The Orexinergic System in Psychiatry

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07.08.2025

- Orexins or hypocretins - excitatory neuropeptides, discovered in the late 1990s
- The Sakurai group (1998) - “orexins” (OrxA and OrxB), from the Greek word “orexis”, meaning “appetite”, due to their ability to stimulate food intake and control the metabolism
- de Lecea and colleagues (1998) – “hypocretins” (Hcrt1 and Hcrt2) since they are secreted from the hypothalamus and due to their significant amino acid homology with the member of the incretin family, the gut hormone secretin (glucagon/vasoactive intestinal polypeptide/secretin)

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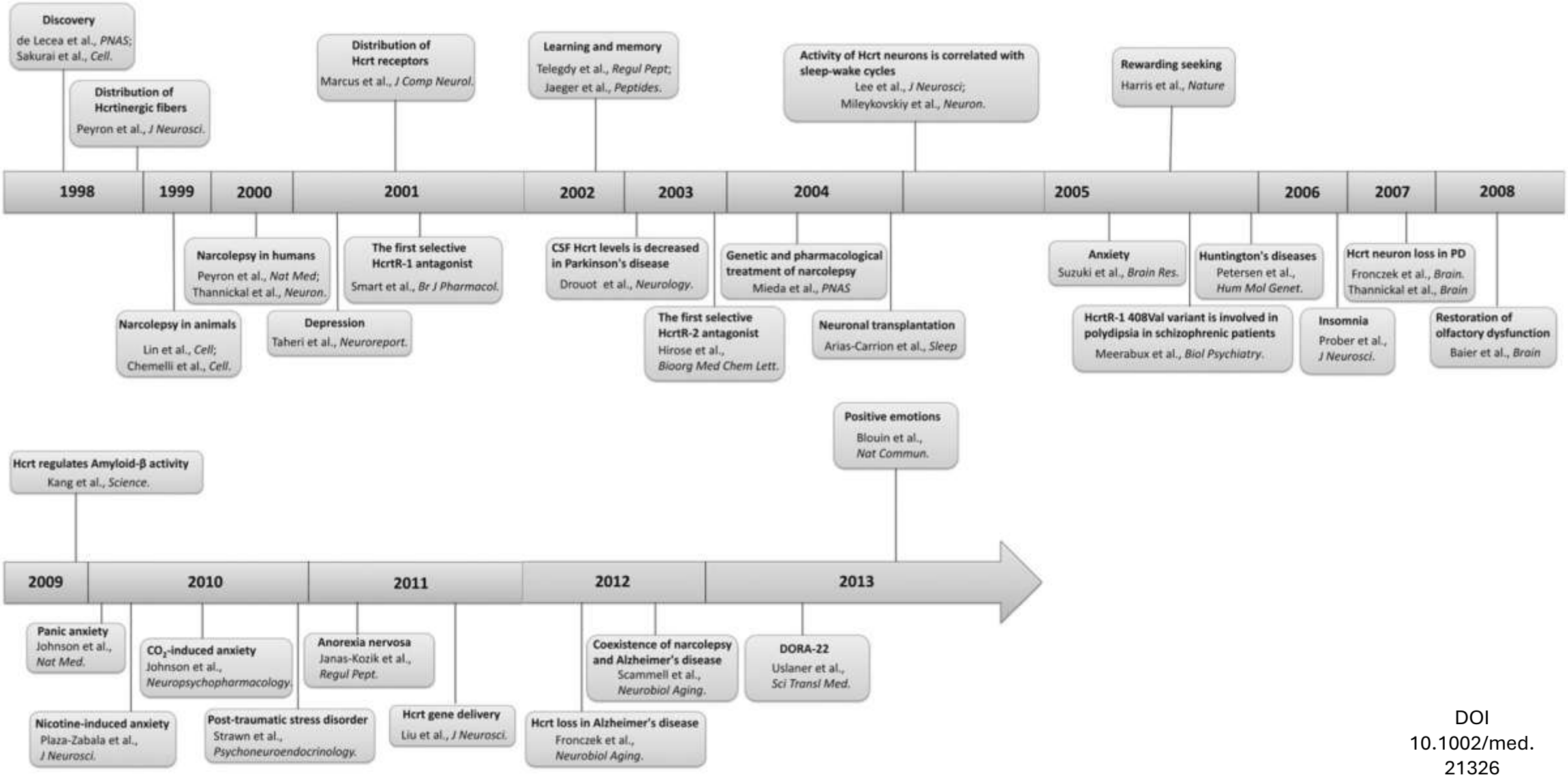

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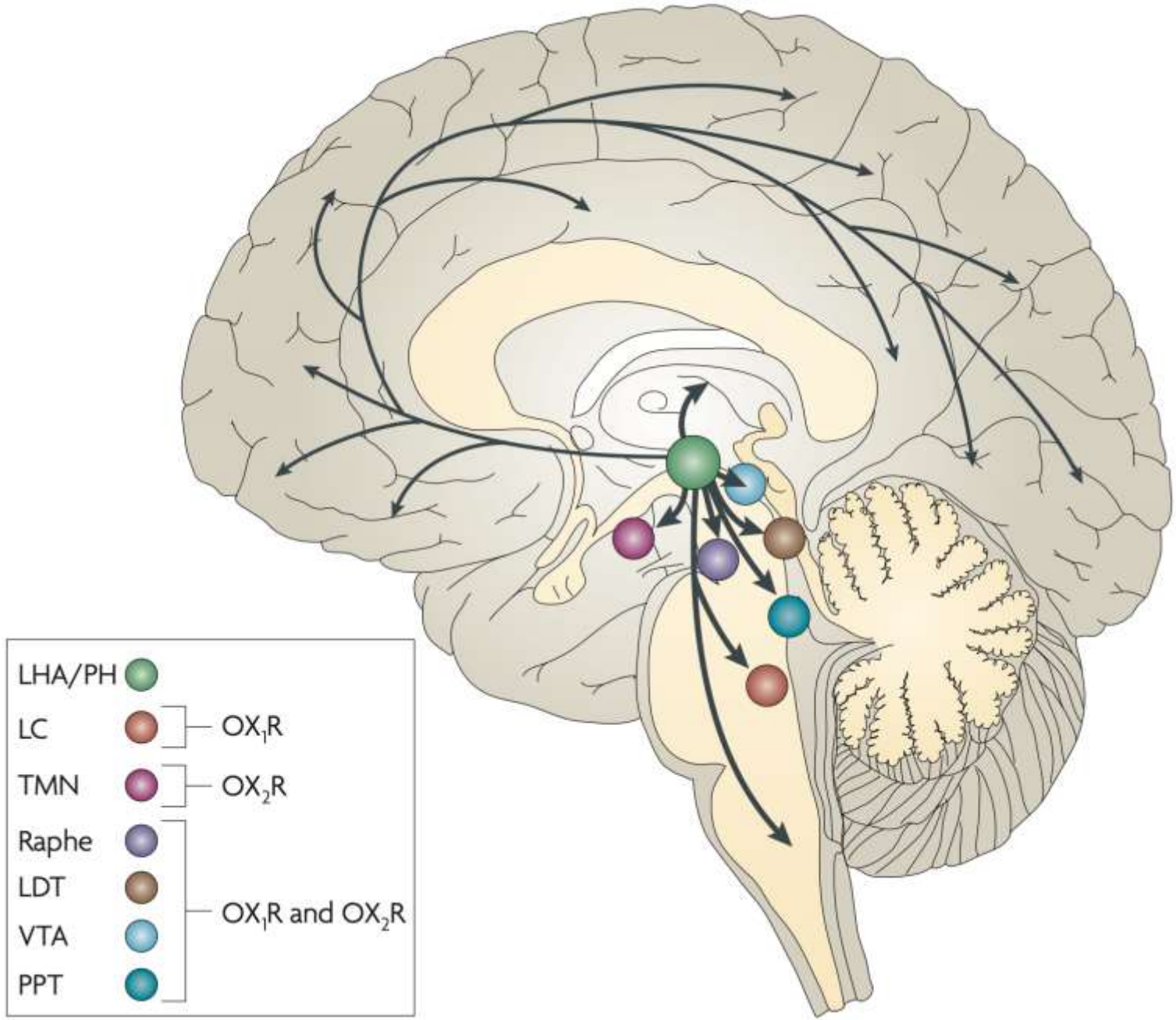
10.1002/med.
21326



doi:10.1038/nrn2092

- Originate in the lateral hypothalamic area (LHA) and posterior hypothalamus (PH)

- Maintenance of arousal
  - Projections to the entire CNS, excluding the cerebellum
  - Dense projections to
    - Locus Coeruleus (LC - NA)
    - Tubero-Mammillary Nucleus (TMN – Histamine)
    - Raphe Nuclei (Raphe - Serotonin)
    - Latero-Dorsal / Pedunculo-Pontine Tegmental nuclei (LDT / PPT - ACh)

- Links with the reward system - VTA

- Links with hypothalamic nuclei that stimulate feeding behaviour

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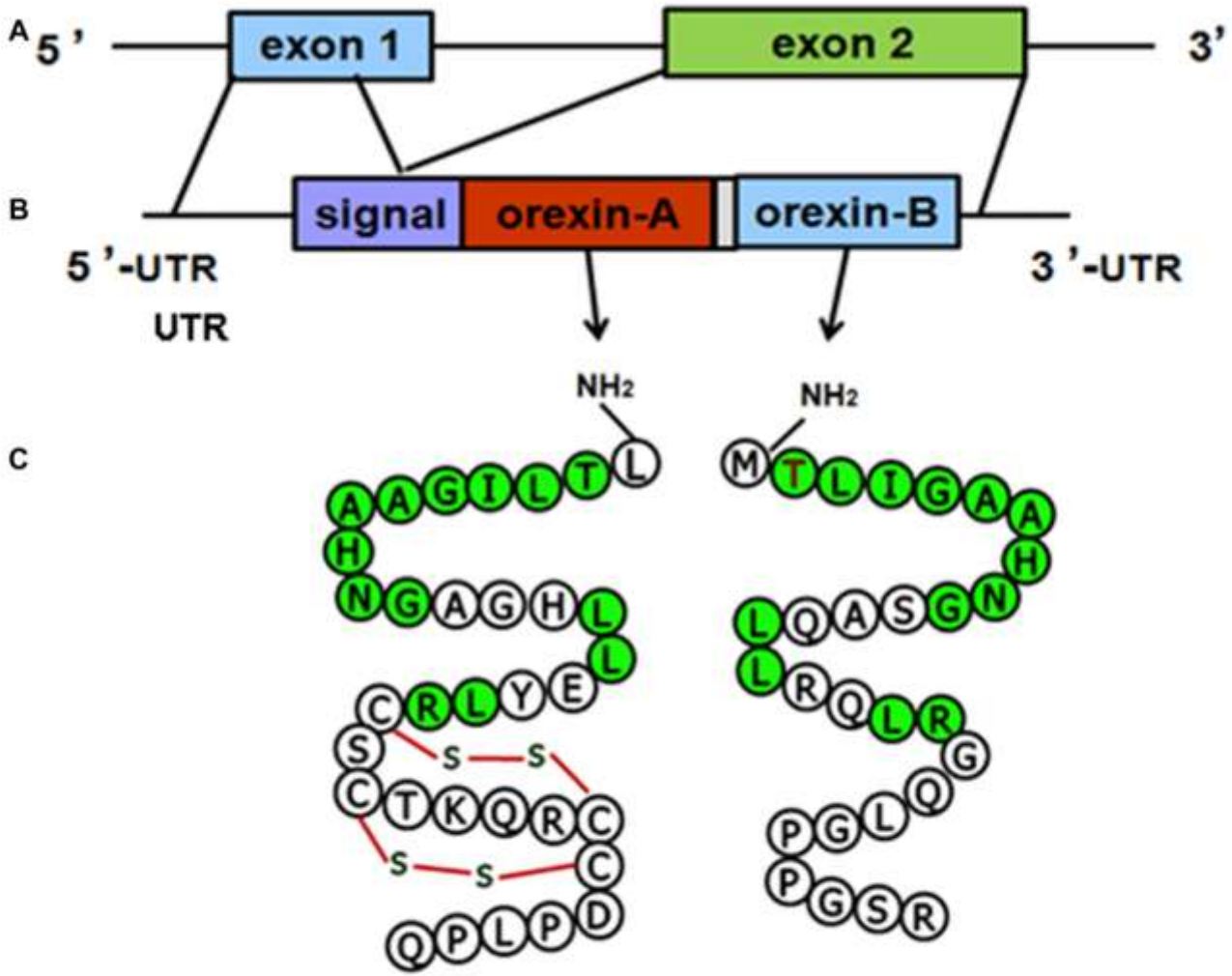

FIGURE 1 | Molecular structures of orexin precursor and orexins. **(A)** Genomic DNA of human prepro-orexin containing two exons and one intron. **(B)** The mRNA of human orexin, including the 5’ untranslated region (UTR), signal peptide, open reading frame (ORF) encoding orexin-A (OA) or orexin-B (OB), and 3’ UTR. **(C)** Amino acid sequences of OA (33 aa) and OB (28 aa). Green labels indicate amino acids that are identical in both OA and OB.

Wang C, Wang Q, Ji B, Pan Y, Xu C, Cheng B, Bai B and Chen J (2018) The Orexin/Receptor System: Molecular Mechanism and Therapeutic Potential for Neurological Diseases.
Front. Mol. Neurosci. 11:220. doi: 10.3389/fnmol.2018.00220

- Orexin A and Orexin B are cleaved from pre-pro-orexin
- OX1R – OA >>>>>> OB (5X to 100X)
- OX2R – OA ~ OB
- Dimerization – OX1R + OX2R, OX(1/2)R + CB(1/2)R
- Activation of OX1R / OX2R - transition of sleep states to wakefulness

1. Equihua AC et al. Front Pharmacol. 2013;4:163. 2. Beuckmann CT et al. J Pharm Mol Ther. 2017;362(2):287-295. 3. Willie JT et al. Neuron. 2003;38(5):715-730

OX_1R Expression Site	OX_2R Expression Site
Nucleus of the Solitary Tract (NTS)	Nucleus of the Solitary Tract (NTS)
Pedunculopontine/Latero-Dorsal Tegmental Nucleus (PPT/LDT)	Arcuate Nucleus (ARC)
Locus Coeruleus (LC)	Pedunculopontine/Latero-Dorsal Tegmental Nucleus (PPT/LDT)
Ventral Tegmental Area (VTA)	Locus Coeruleus (LC)
Dorsal Raphe Nucleus (DRN)	Ventral Tegmental Area (VTA)
Anterior Hypothalamus	Dorsal Raphe Nucleus (DRN)
Bed Nucleus of the Stria Terminalis (BNST)	Paraventricular Thalamus (PVT)
Basal Forebrain (BF)	Paraventricular Nucleus (PVN)
Paraventricular Thalamus (PVT)	Preoptic Area (POA)
Paraventricular Nucleus (PVN)	Lateral Hypothalamus (LH)
Preoptic Area (POA)	Basal Forebrain (BF)
Hippocampus (CA1 And CA2)	Bed Nucleus of the Stria Terminalis (BNST)
Dentate Gyrus (DG)	Dorsomedial Hypothalamic Nucleus (DMH)
Amygdala	Tuberomammillary Nucleus (TMN)
Ventral Pallidum (VP)	Hippocampus (CA3)
Olfactory Bulb (OB)	Dentate Gyrus (DG)
Prefrontal and Infralimbic Cortex (IL)	Amygdala
Insular Cortex (IC)	Nucleus Accumbens (NAC)
	Lateral Septum (LS)
	Medial Septum (MS)
	Anterior Commissure (AC)

