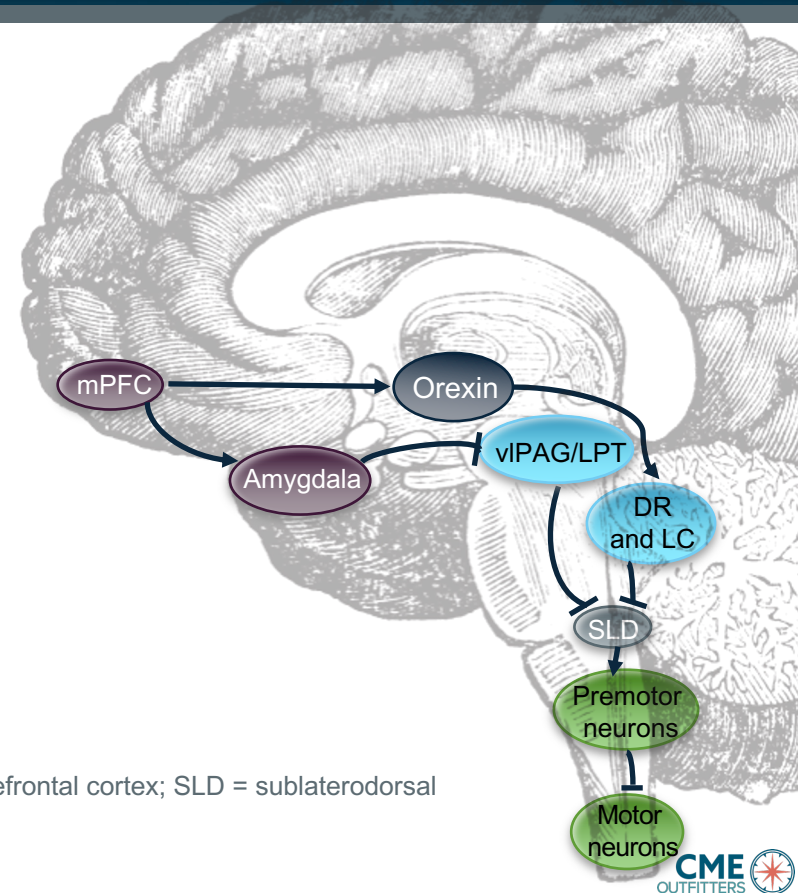
Tuberomammillary
nucleus

Wake-Promoting Neurotransmitters - Orexin



Narcolepsy: REM and REM Atonia

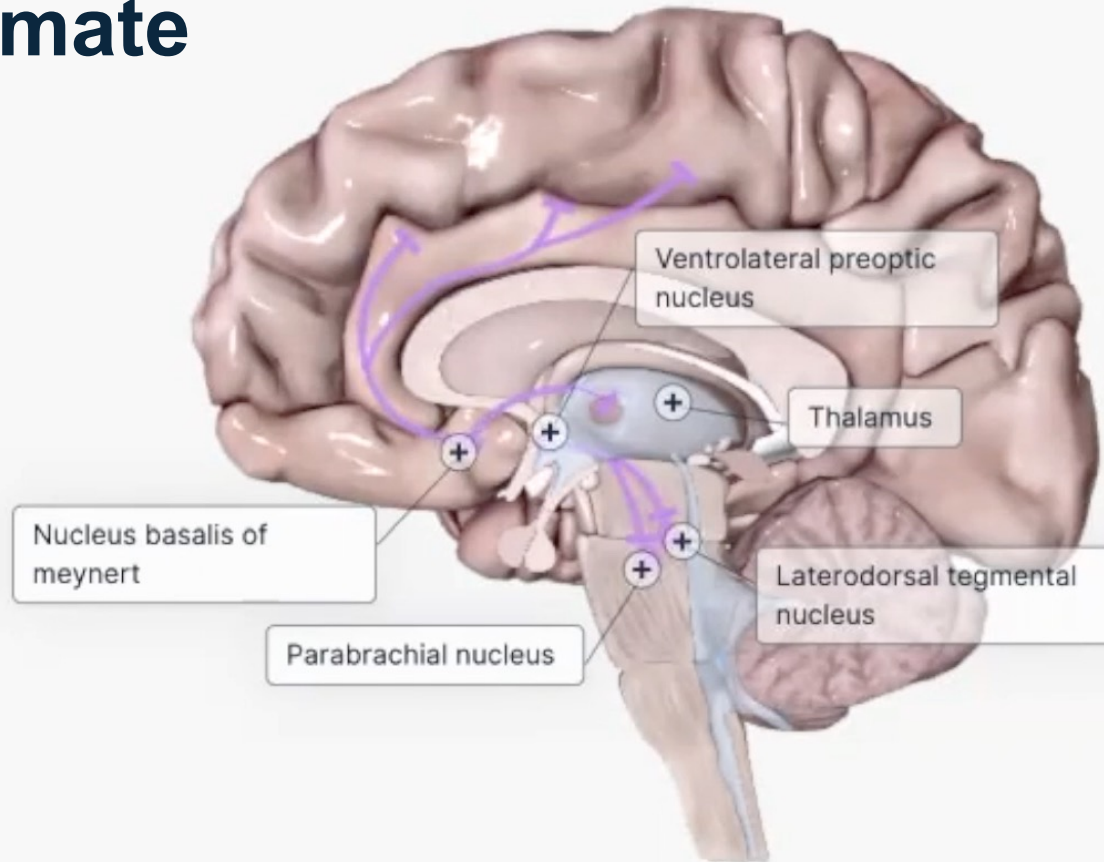
- In wake, orexin neurons excite GABA neurons in **vIPAG/LPT** and **DR/LC**
- These **neurons** thereby inhibit the SLD and REM sleep
- Emotions from the **mPFC** activate orexin neurons and GABA neurons in the **amygdala**, which weakly oppose the inhibition of SLD (via **blue** neurons)
- SLD drives muscle paralysis through GABA inhibition or **premotor neurons**