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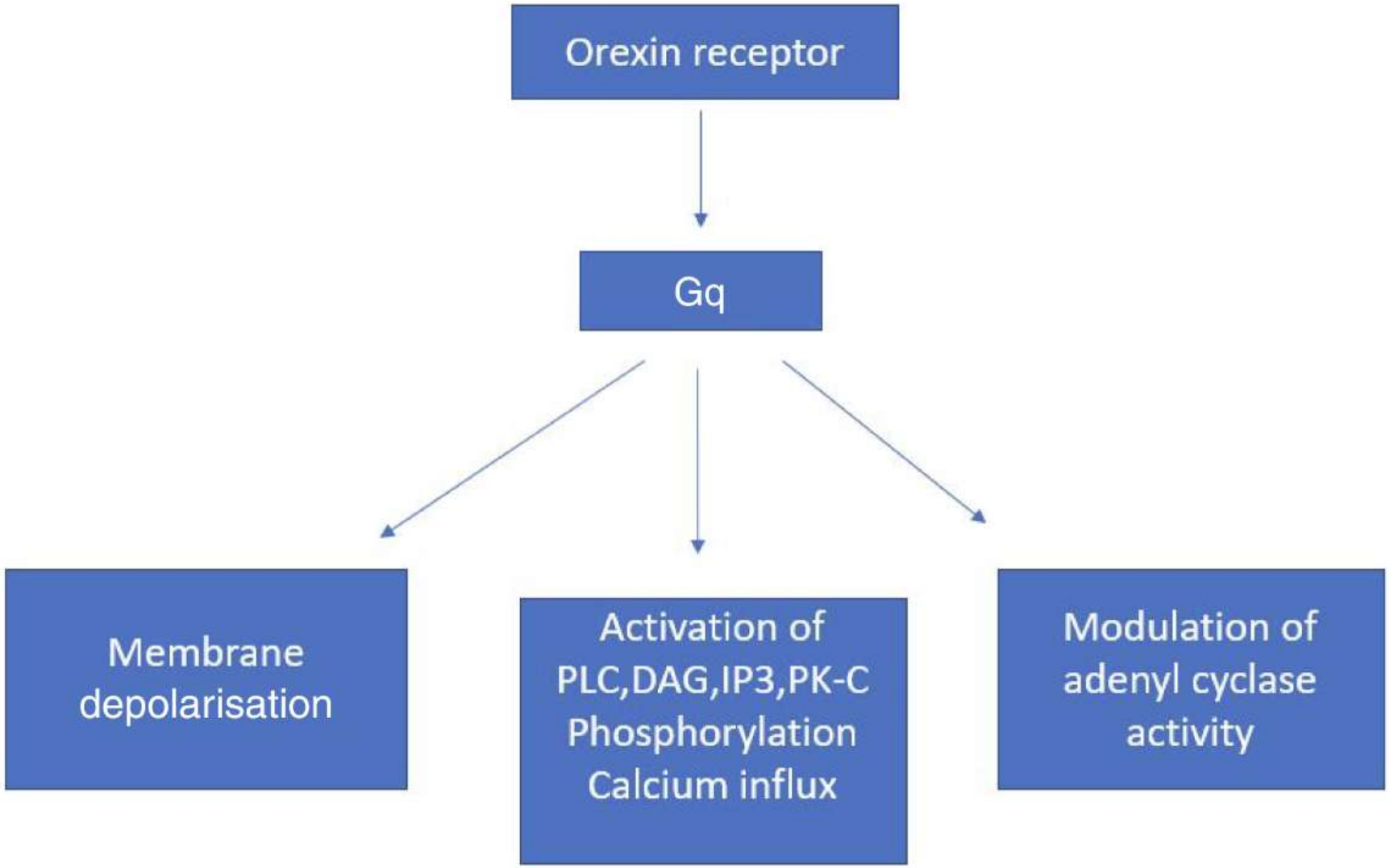
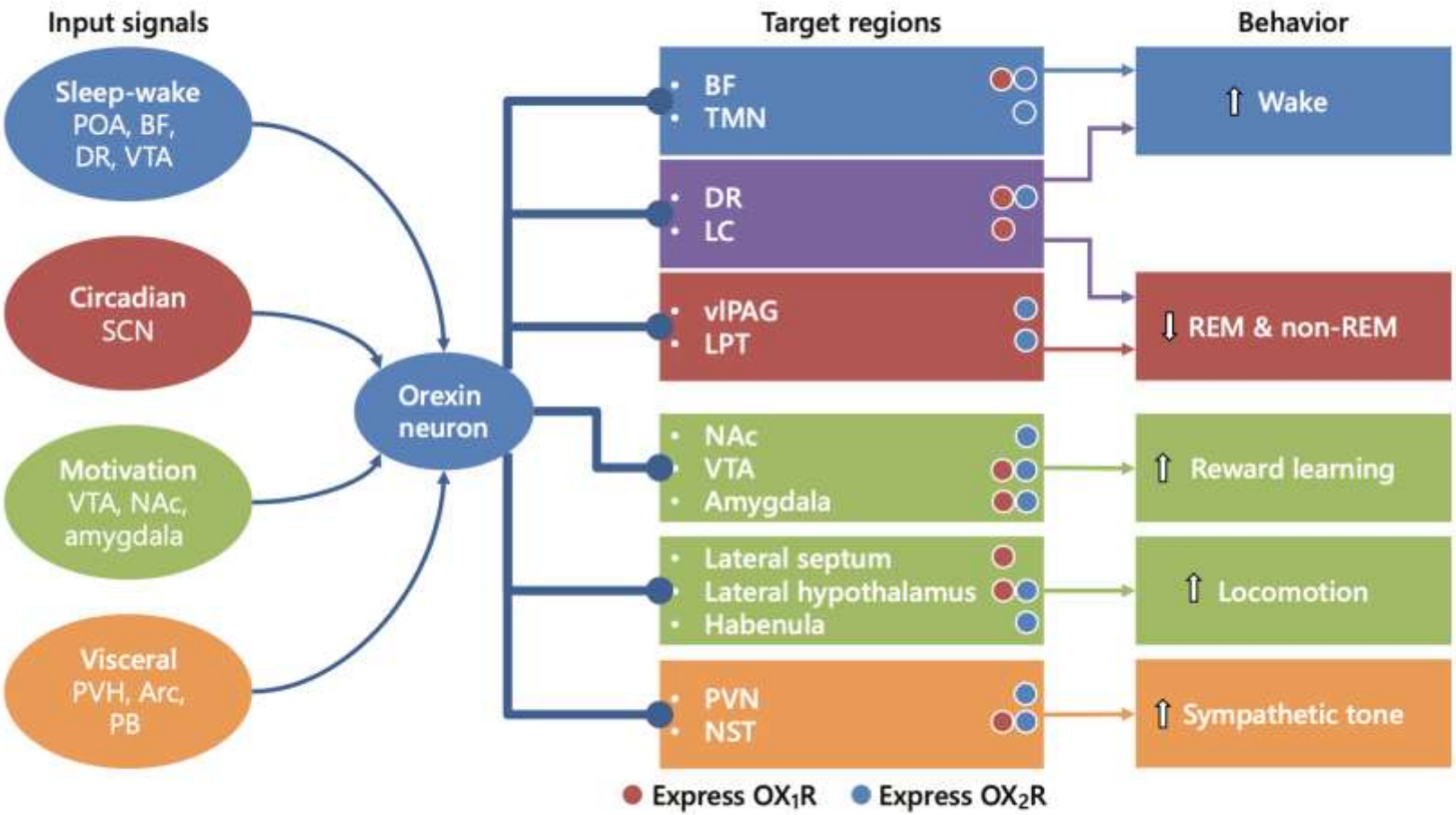
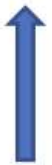
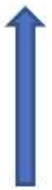


Subramanian, S, Ravichandran, M. Orexin receptors: Targets and applications. Fundam Clin Pharmacol. 2022; 36(1): 72- 80. doi:10.1111/fcp.12723



Steiner MA, Yanagisawa M, Clozel M (eds): The Orexin System. Basic Science and Role in Sleep Pathology. Front Neurol Neurosci. Basel, Karger, 2021, vol 45, pp 38–51 (DOI: 10.1159/000514960)

Afferents	Efferent	Functions
Sleep: • Preoptic area • Dorsal raphe	• Cortex • Tuberomamillary nucleus • Periaqueductal gray matter	 ✓ Wakefulness ✓ Attention
Stress, Emotions: • Amygdala • Periaqueductal gray matter Motivation: • Nucleus accumbens	• Nucleus accumbens • Substantia nigra • Ventral tegmental area	 ✓ Motivation ✓ Reward ✓ Feeding
Hunger: • Arcuate nucleus • Increased Ghrelin	• Nucleus tractus solitarus • Ventrolateral medulla	 ✓ Sympathetic tone ✓ Feeding

Subramanian, S, Ravichandran, M. Orexin receptors: Targets and applications. Fundam Clin Pharmacol. 2022; 36(1): 72- 80. doi:10.1111/fcp.12723

Table 1 | **Factors that influence the activity of orexin neurons**

Factor	Receptor involved	References
Excitatory		
Glutamate	AMPAR, NMDAR, mGluRs	11,70
Ghrelin	GHSR	71
Cholecystokinin	CCK-A	74
Neurotensin	ND	74
Vasopressin	V1a	74
Oxytocin	V1a	74
Glucagon-like peptide 1	ND	105
CRF	CRFR1	69
mACh (effect in 27% of orexin neurons)	M3	14
ATP	P2X	106
Inhibitory		
Glucose	Unknown	11
GABA	$GABA_A$, $GABA_B$	11,70,89
Serotonin	$5\text{-}HT_{1A}$	71,91
Noradrenaline	α_2	71,72
Dopamine	α_2	71
Neuropeptide Y	Y_1	107
Leptin	OB-R	11
mACh (effect in 6% of orexin neurons)	ND	14,71
Adenosine	A_1	75

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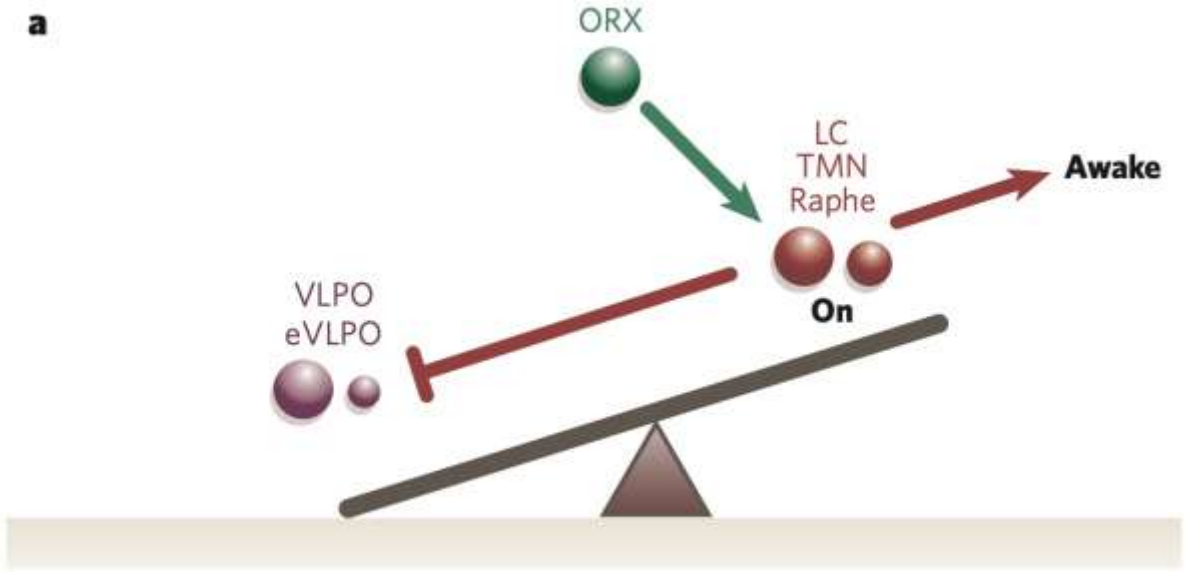
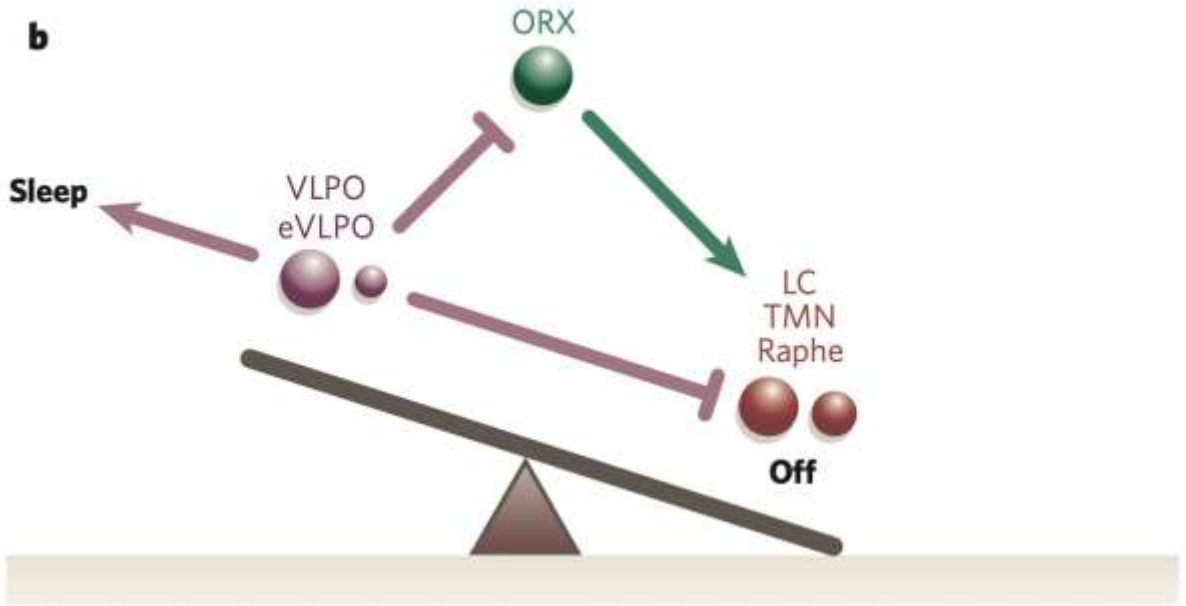




Saper et al. (2005) Nature 437:1257

- **During wakefulness**
  - the monoaminergic nuclei (red) inhibit the ventrolateral preoptic nucleus (VLPO; purple)
  - relieving the inhibition of the monoaminergic cells, and that of the orexin (ORX) neurons (green), and the cholinergic pedunculopontine (PPT) and laterodorsal tegmental nuclei (LDT; yellow)

- **VLPO neurons do not have orexin receptors**
  - the orexin neurons serve primarily to reinforce the monoaminergic tone, rather than directly inhibiting the VLPO on their own

Modified from: Saper et al. (2005) Nature 437:1257

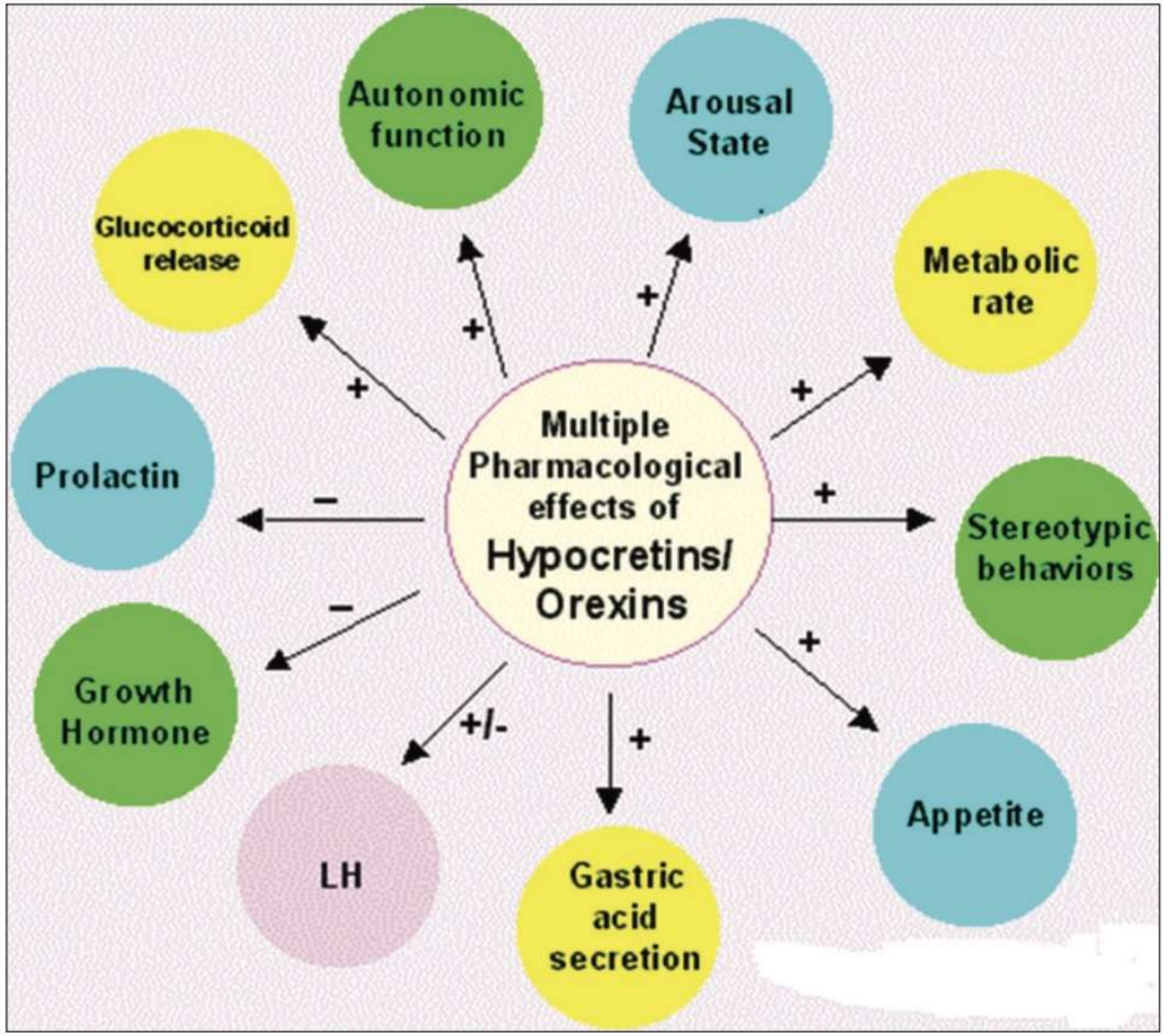
- **During sleep**
  - the firing of the VLPO neurons inhibits the monoaminergic cell groups, thereby relieving their own inhibition
  - inhibit the orexin neurons, further preventing monoaminergic activation that might interrupt sleep

- **Direct mutual inhibition** between the VLPO and the monoaminergic cell groups forms a classic flip-flop switch, which produces sharp transitions in state, but is relatively unstable
  - addition of the orexin neurons stabilizes the switch

Modified from: Saper et al. (2005) Nature 437:1257

- Orexin-A levels are higher in patients with insomnia and correlate with age and insomnia severity

Tang S et al. Peptides. 2017;88:55-61., Matsumura T et al. Exp Gerontol. 2002;37(8-9):1127-1130.



Brain Circ 2020;6:70-80.

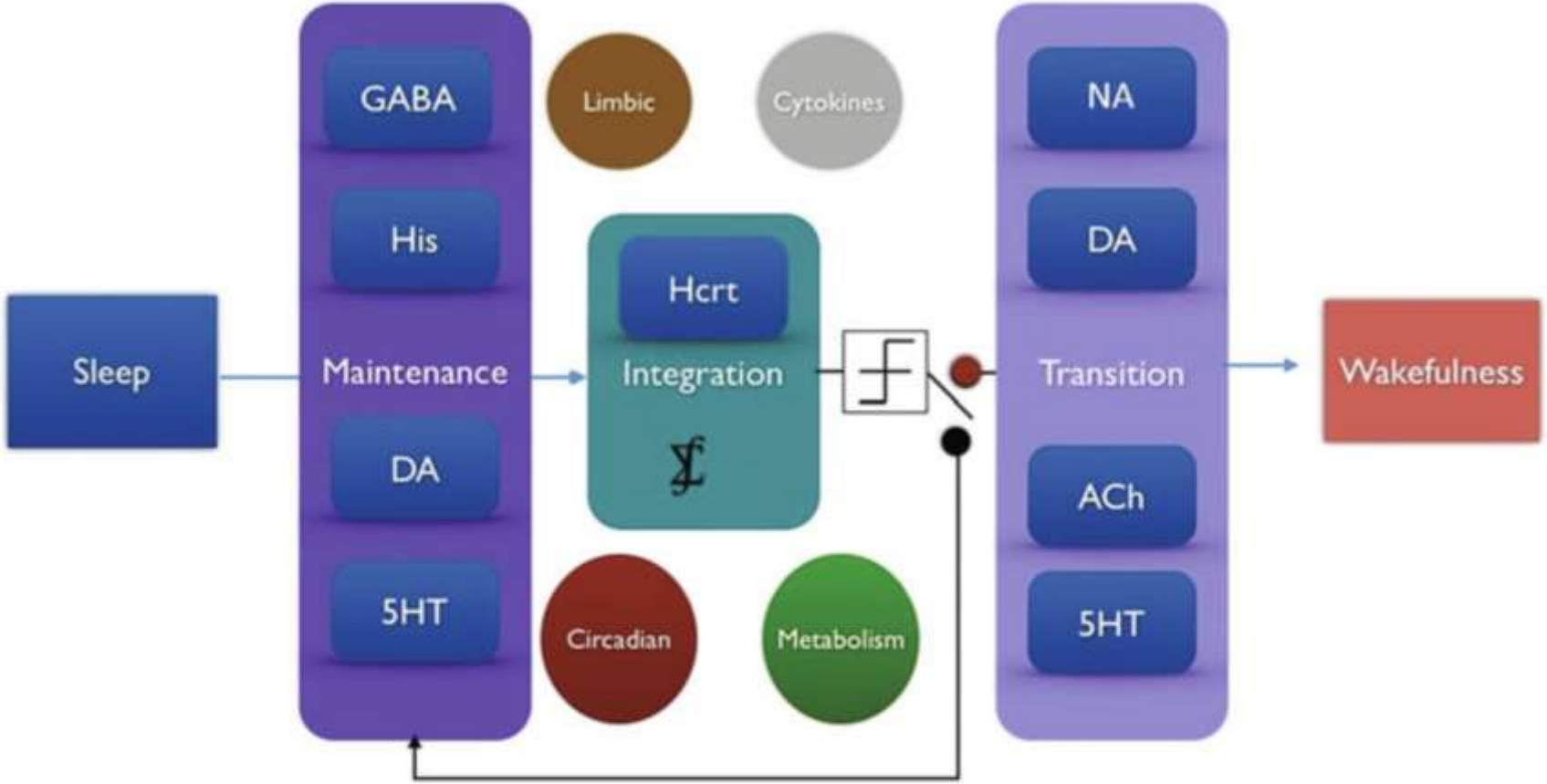


Fig. 1 Hcrt neurons integrate the inputs from the circadian, metabolic, limbic, and cytokine systems. The integration of the activities of these systems either leads to maintenance of sleep, in which the GABAergic, histaminergic, dopaminergic, and serotonergic systems are involved, or triggers the transition to arousal, in which the noradrenergic, dopaminergic, cholinergic, and serotonergic systems are implicated. Depending on the integrated signals arriving in Hcrt neurons, sleep will either be maintained or will transition into wakefulness

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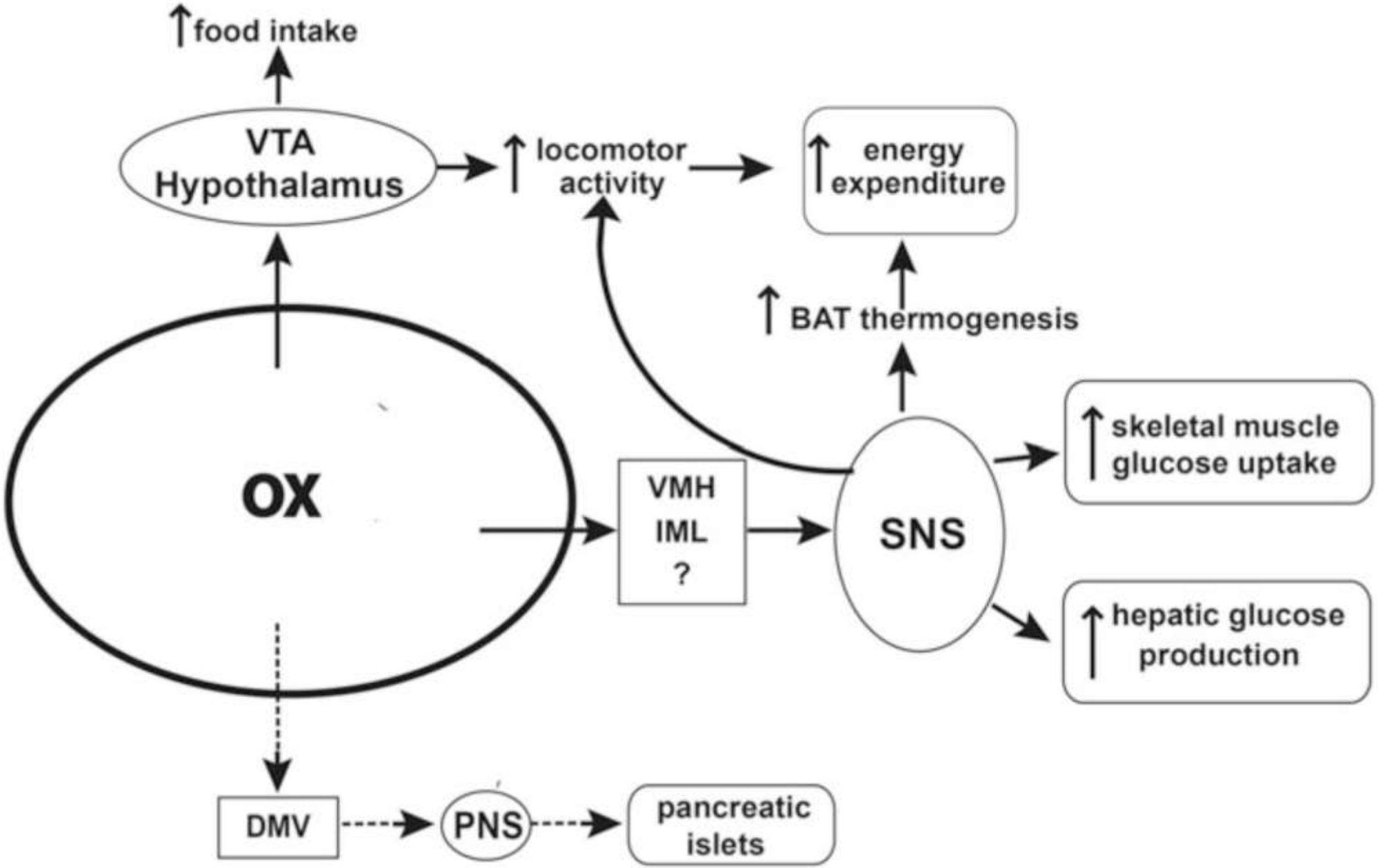
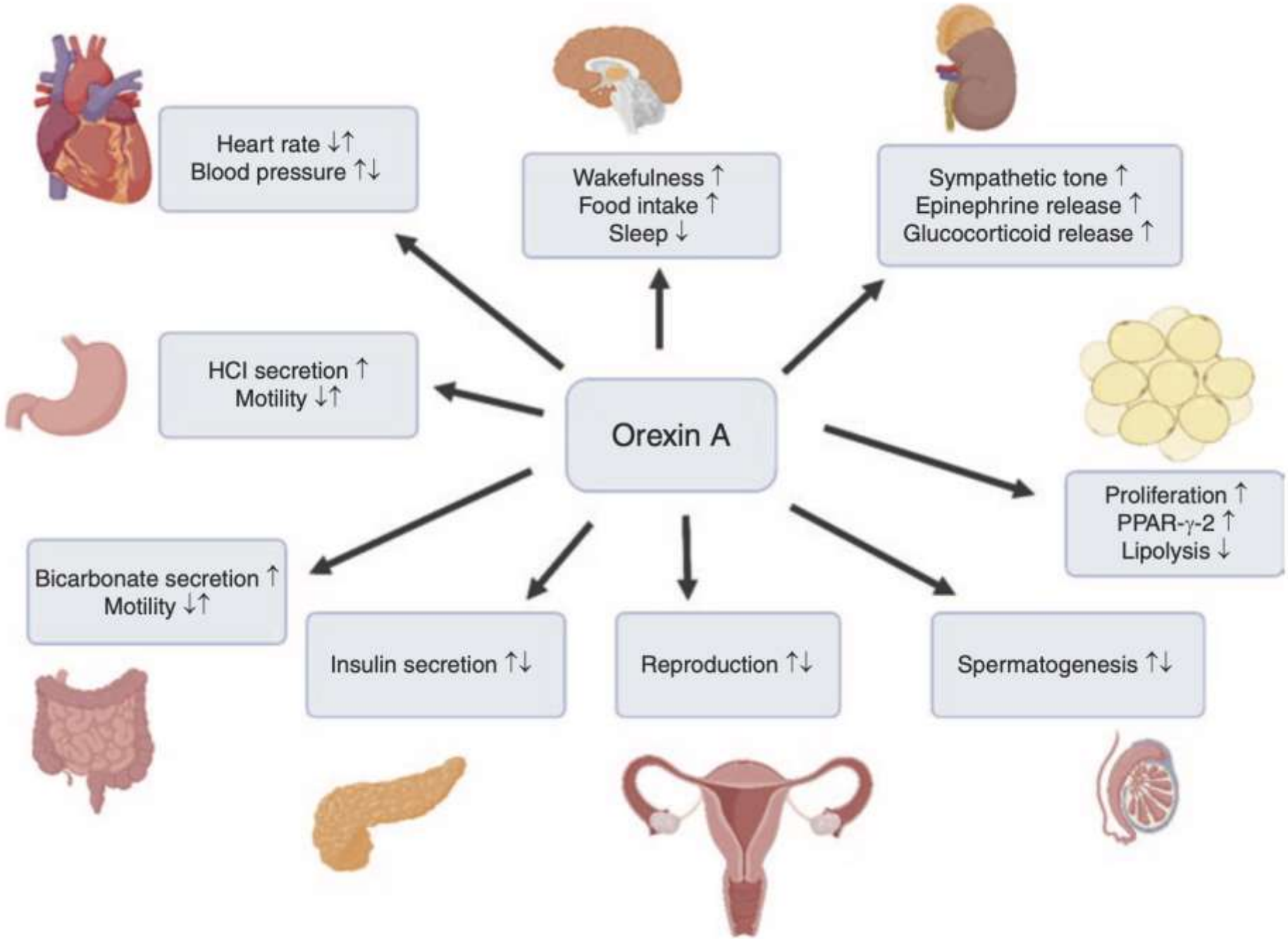
10.1007/7854_2
016_58