GABA = gamma amino-butyric acid; LPT = lateral pontine tegmentum; mPFC = medial prefrontal cortex; SLD = sublateralodorsal nucleus (glutamate); vIPAG = ventrolateral periaqueductal grey

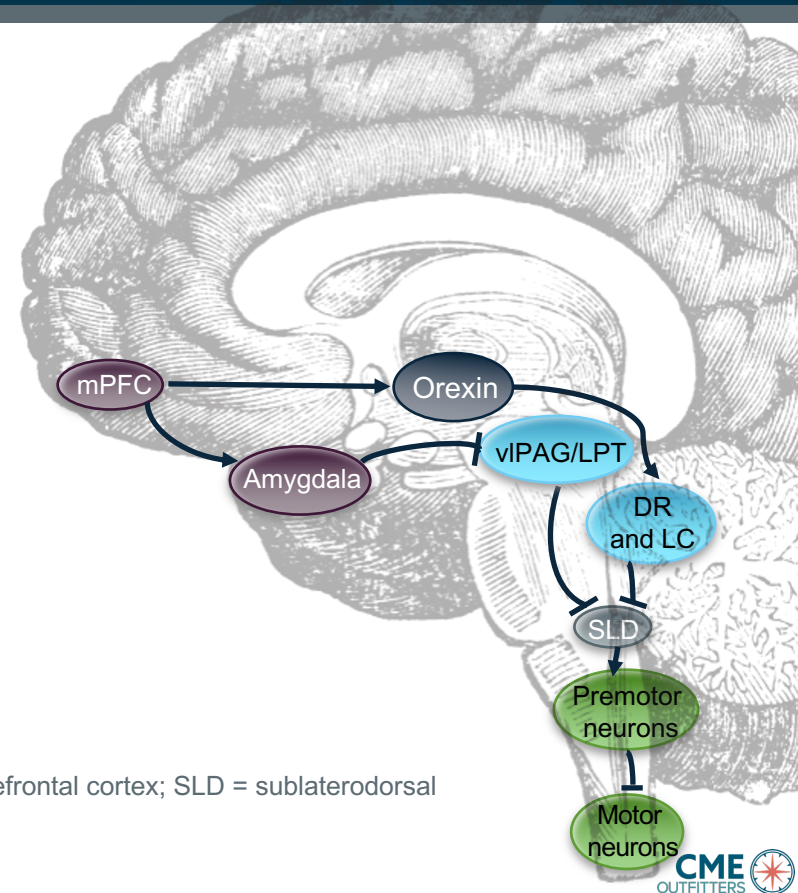
Mahoney CE, et al. *Nat Rev Neurosci.* 2019;20:83-93.

Wake-Promoting Neurotransmitters - Glutamate



Narcolepsy: REM and REM Atonia

- In wake, orexin neurons excite GABA neurons in **vIPAG/LPT** and **DR/LC**
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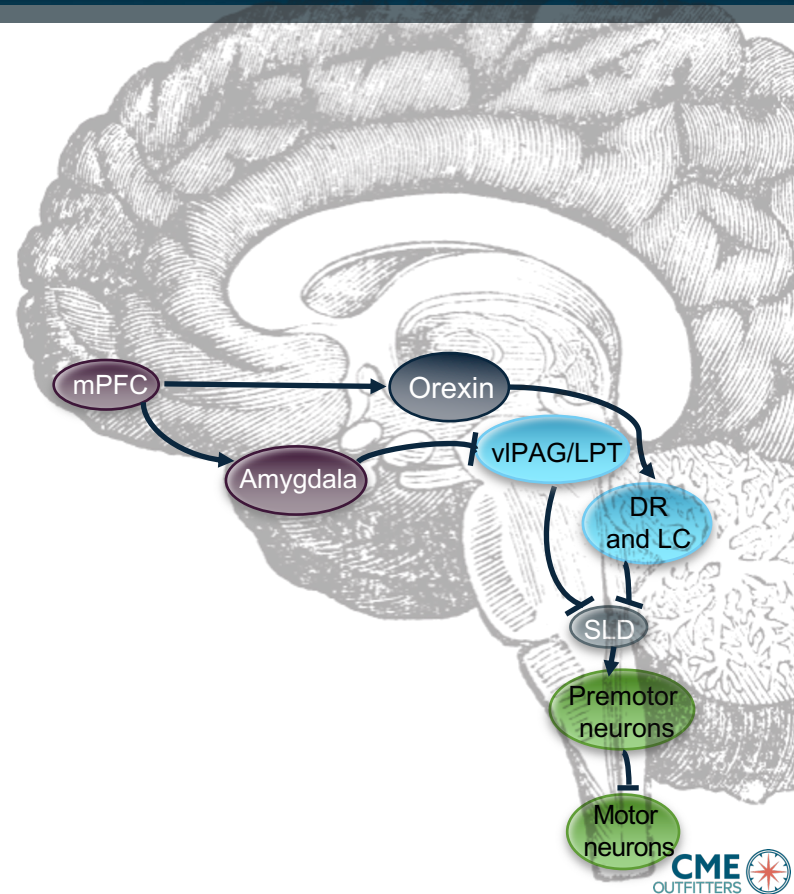


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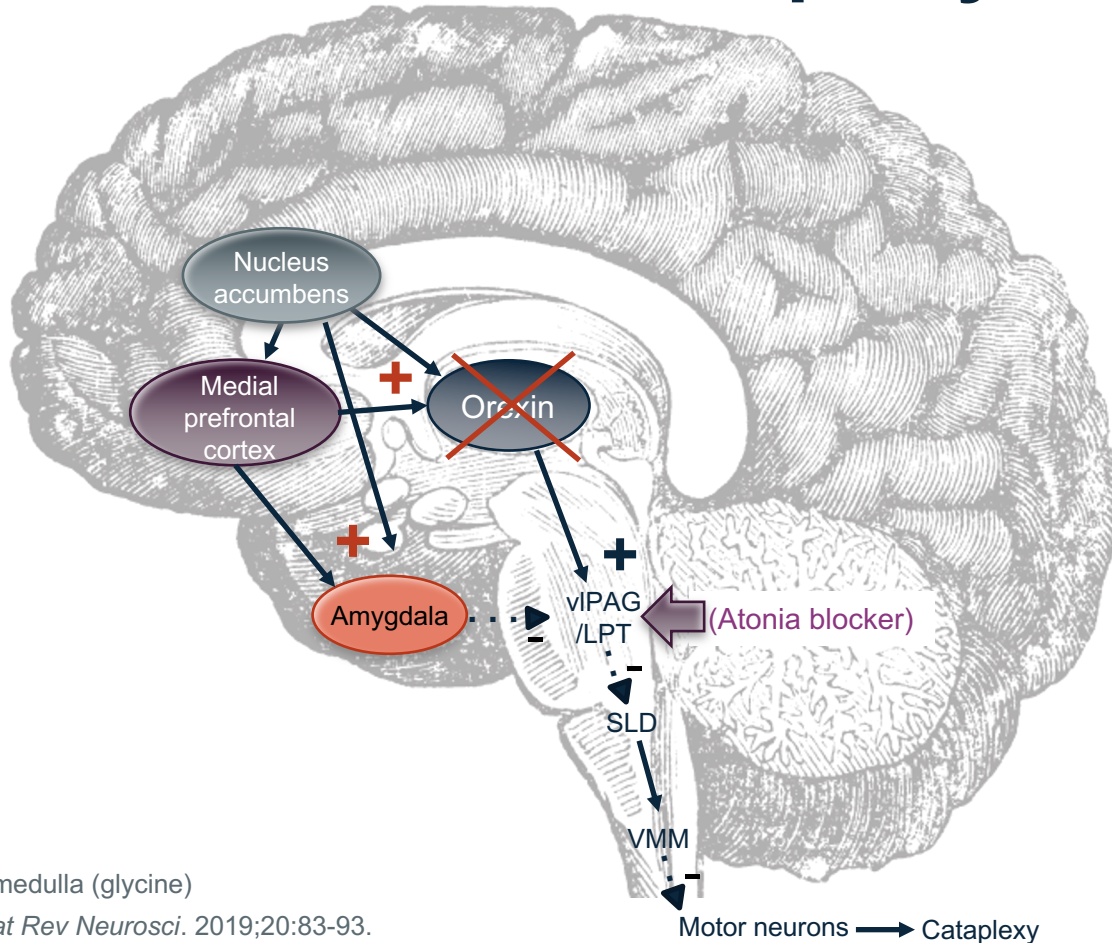
Mahoney CE, et al. *Nat Rev Neurosci.* 2019;20:83-93.