DOI
10.1007/7854_20
16_51

Fig. 2 Pathways of OX-dependent regulation of energy balance. OX signaling increases feeding at least in part by acting in the VTA and at several hypothalamic sites, including the LH and ARC, to increase food-seeking. OX also promotes energy expenditure in part via the VTA, NAc, and hypothalamus and the control of locomotor activity, as well as by acting via sites (potentially including the VMH and IML, among others) to increase SNS activity, which increases activity and basal metabolic rate. OX-mediated activation of the SNS also increases hepatic glucose production and skeletal muscle glucose uptake. Modulation of the PNS by OX (potentially via the DMV) may contribute to the control of pancreatic hormone secretion. *Abbreviations*: *VTA* ventral tegmental area, *VMH* ventromedial hypothalamus, *LH* lateral hypothalamus, *NAc* nucleus accumbens, *ARC* arcuate nucleus, *IML* intermediolateral nucleus, *SNS* sympathetic nervous system, *PNS* parasympathetic nervous system, *BAT* brown adipose tissue

DOI 10.1007/7854_2016_51



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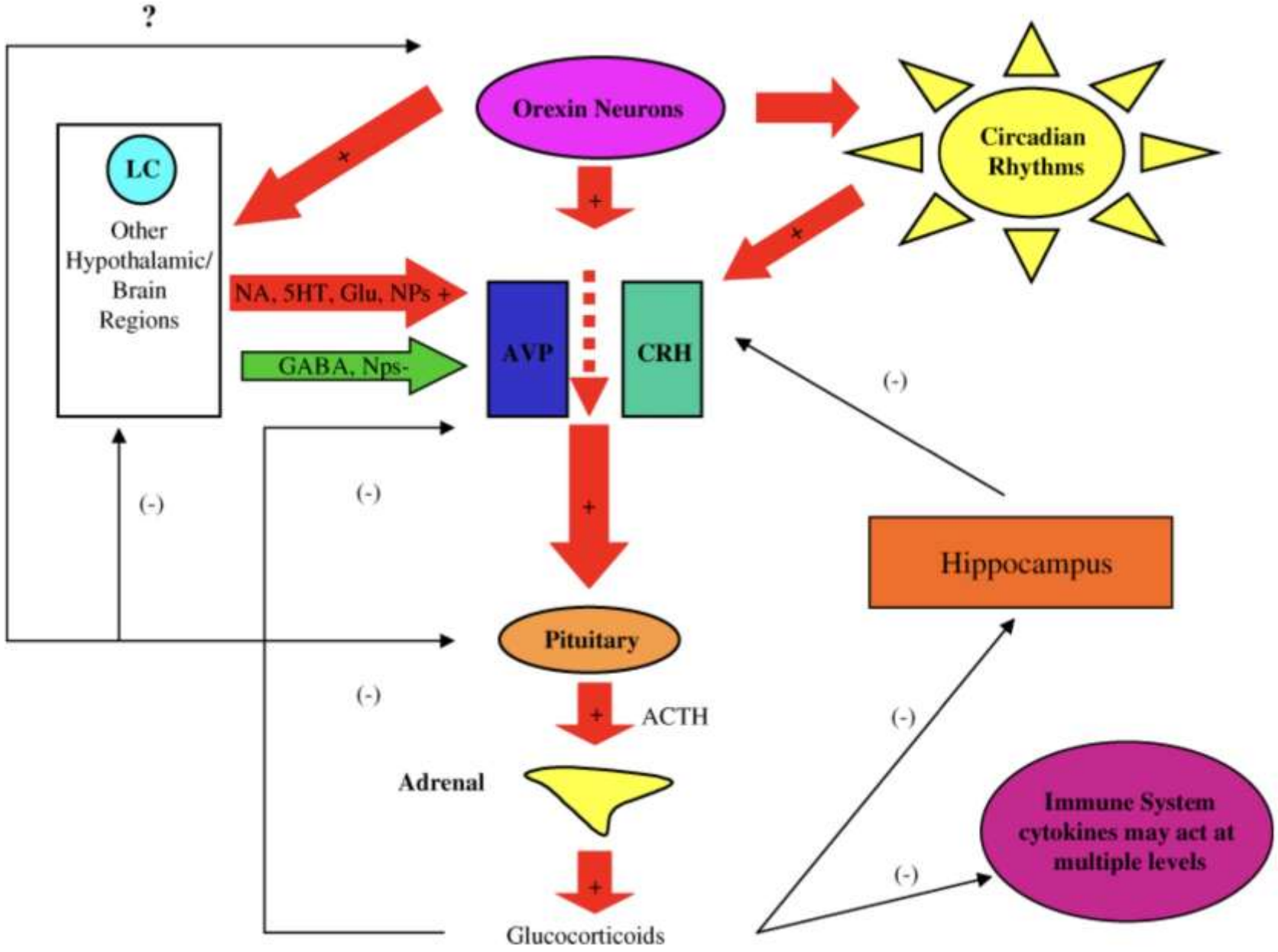

Contemporary Clinical Neuroscience: The Orexin/Hypocretin System: Physiology and Pathophysiology Edited by: S. Nishino and T. Sakurai

Fig. 4. Control of the hypothalamo-pituitary-adrenal (HPA) axis and the role of the orexins. Corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) neurons release their hormones into the portal circulation. CRH and AVP then stimulate adrenocorticotropic hormone (ACTH) secretion by pituitary corticotrophs, which, in turn, stimulates adrenocortical glucocorticoid secretion. Glucocorticoids feed back at pituitary and hypothalamic levels to reduce ACTH, and CRH and AVP secretion respectively. Glucocorticoids also act on the hippocampus, which acts on the hypothalamus to reduce CRH and AVP. Other influences include stimulation by noradrenergic (NA), serotoninergic (5HT), and glutamatergic (Glu) inputs. Inhibition occurs via γ-aminobutyric (GABA) ergic inputs. A number of neuropeptides may stimulate or inhibit HPA axis activity. The orexins may influence HPA activity directly or indirectly via brainstem (e.g., locus coeruleus [LC] noradrenergic) and hypothalamic (e.g., NPY) circuits, and/or via altering the circadian influences on HPA axis activity. The role of negative feedback onto orexin neurons by glucocorticoids is not completely determined. The immune system can influence the stress axis at multiple junctions.

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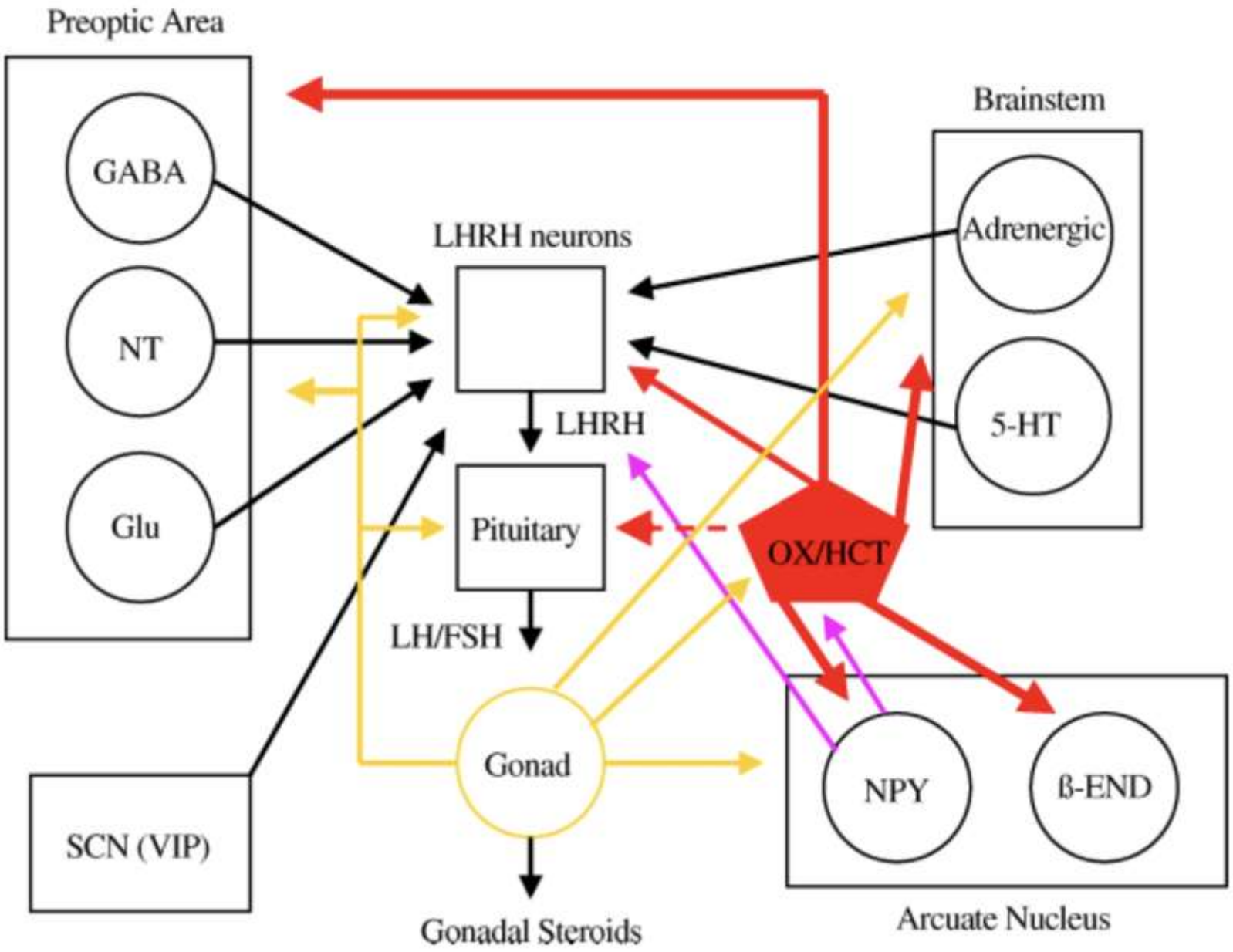

Contemporary Clinical Neuroscience: The Orexin/Hypocretin System: Physiology and Pathophysiology Edited by: S. Nishino and T. Sakurai

Fig. 2. Control of the hypothalamo-pituitary-gonadal (HPG) axis. The control of the HPG axis is complex and involves multiple neuronal circuits. The orexins may influence luteinizing hormone-releasing hormone (LHRH) secretion directly or indirectly via other neural pathways. These peptides may also act at the pituitary levels. Gonadal steroids are able to regulate orexin neurotransmission as orexin-A immunoreactivity changes throughout the estrous cycle and is altered by gonadal hormone manipulation. OX/HCT, orexin/hypocretin; SCN, suprachiasmatic nucleus; VIP, vasoactive intestinal peptide; NT, neurotensin; GABA, γ-aminobutyric acid; Glu, glutamate; 5-HT, serotonin; NPY, neuropeptide tyrosine (Y); β-END, β-endorphin.

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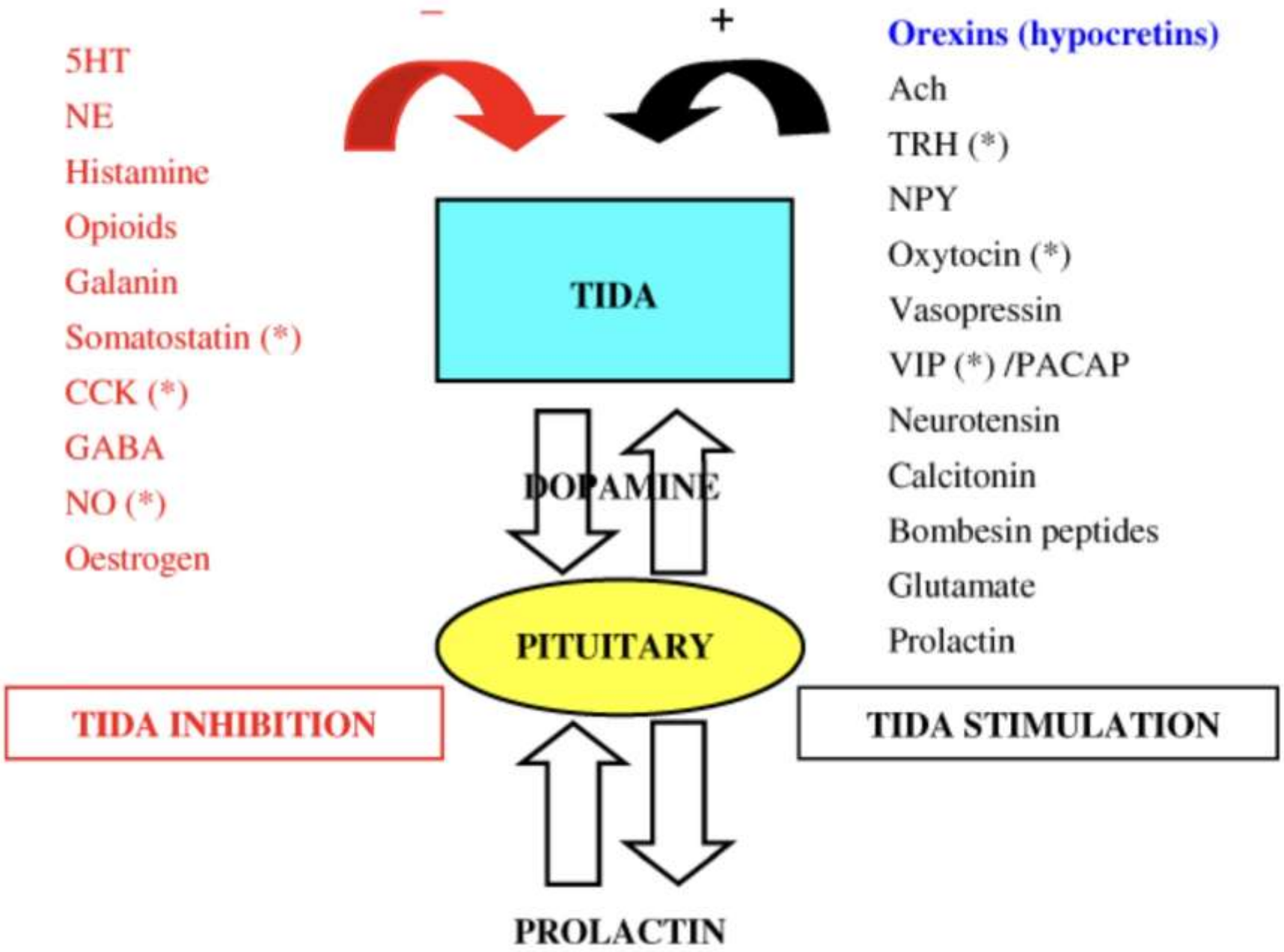

Contemporary Clinical Neuroscience: The Orexin/Hypocretin System: Physiology and Pathophysiology
Edited by: S. Nishino and T. Sakurai

Fig. 3. Central factors that either stimulate or inhibit prolactin release via the tuberoinfundibular dopamine (TIDA) system. Pituitary prolactin release is under tonic inhibition from TIDA dopamine. (*) indicates independent effects at the pituitary levels that may be opposite to central effects. To date, direct innervation of the TIDA has not been reported. The inhibition of prolactin secretion by the orexins is not entirely reversed by the administration of the D_2 antagonist domperidone, suggesting that other pathways are involved. Orexins may affect multiple conflicting pathways. For example, they densely innervate adrenergic, histaminergic, and serotoninergic neurons that can increase prolactin secretion via the TIDA, while acting on neuropeptide Y (NPY) neurons may stimulate the TIDA and thus decrease prolactin secretion. Orexins may stimulate prolactin-inhibitory factors (PIFs) or inhibit prolactin-releasing factors (PRFs) that are independent of the TIDA. 5HT, serotonin; NE, norepinephrine; CCK, cholecystokinin; GABA, γ-aminobutyric acid; NO, nitric oxide; Ach, acetylcholine; TRH, thyroid-releasing hormone; VIP, vasoactive intestinal peptide; PACAP, pituitary adenylate cyclase-activating peptide.

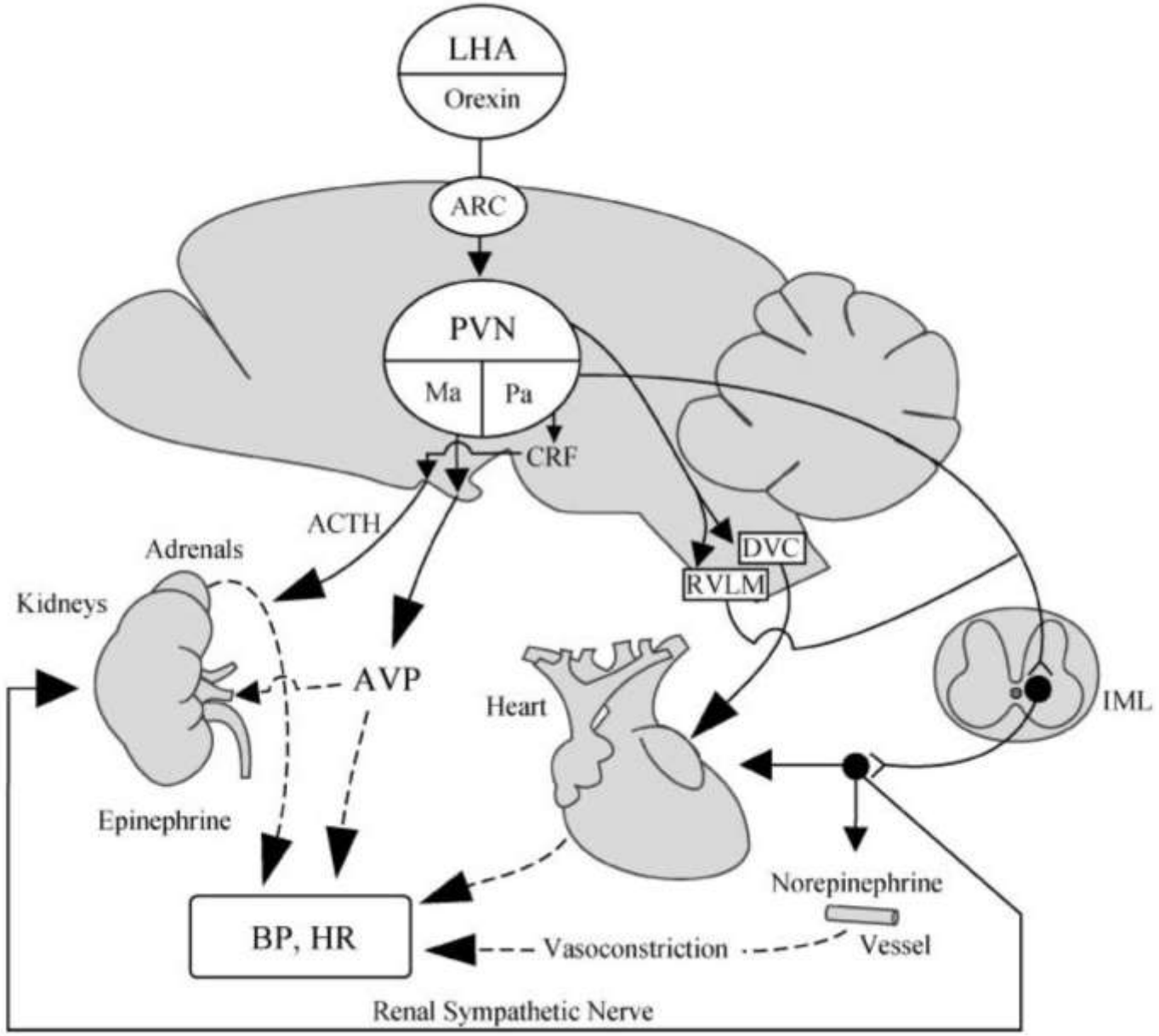

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Fig. 6. Schematic diagram of possible mechanisms for the action of central orexins in cardiovascular, neuroendocrine, and sympathetic outflows. Orexins bind to their receptors of the magnocellular or parvocellular neurons of the hypothalamic paraventricular nucleus, or arcuate nucleus neurons, causing their depolarization. Excitation of magnocellular neurons induces secretion of arginine vasopressin (AVP) from the posterior pituitary, antidiuresis, and vasoconstriction. Conversely, parvocellular neurons activate autonomic centers in the brainstem and spinal cord, increasing the heart rate (HR) and blood pressure (BP), or causing the release of corticotropin-releasing factor (CRF). Secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary is controlled by CRF and AVP, synthesized by the parvocellular neurons. The right lower vessel indicates that norepinephrine released from the sympathetic nerve ending induces vasoconstriction. Activation of the renal sympathetic nerve induces antidiuresis and secretion of renin. The solid lines indicate a neural or humoral pathway. The dotted lines indicate a functional influence. ARC, arcuate nucleus; DVC, dorsal vagal complex; IML, intermediolateral cell column; LHA, lateral hypothalamus; PVN, paraventricular nucleus; Ma, magnocellular neuron; Pa, parvocellular neuron; RVLM, rostral ventrolateral medulla. (Reprinted from ref. *36*.)

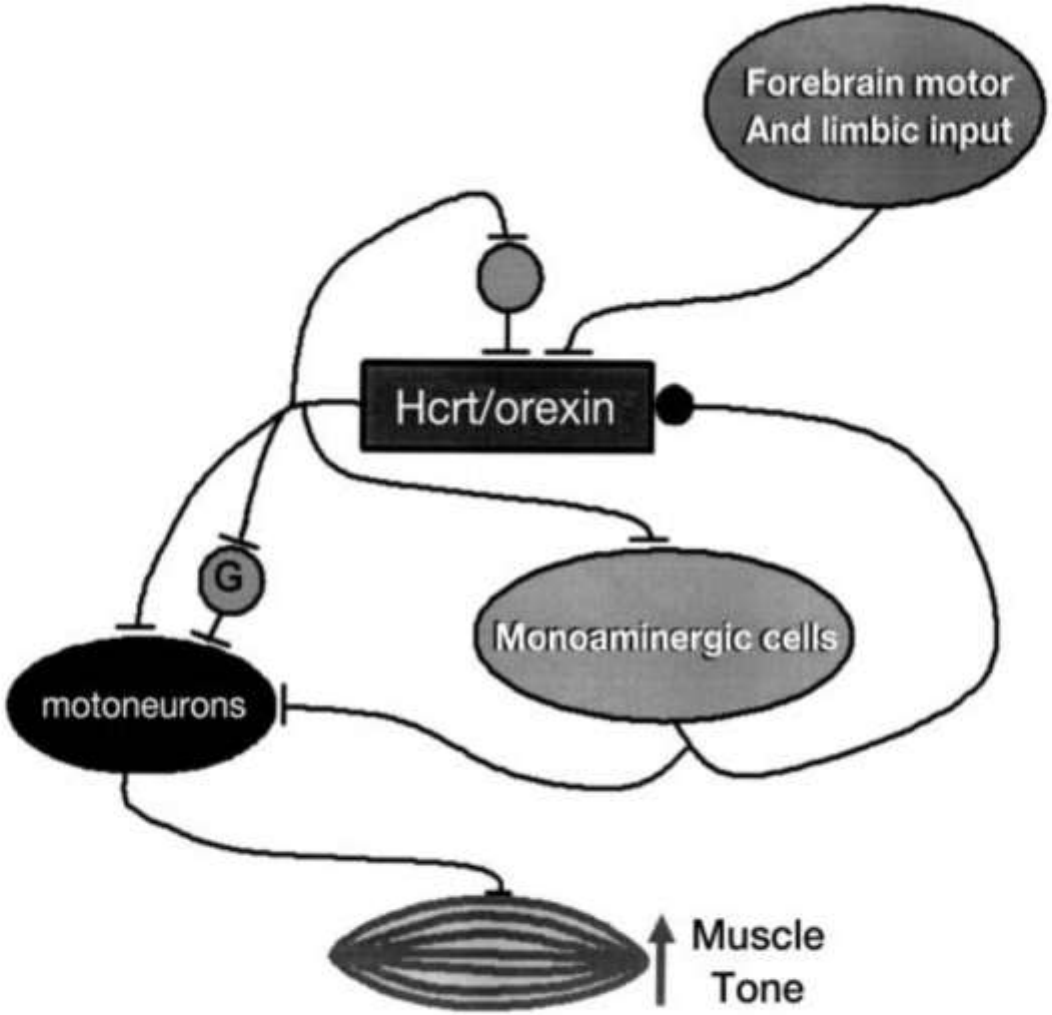

Fig. 9. Hypocretin (Hcrt/orexin) can increase muscle tone by direct action on motoneurons, but more potently by indirect action mediated by glutamate-and monoamine-containing cells. Simplified model of connections between hypocretin neurons and motoneurons. G indicates glutamate cells.

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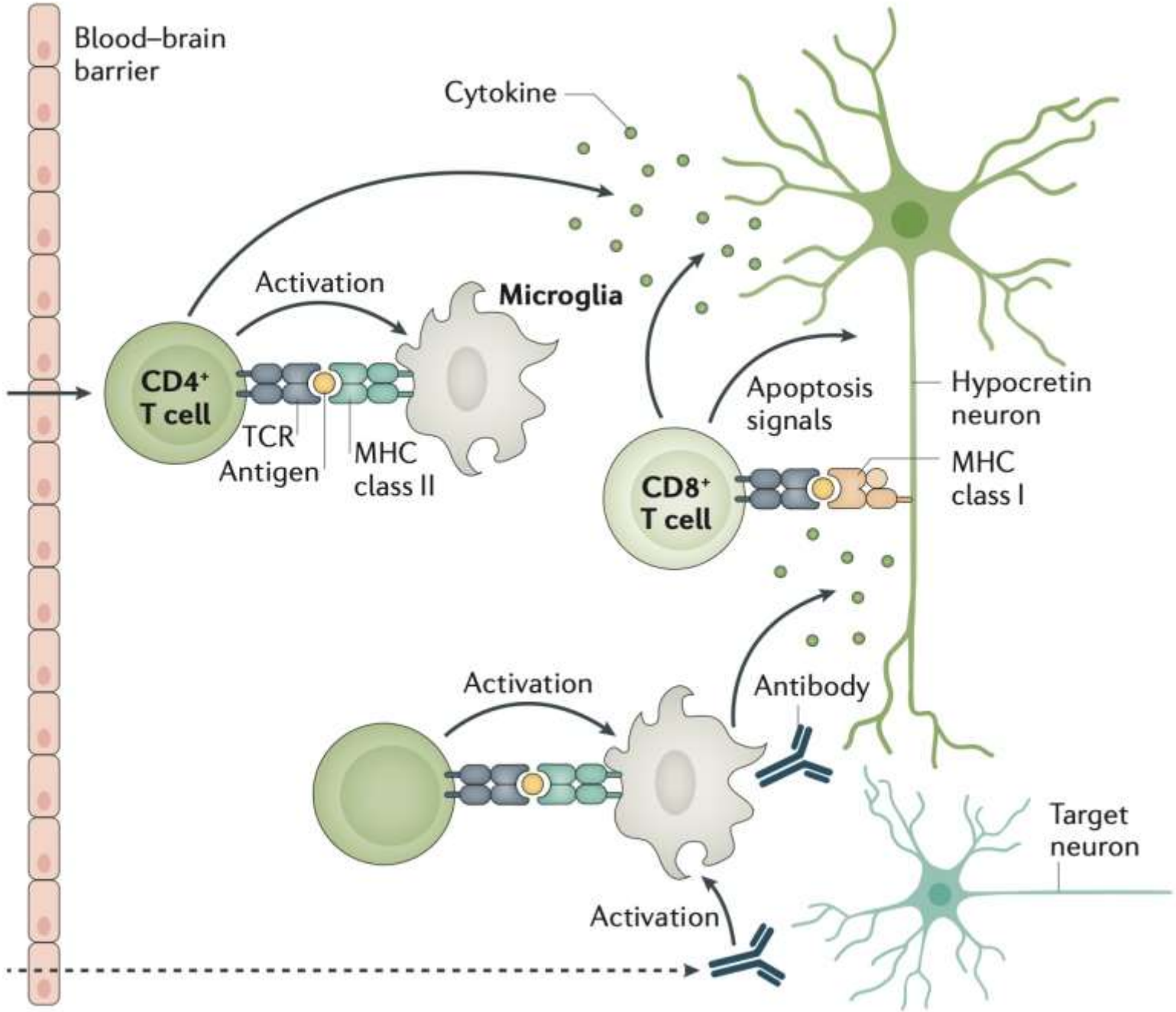
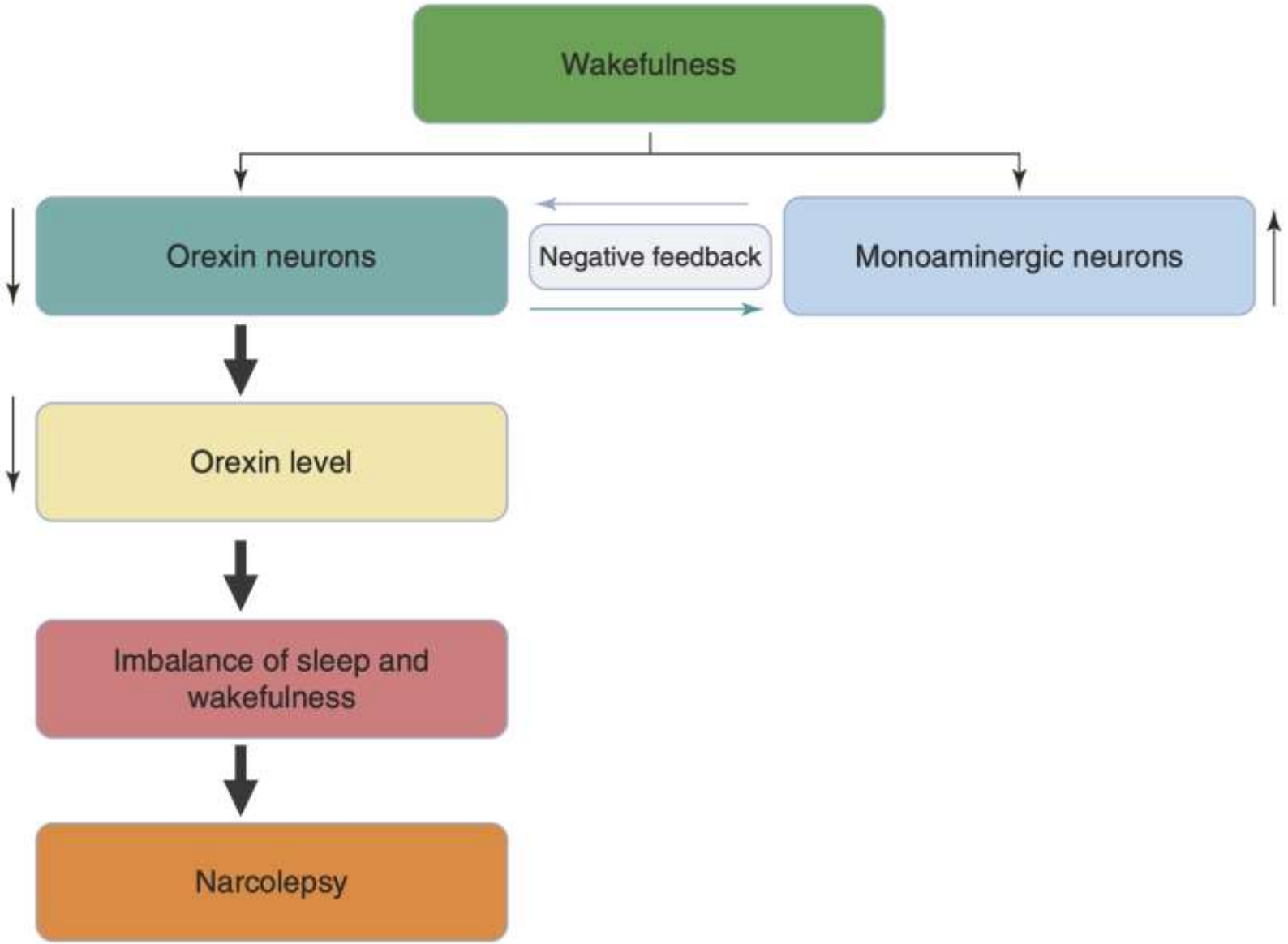