Narcolepsy: Expression of Symptoms

- Lack of orexin neurons reduce activity of **vIPAG/LPT** and **DR/LC**
- Emotions via the **amygdala** strongly inhibit the **vIPAG/LPT**, enabling the SLD, thereby resulting in cataplexy



Proposed Model for Cataplexy

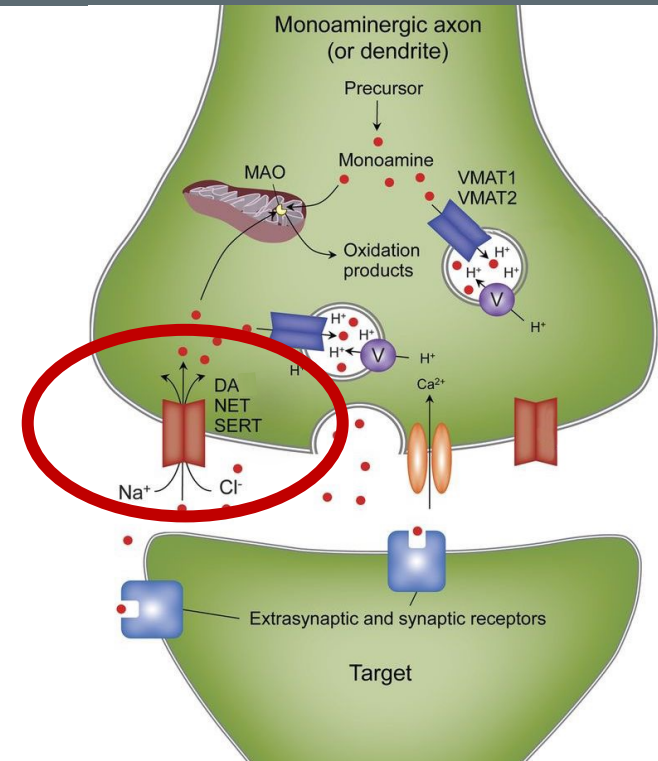


VMM = ventromedial medulla (glycine)

Mahoney CE, et al. *Nat Rev Neurosci.* 2019;20:83-93.

Mechanism of Action and Clinical Impact on EDS: Dopamine, Norepinephrine, Serotonin

- Monoaminergic neurons:
 - generally high rates of firing during wake (especially active wake), slow firing during NREM sleep, and a virtual cessation of firing during REM sleep
 - High DA tone promotes wakefulness, while low DA tone promotes sleep
 - NE is key in arousal and maintaining normal sleep states
 - Serotonin precursors and reuptake inhibitors promote wakefulness



Ca = calcium; Cl = chlorine; DA = dopamine; MAO = monoamine oxidase; Na = sodium; NE = norepinephrine; NET = norepinephrine transporter; NREM = non-rapid eye movement; SERT = serotonin transporter; VMAT = vesicular monoamine transporter

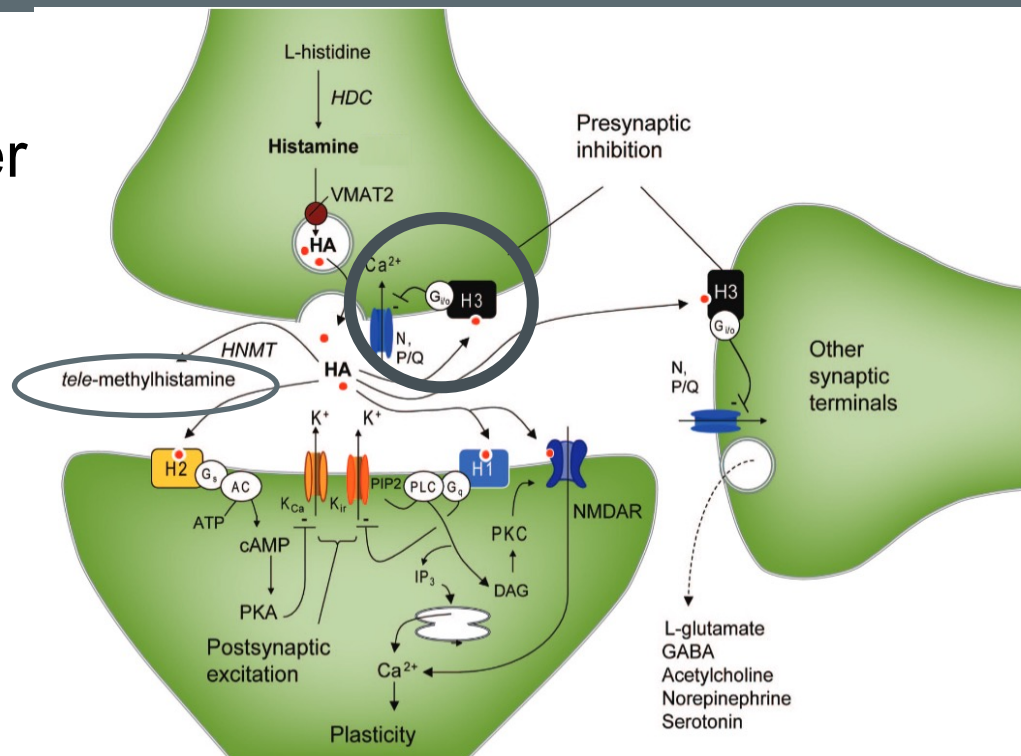
Mechanism of Action and Clinical Impact on EDS and Cataplexy: Histamine

- Histamine is a wake-promoting neurotransmitter
- Histamine neurons promote arousal