10.1038/nrdp.2016.100



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Narcolepsy	Hcrt neurons↓	Hypothalamus
	Hcrts↓	Perifornical area Frontal cortex and pons CSF
	Normal Hcrts	Plasma Plasma Frontal cortex and pons
	Normal Hcrt neurons	Hypothalamus
	Normal antibodies to prepro-Hcrts, Hcrts, HcrtRs	Serum

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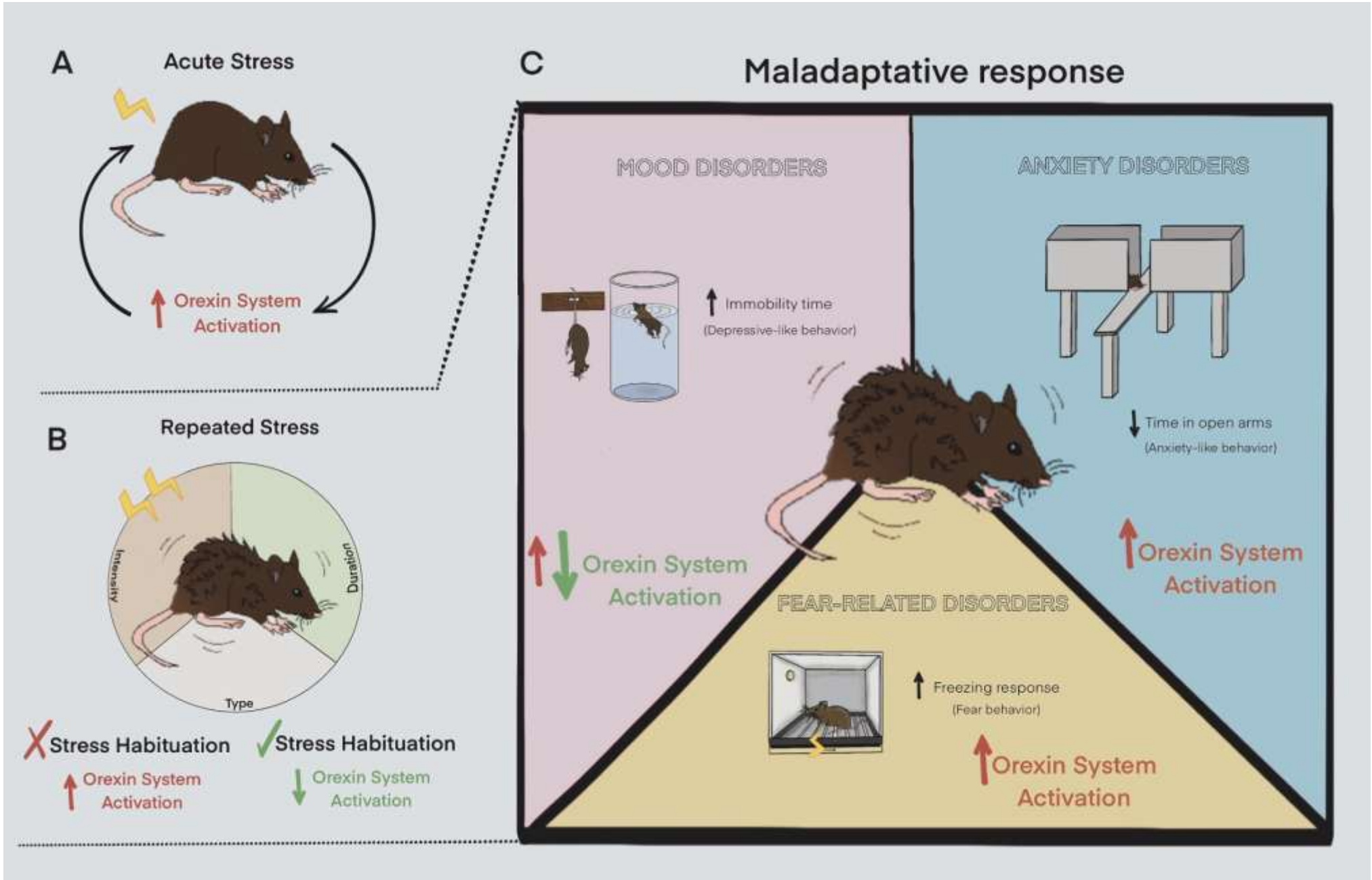

doi.org/10.1016/j.yfrne.2023.101066

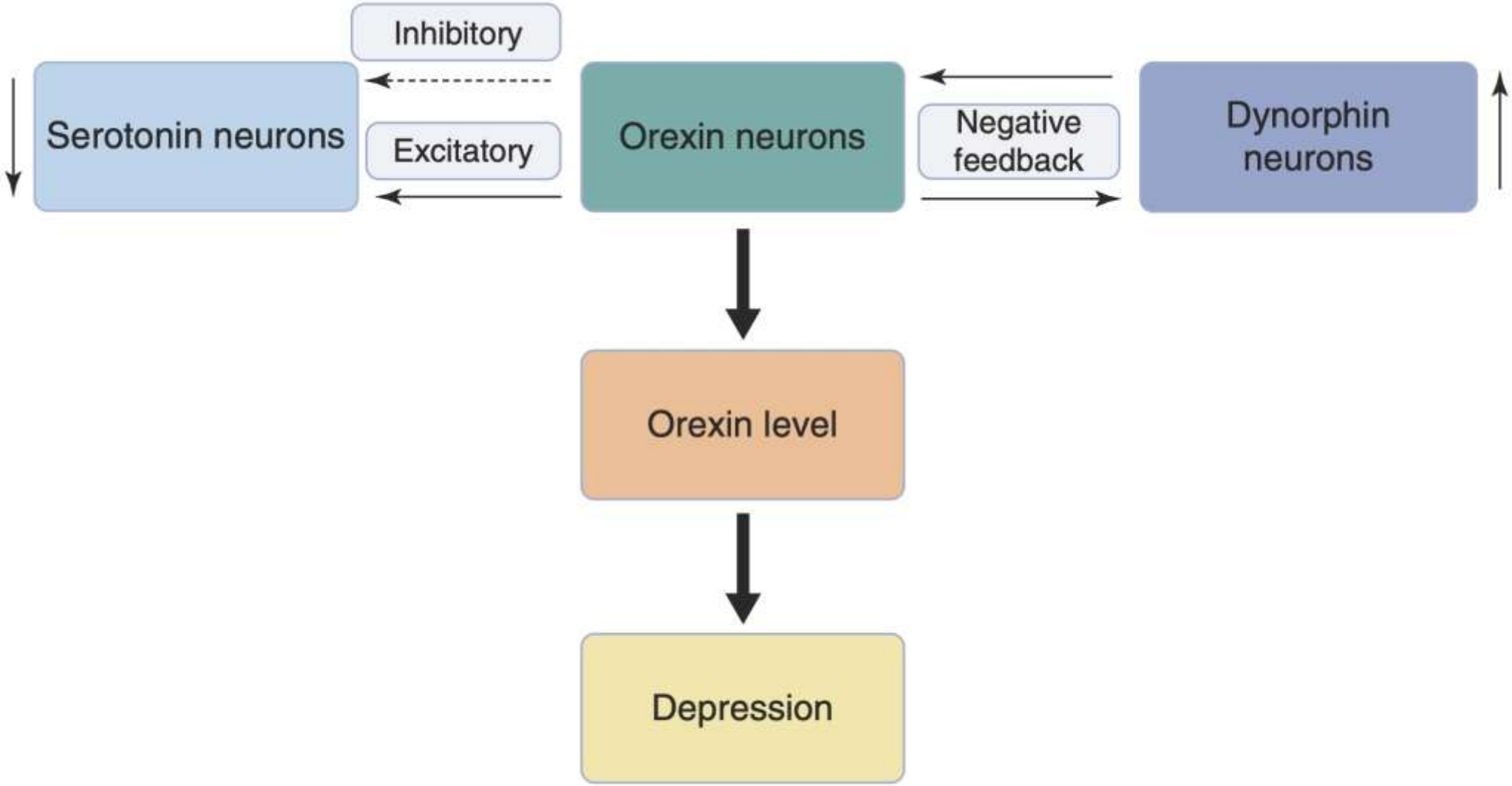

Fig. 10.9 Role of Orexin in depression [26]

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Depression	Hcrt neurons↓	Hypothalamus
	Neural size↓	
	Hcrt neurons↑	
	Hcrt-1↓	CSF
	Hcrt-1 mRNA↓	Blood
	Promoter-methylation	
	Neuronal activation	DMH-PFA
	HcrtR-2↓	Thalamus and hypothalamus
	Hcrt-1↑	CSF
	Fluctuation↓	
Anxiety	Neuronal activation	DMH-PFA

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PTSD	Hcrt-1↓	CSF, plasma
Anorexia nervosa	Hcrt-1↓	Plasma
	Hcrt-1↑	Plasma

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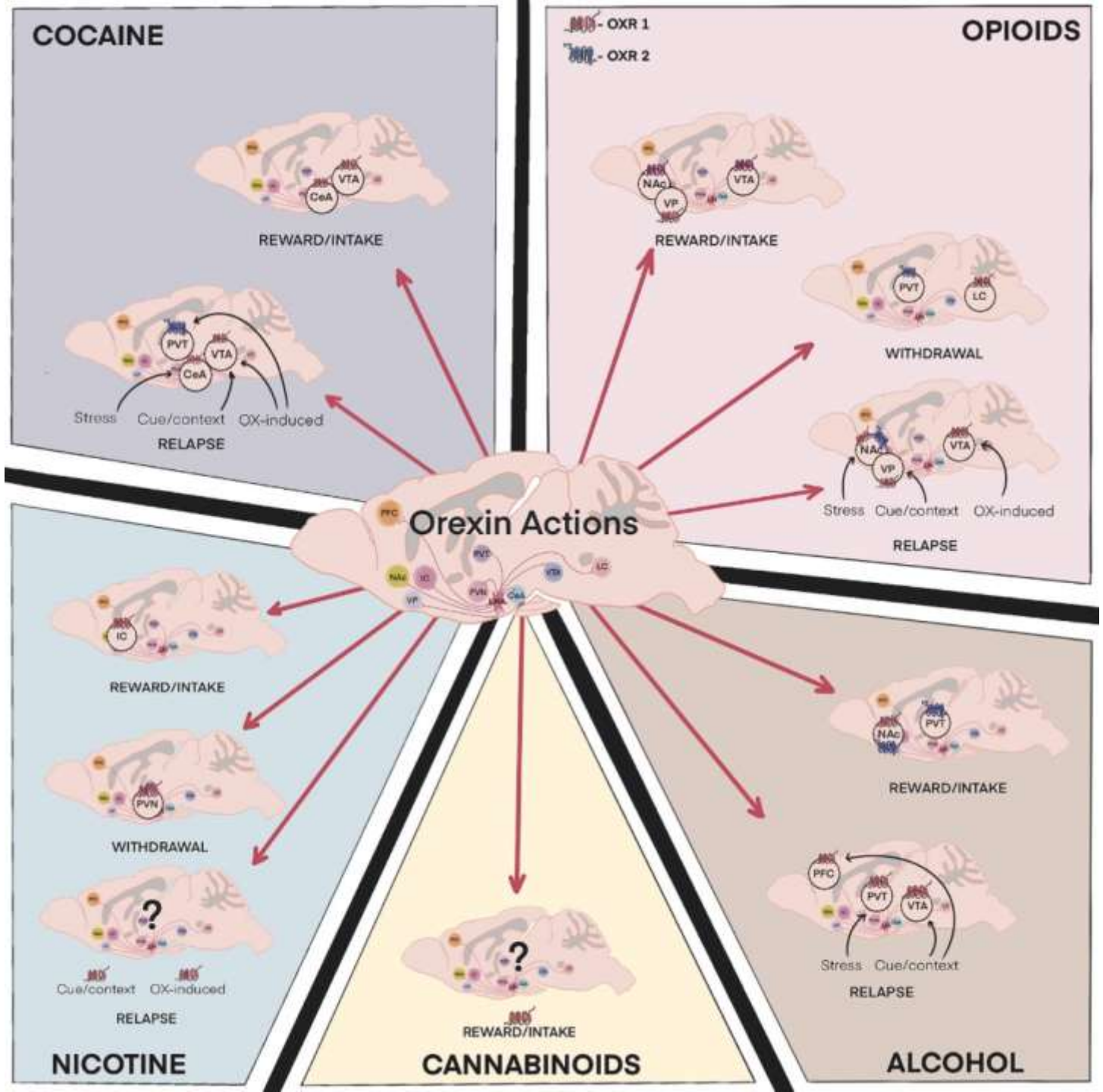

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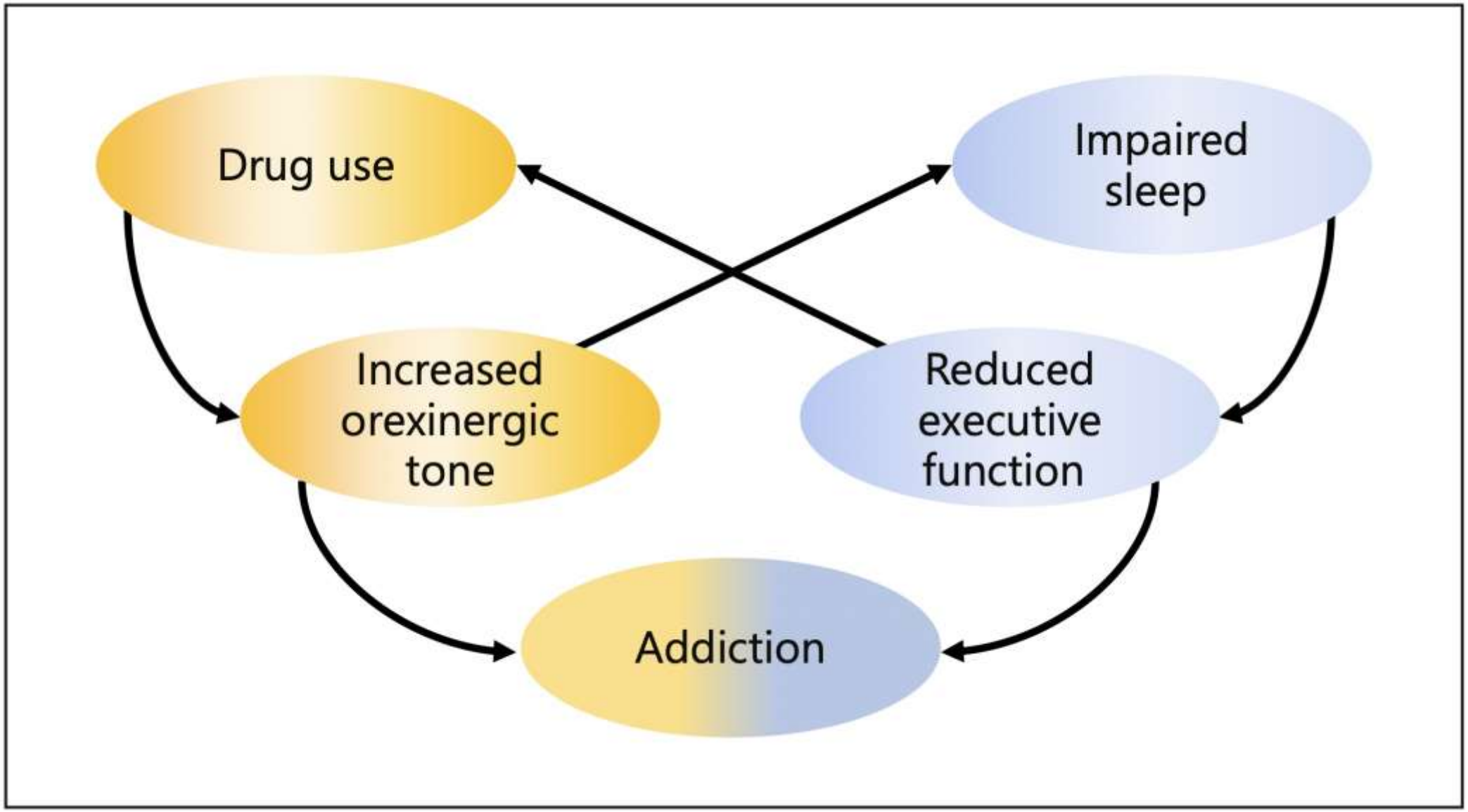


Steiner MA, Yanagisawa M, Clozel M (eds): The Orexin System. Basic Science and Role in Sleep Pathology. Front Neurol Neurosci. Basel, Karger, 2021, vol 45, pp 117–127 (DOI: 10.1159/000514965)

- Chronic use of alcohol and opioid associated with greater number of orexin neurons
- Opioid withdrawal increase activity of orexin neurons
- Appears to be mediated through OX_1R

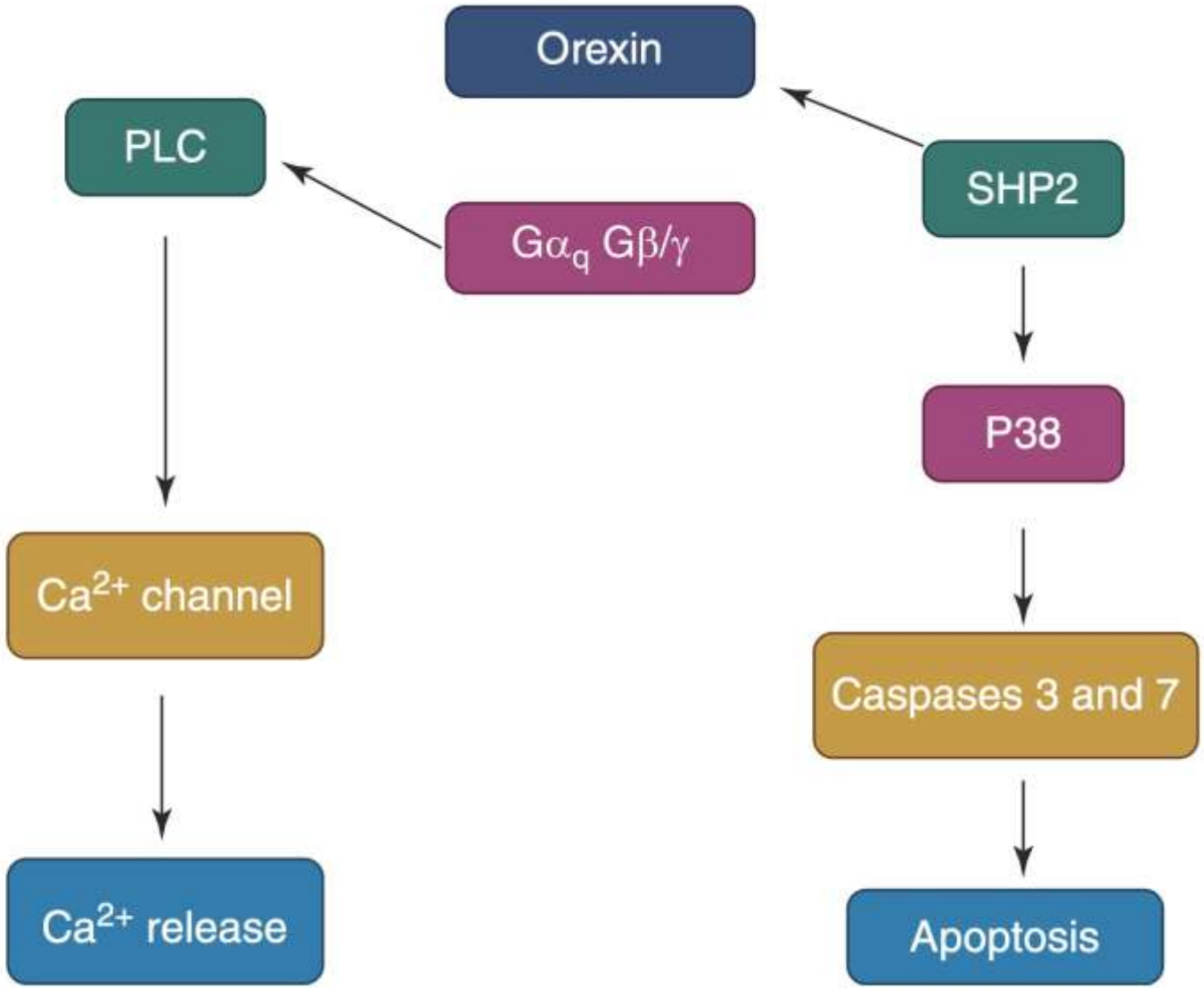
Steiner MA, Yanagisawa M, Clozel M (eds): The Orexin System. Basic Science and Role in Sleep Pathology. Front Neurol Neurosci. Basel, Karger, 2021, vol 45, pp 117–127 (DOI: 10.1159/000514965)

Table 1. Clinical trials of orexin receptor antagonists for the treatment of substance abuse disorders

Title of trial	Status	Conditions	ClinicalTrials.gov Identifier
Medication Development in Alcoholism: Suvorexant versus Placebo	Not yet recruiting	Alcohol use disorder	NCT04229095
Suvorexant in the Management Comorbid Sleep Disorder and Alcohol Dependence	Recruiting	Alcohol use disorder	NCT03897062
Suvorexant and Cocaine	Recruiting	Cocaine use disorder	NCT03937986
Role of the Orexin Receptor System in Stress, Sleep and Cocaine Use	Completed	Cocaine use disorder/ Anxiety	NCT02785406
Medical Management of Sleep Disturbance During Opioid Tapering	Recruiting	Opioid use disorder	NCT03789214
Examining the Role of the Orexin System in Sleep and Stress in Persons with Opioid Use Disorder	Recruiting	Opioid use disorder	NCT04287062
Dual-Orexin Antagonism as a Mechanism for Improving Sleep and Drug Abstinence in Opioid Use Disorder	Recruiting	Opioid use disorder	NCT04262193
The Efficacy of Suvorexant in Treatment of Patients with Substance Use Disorder and Insomnia: A Pilot Open Trial	Enrolling by invitation	Opioid use disorder Alcohol use disorder	NCT03412591
Suvorexant to Reduce Symptoms of Nicotine Use	Not yet recruiting	Nicotine dependence	NCT04234997
Targeting Orexin to Treat Nicotine Dependence	Recruiting	Nicotine dependence	NCT03999099

Steiner MA, Yanagisawa M, Clozel M (eds): The Orexin System. Basic Science and Role in Sleep Pathology. Front Neurol Neurosci. Basel, Karger, 2021, vol 45, pp 117–127 (DOI: 10.1159/000514965)

Fig. 10.10 Proapoptotic signaling pathway induced by orexins [163]



https://doi.org/10.1007/978-3-031-07897-2_10

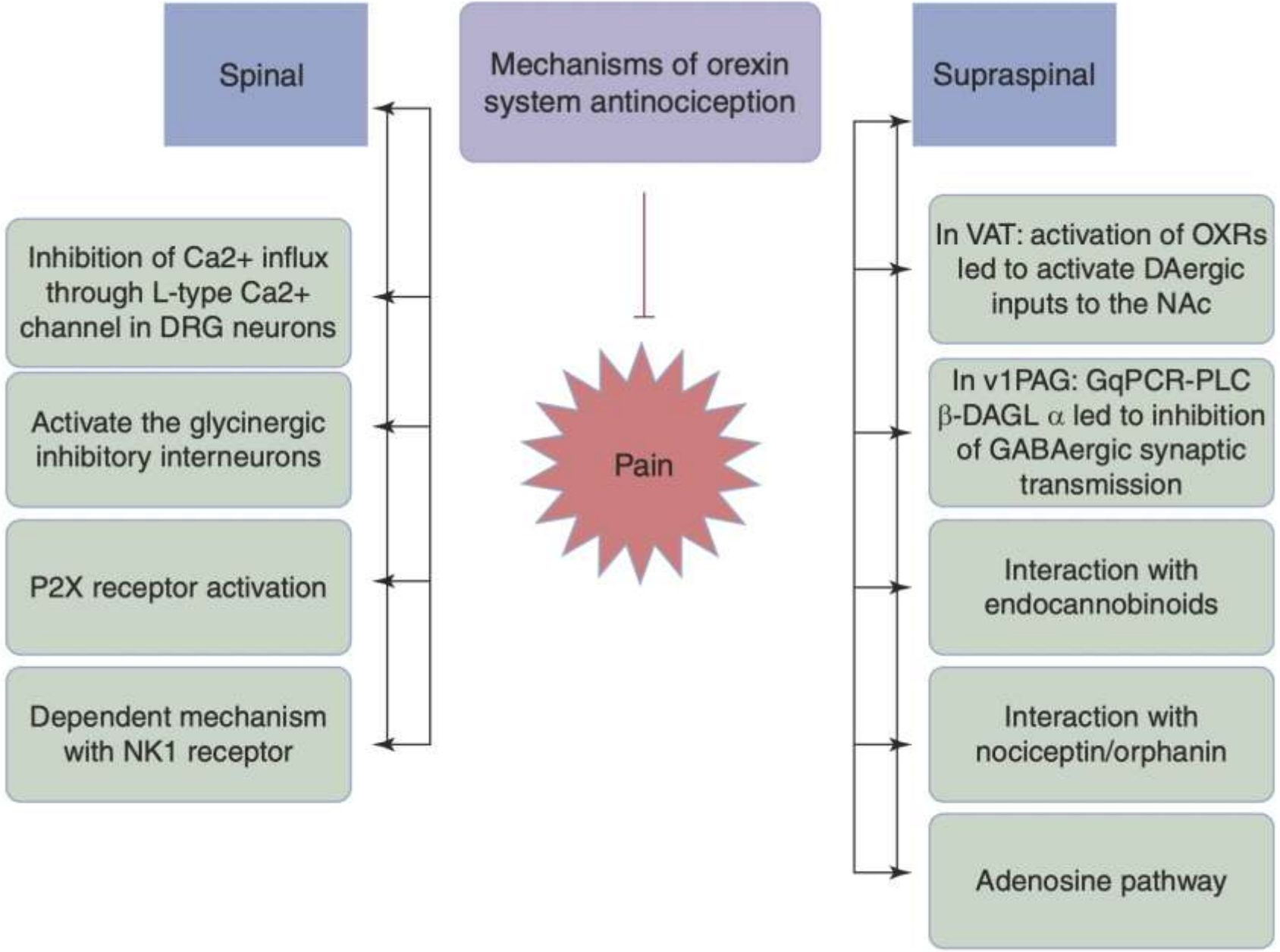
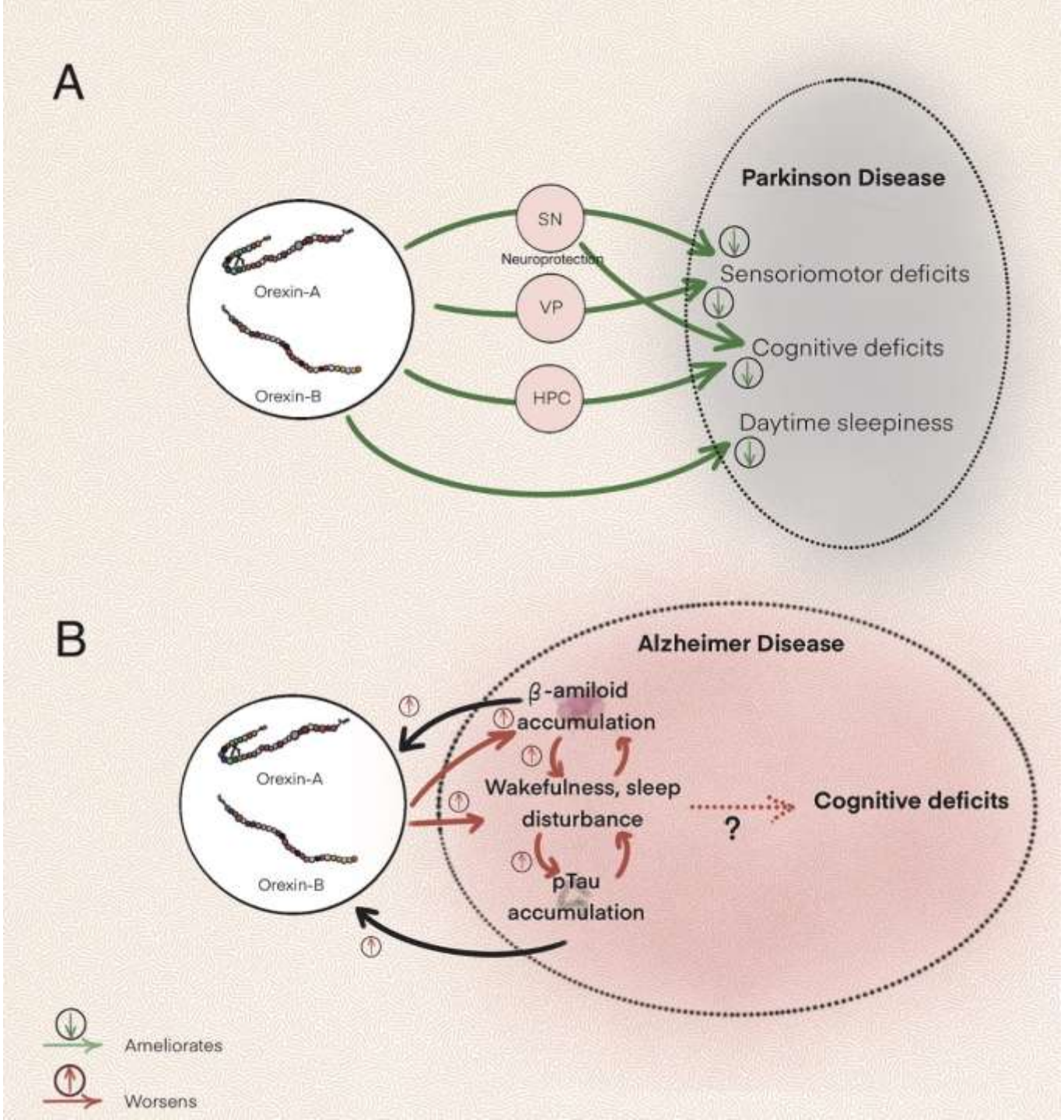


Fig. 10.12 Mechanism of orexin antinociception action [185]

https://doi.org/10.1007/978-3-031-07897-2_10



doi.org/10.1016/j.yfrne.2023.101066

Fig. 4. Orexins are a potential therapeutic target for Parkinson Disease (PD) and Alzheimer Disease (AD). (A) Orexins may exert beneficial effects on PD symptoms by neuroprotecting dopaminergic neurons within the substantia nigra and through other brain regions. (B) In contrast, high orexin levels in AD may increase β-amyloid and tau accumulation by promoting wakefulness among other mechanisms, which in turn increases orexin levels in a positive feedback loop. The consequences for cognitive decline are still unclear. HPC, hippocampus; SN, substantia nigra; VP, ventral pallidum.