↓ Partial cataplexy

↑ REM sleep latency

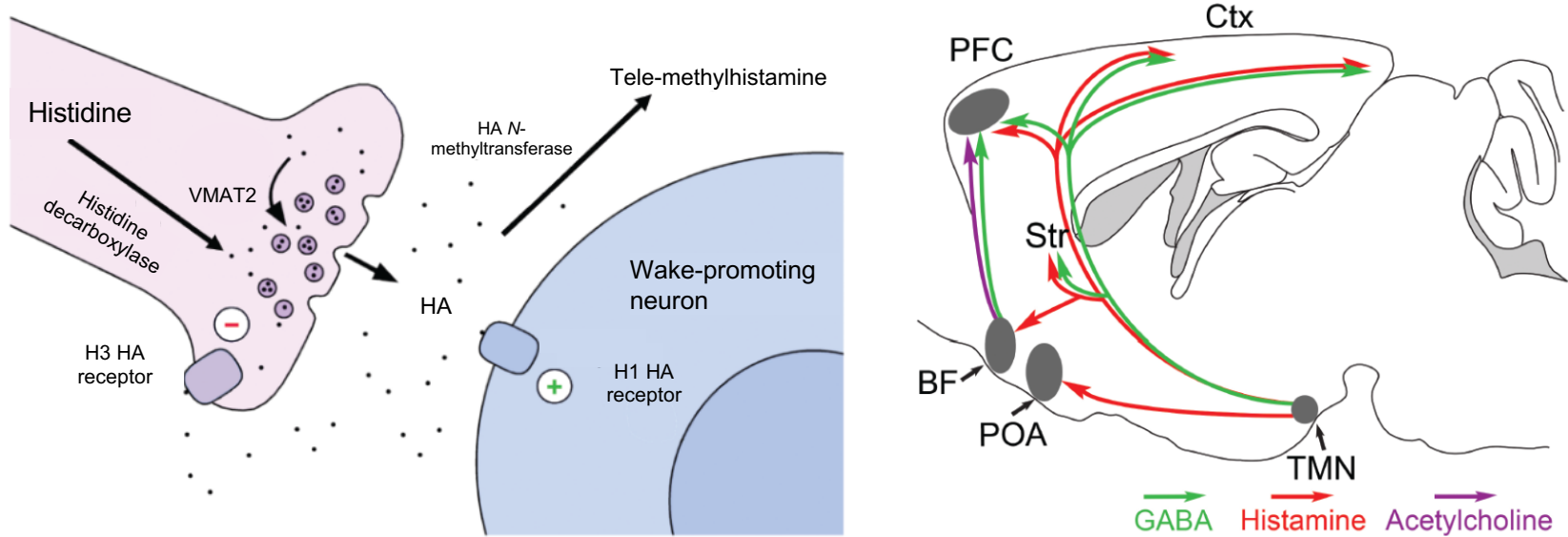
↓ EDS



AC = adenylyl cyclase; ATP = adenosine triphosphate; cAMP = cyclic adenosyl monophosphate; DAG = diacylglycerol; HA = histamine; HDC = histidine-decarboxylase; IP₃ = inositol triphosphate; NMDAR = N-methyl-D-aspartate receptor; PIP2 = phosphatidylinositol biphosphate; PKA = protein kinase A; PKC = protein kinase C

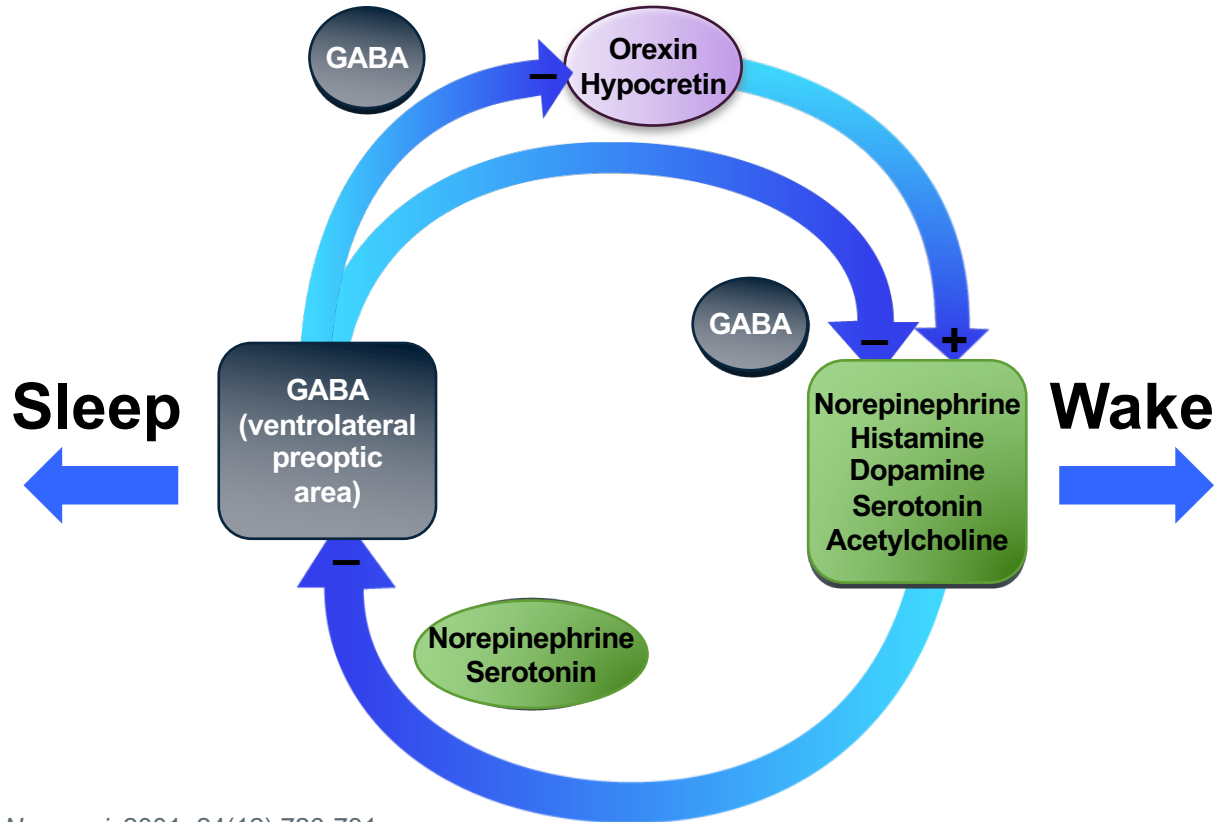
Dauvilliers Y, et al. *Sleep*. 2019;42(11).pii:zsz174. Benarroch EE. *Neurology*. 2013;81(8):761-768.

Role of Histamine in Wake Regulation



Ctx = cyclophosphamide; PFC = prefrontal cortex; POA = preoptic area; Str = striatum
Scammell TE, et al, *Sleep*. 2019; 42(1):zsy183.

Regulation of Wake and Sleep



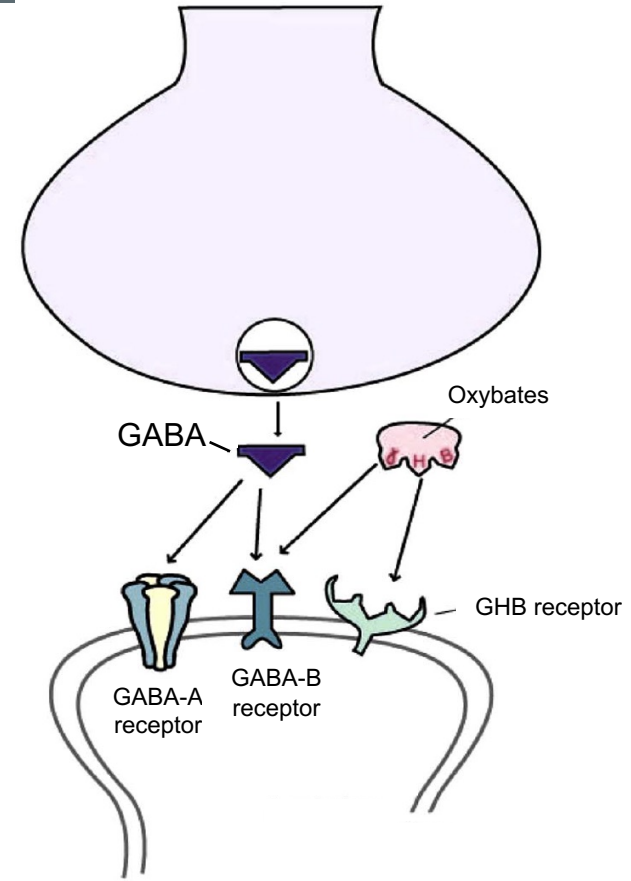
Mechanism of Action and Clinical Impact on EDS and Cataplexy: GABA

- GABA shuts off wake-promoting impact during the sleep-wake cycle
- GABA-B selectivity results in narcolepsy:

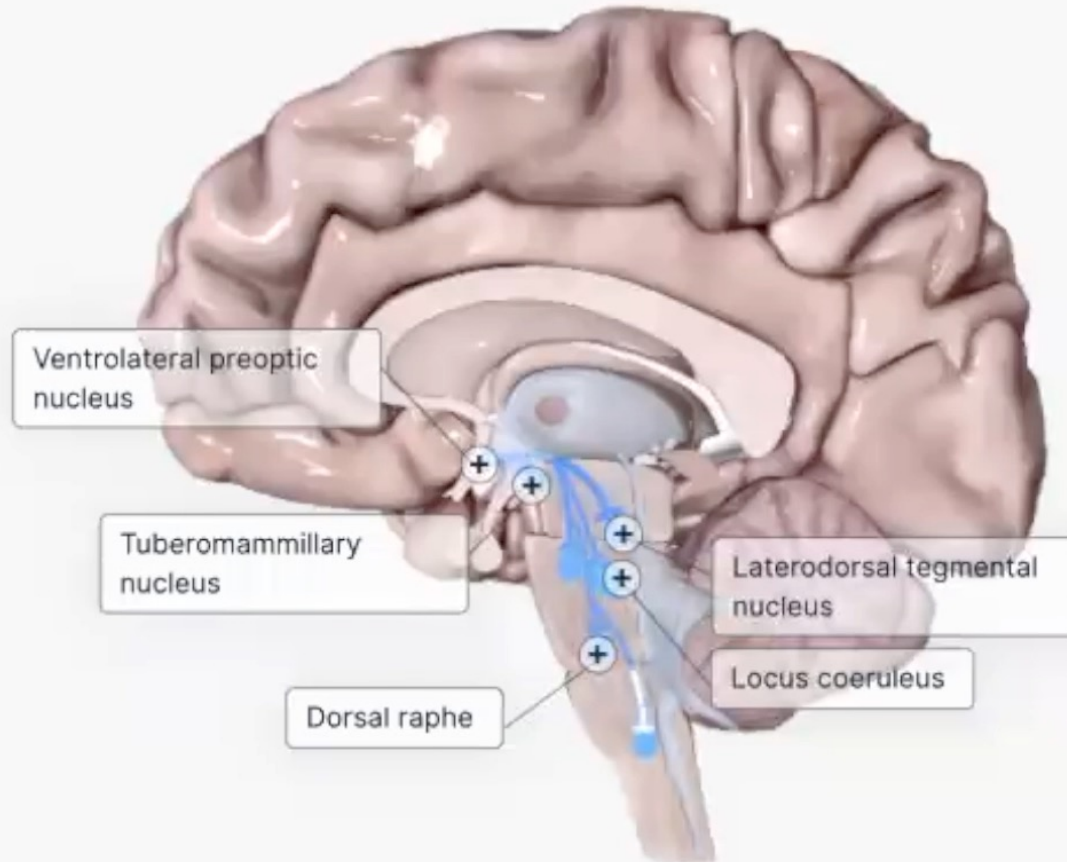
↓ Cataplexy

↑ Slow-wave sleep

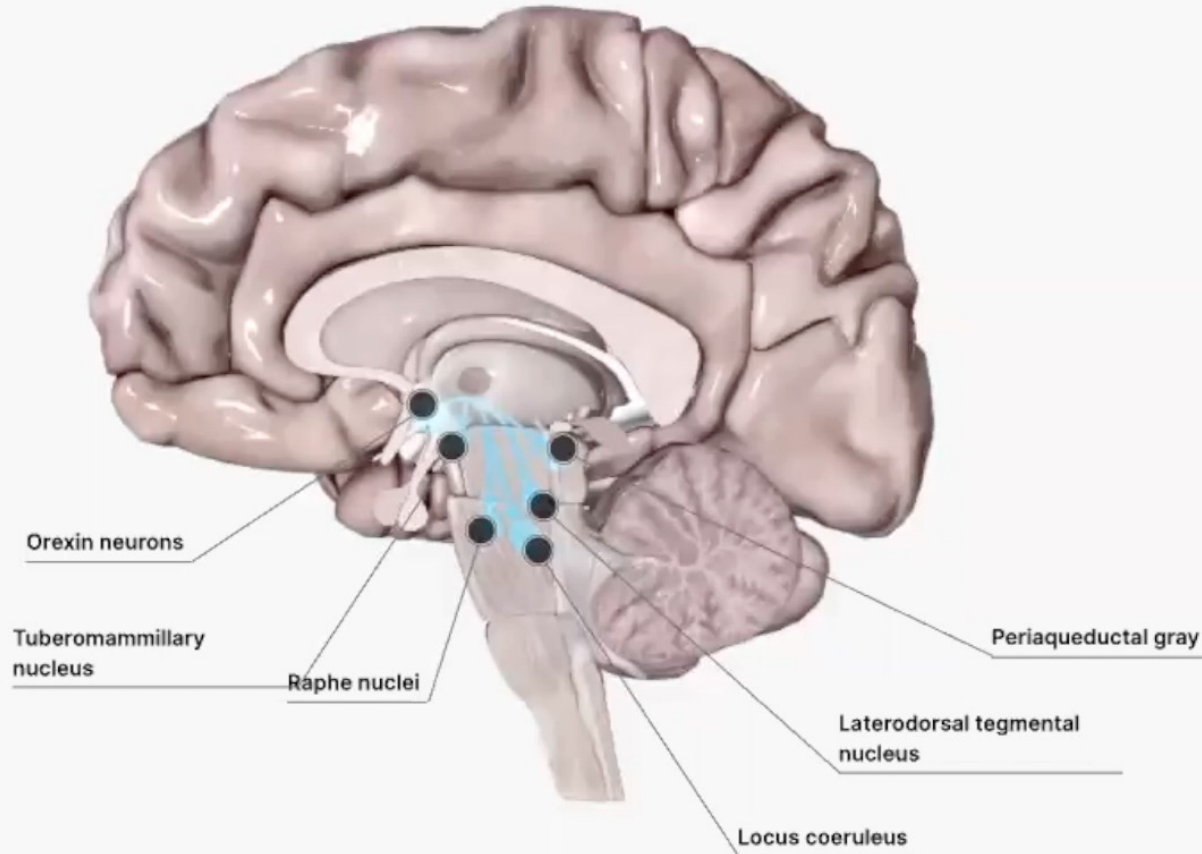
↓ EDS



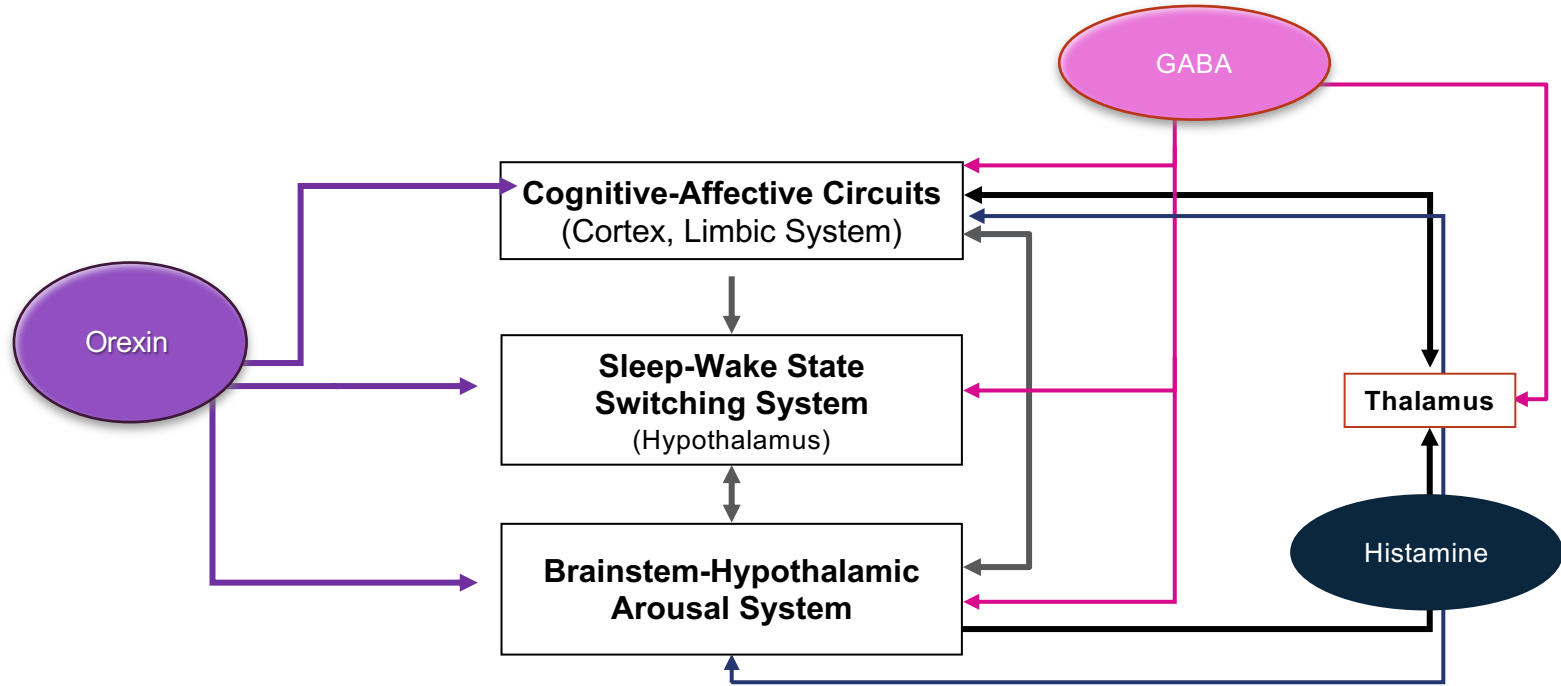
Wake-Promoting Neurotransmitters - GABA



Wake-Promoting Neurotransmitters - Orexin



Conceptual Model of Pharmacologic Approaches



FDA-Approved Treatments for Narcolepsy

Drug	MOA	EDS	Cataplexy	Adults	Children
Modafinil	DA reuptake inhibitor	X		X	
Armodafinil	DA reuptake inhibitor	X		X	
Solriamfetol	DA-NE reuptake inhibitor	X		X	
Pitolisant	Histamine H3 antagonist/inverse agonist	X	X	X	
Sodium oxybate (SXB) / lower sodium oxybate (LXB)	GABA _B agonist	X	X	X	X
Amphetamines / Methylphenidate	Sympathomimetic; enhance DA, NE, serotonin			X	X

Amphetamines and methylphenidate are approved for narcolepsy but not specifically cataplexy or EDS

EDS = excessive daytime sleepiness

Barateau L, et al. *Ther Adv Neurol Disord*. 2019;12:1756286419875622.

Conclusions

- Sleep is a crucial biological process that is regulated through complex interactions between multiple brain regions and neurotransmitters
- Several neurotransmitters are involved in the sleep-wake cycle, including monoamines, GABA, histamine, and orexin
- It is important to understand how targeted therapies impact the sleep-wake cycle in general, but EDS and cataplexy, in particular, in patients with narcolepsy

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Identify key neurotransmitters involved in the sleep-wake cycle
- Recognize how therapies targeted to the key neurotransmitters in the sleep-wake cycle exert their therapeutic effect on EDS in narcolepsy

CME **CAST** EPISODE 1

Addressing the Burden of
Narcolepsy: Residual Symptoms
Are Nothing to Snooze On

CME **CAST** EPISODE 3

Examining the Latest Evidence on EDS and
Cataplexy in Narcolepsy: What are the
Implications for Your Practice?

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