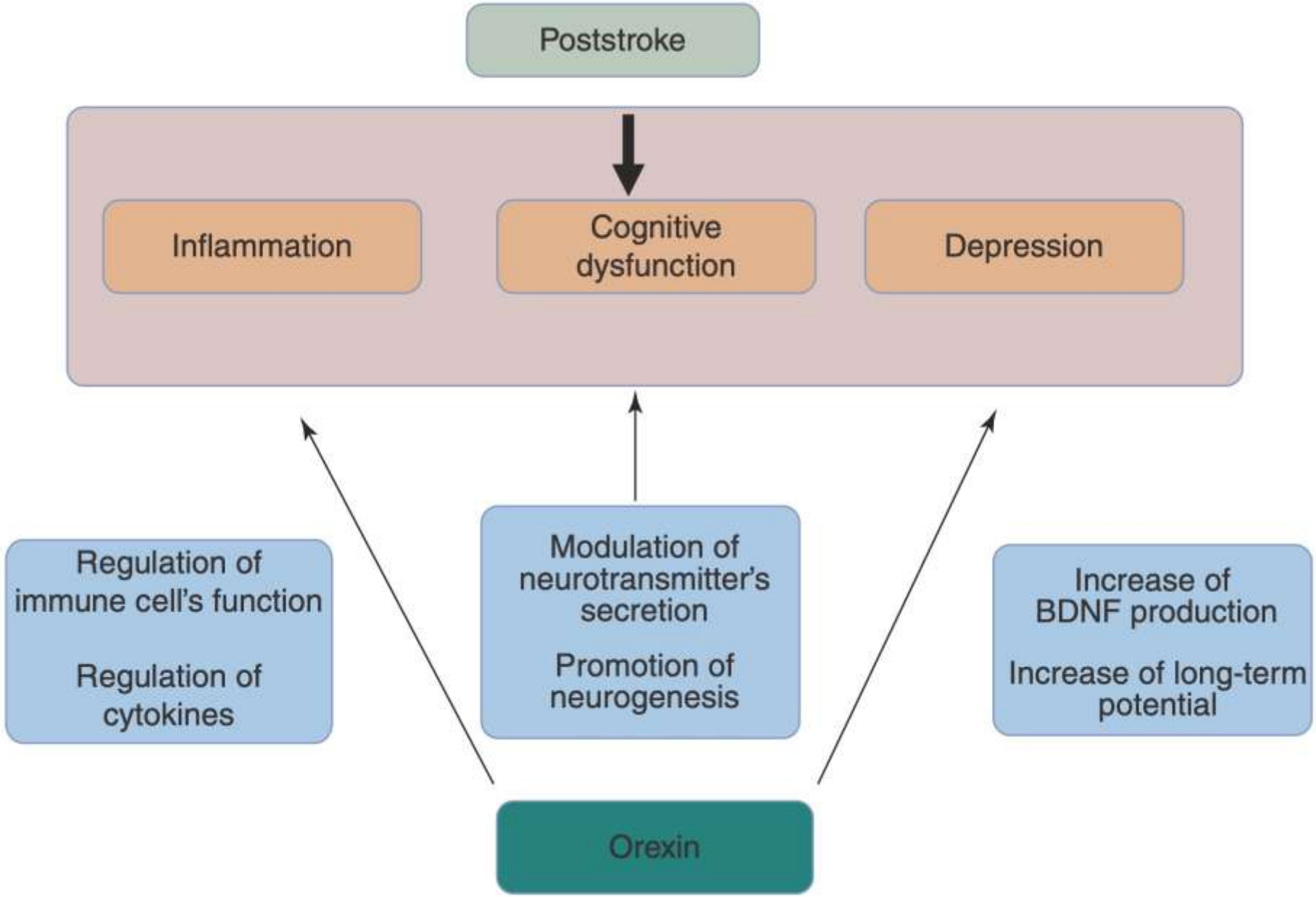
doi.org/10.1016/j.yfrne.2023.101066

- Ageing and Neurogenesis
- AD, PD – reduction
- Orexin - hippocampal neurogenesis enhancer - memory and learning processes
    - Ability to discriminate familiar from new conspecifics and remember them - social memory
- Physical activity increases plasma orexin levels – can enhance hippocampal neurogenesis and function, improve cognition, and regulate mood

doi.org/10.3390/ijerph19148353

AD	Hcrt neurons ↓	Hypothalamus
	Hcrt↓	CSF
	Hcrt↑	CSF
	Normal Hcrt	Left temporal cortex
		CSF
HD	Hcrt neurons ↓ and atrophy	Hypothalamus
	Hcrt neurons ↑ and atrophy	Hypothalamus
	Hcrt-1↓	PFC
	Normal Hcrt-1	CSF

DOI 10.1002/med.21326



https://doi.org/10.1007/978-3-031-07897-2_10

Prader-Willi syndrome	Hcrt-1↓ Normal Hcrt neurons	CSF Hypothalamus
Schizophrenia	Normal Hcrt-1	CSF
PD	Hcrt neurons↓	Hypothalamus
	Hcrt-1↓	CSF
	Normal Hcrt-1	CSF

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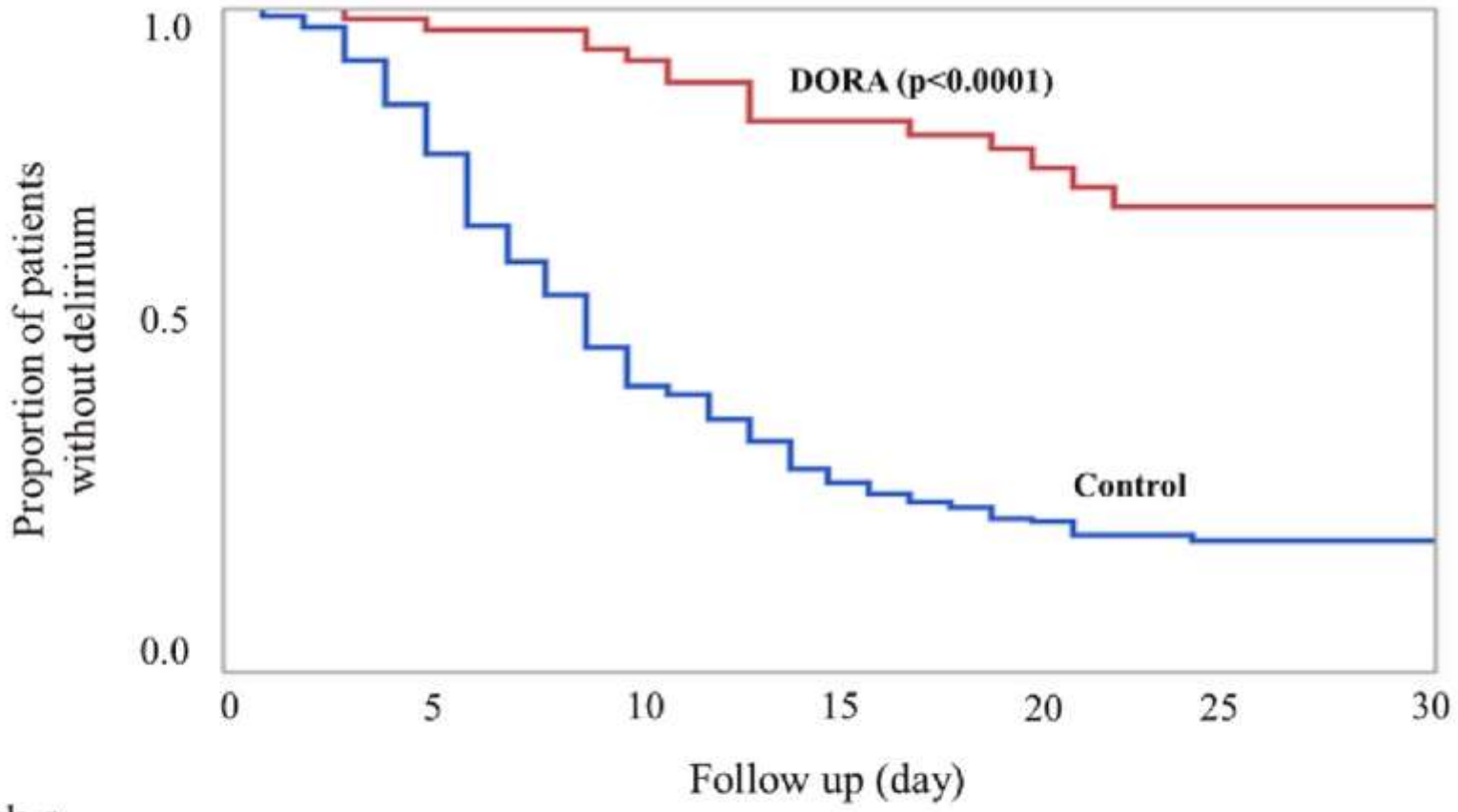
- **297 patients**: 67 - DORA group; 50 - Suvorexant and 17 - Lemborexant
- DORA group - lower incidence of delirium than the control group
- Risk of delirium - lower in the DORA group compared the control group
- Risk of developing delirium was lower with suvorexant (HR 0.22; 95% CI 0.11–0.41) and lemborexant (HR 0.25; 95% CI 0.08–0.81)

Ayaka Matsuoka et al. Evaluation of the delirium preventive effect of dual orexin receptor antagonist (DORA) in critically ill adult patients requiring ventilation with tracheal intubation at an advanced emergency center: A single-center, retrospective, observational study. General Hospital Psychiatry 83 (2023) 123–129



Patients at risk, n

DORA	67	65	57	43	27	25	19
Control	230	191	96	54	30	23	18

Ayaka Matsuoka et al. Evaluation of the delirium preventive effect of dual orexin receptor antagonist (DORA) in critically ill adult patients requiring ventilation with tracheal intubation at an advanced emergency center: A single-center, retrospective, observational study. General Hospital Psychiatry 83 (2023) 123–129

OREXIN RECEPTOR TARGETING

Anxiety Disorders

Fear-related Disorders

Addictive Disorders

Eating Disorders

ANTAGONISM

Insomnia

Alzheimer Disease

AGONISM

Mood Disorders

Parkinson Disease

Narcolepsy

doi.org/10.1016/j.yfrne.2023.101066

Drug group	Compounds	Target nuclei
Orexin-1 receptor antagonist	SB-334867 SB-408124 SB-674042 ACT-335827	Dorsal raphe Locus coeruleus Laterodorsal tegmental nucleus Pedunculopontine tegmental nucleus
Orexin-2 receptor antagonist	TCS-OX2–29 JNJ-10397049 EMPA	Dorsal raphe Tuberomammillary nucleus
Duel orexin receptor antagonist	Almorexant SB-649868 Suvorexant MK-6096	Dorsal raphe Locus coeruleus Laterodorsal tegmental nucleus Tuberomammillary nucleus Pedunculopontine tegmental nucleus

https://doi.org/10.1007/978-3-031-07897-2_10

Pharmacokinetics:

- Lemborexant reached peak concentration in ~1 to 3 hours
- The effective half-life of Lemborexant 5 mg and 10 mg is 17 and 19 hours, respectively

Drug (*examples*)	Recommendation
CYP3A Inhibitors	
Weak (*chlorzoxazone, ranitidine*)	The maximum recommended dose of Lemborexant is 5 mg no more than once per night when co-administered with weak CYP3A inhibitors
Moderate (*fluconazole, verapamil*)	Avoid concomitant use of Lemborexant with moderate or strong CYP3A inhibitors
Strong (*itraconazole, clarithromycin*)	
CYP3A Inducers	
Moderate (*bosentan, efavirenz, etravirine, modafinil*)	Avoid concomitant use of Lemborexant with moderate or strong CYP3A inducers
Strong (*rifampin, carbamazepine, St John's wort*)	
Alcohol	Avoid alcohol consumption with Lemborexant
CYP2B6 Substrates *(bupropion, methadone)*	Patients receiving Lemborexant and CYP2B6 substrates concurrently should be monitored for adequate clinical response. Increasing the doses of CYP2B6 substrates may be considered as needed

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212028s000lbl.pdf

Dosage and Administration

- Recommended proven starting dose of Lemborexant is 5 mg
- Maximum recommended dose is 10 mg, based on clinical response and tolerability
- Taken immediately before going to bed and with at least 7 hours remaining before the planned time of awakening
- Lemborexant should not be taken more than once per night
- Time to sleep onset may be delayed if taken with, or soon after, a meal

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212028s000lbl.pdf

Dosage and Administration

- No need for dose adjustment based on age, sex, and BMI
- Exercise caution when using 10 mg in patients ≥65 years of age
- No dosage adjustments needed in Mild, Moderate or Severe Renal Impairment is needed
- No dosage adjustment needed in Mild Hepatic Impairment; 5 mg dosage in recommended in Moderate Hepatic Impairment while it has not been studied in Severe Hepatic Impairment and not recommended

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212028s000lbl.pdf

Full study period (combined Period 1 and Period 2)	LEM5 ($n = 61$)	LEM10 ($n = 58$)
Category, *n* (%)		
Any TEAE	27 (44.3)	33 (56.9)
Any treatment-related TEAE	9 (14.8)	12 (20.7)
Any severe TEAE	2 (3.3)	0
Any serious TEAE	2 (3.3)	0
TEAE leading to study drug withdrawal	2 (3.3)	2 (3.4)
TEAEs with incidence >4% in any active treatment group, *n* (%)		
Nasopharyngitis	8 (13.1)	14 (24.1)
Somnolence	6 (9.8)	9 (15.5)
Influenza	2 (3.3)	4 (6.9)
Headache	3 (4.9)	2 (3.4)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212028s000lbl.pdf

Rebound Insomnia and Withdrawal Effects

- No rebound insomnia following treatment discontinuation
- No evidence of withdrawal effects following discontinuation at either dose

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212028s000lbl.pdf

Special Safety Assessments

- **Postural Stability Study:**
  - No clinically significant impact on postural stability was observed with Lemborexant (5 mg or 10 mg) upon Morning Awakening (post 8 hours of dose)

- **Driving Performance Study:**
  - Lemborexant (5 mg or 10 mg) did not cause statistically significant impairment in morning driving performance of healthy volunteers vs those taking placebo

- **Abuse Potential Studies:**
  - Not associated with physical dependence, or reinforcing effects

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212028s000lbl.pdf

Additional Safety Studies

- **Respiratory Safety**
  - Lemborexant did not decrease the SpO_2 – Healthy / OSA
- **Co-administered Alcohol**
  - No impact on postural stability
  - An additive negative effect on cognitive performance
- **Drug Abuse Potential**
  - Negative results

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212028s000lbl.pdf

Table III. Orexin System Targeted Therapeutic Strategies

Strategies	Agents	Brain areas/delivery methods	Subjects	Effects
Gene delivery	Prepro-orexin	Whole brain	Mice	Cataplexy↓↓ REM sleep abnormality
		Zona incerta LH	Mice	Cataplexy↓ CSF orexin-A↑
		Dorsolateral pons	Mice	Cataplexy↓Wake maintenance↑
	Hcrtr1	Mediobasal hypothalamus	Mice	Wakefulness ↑ fragmented sleep↓
		Tuberomammillary nucleus Posterior hypothalamus	Mice	Wake maintenance↑
Agonist	Orexin-A	ICV	Mice	Cataplexy↓ Wakefulness↑
		IV	Canines	Cataplexy↓ Waking, activity level↑ REM sleep↓
		ICV/IV	Canines	No effects
		Intranasal administration	Humans	REM sleep↓↓ Wake to REM transitions
		Intranasal administration	Humans	Olfactory dysfunction is improved
OX_1 receptor antagonist	SB334867	ICV	Rats	Food intake, active behaviors↓ Resting↑
OX_2 receptor antagonist	EMPA	IP	Mice	Hyperlocomotion↓↓
			Rats	Spontaneous locomotor activity
	TCS-OX2–29	ICV	Rats	Wakefulness↓ REM sleep↑
Dual receptor antagonists	Almorexant	ICV	Mices	Sleep↑ Orexin-induced locomotion↓
		Oral administration	Rats	Sleep↑
			Canines	Somnolence and REM sleep↑
			Humans	Subjective and objective sleep↑
	Suvorexant	Oral administration	Rats	Sleep↑
			Canines Rhesus monkeys	Locomotor activity↓
		Oral administration	Humans	Sleep efficiency ↑ Sleep induction, maintenance↑
		Oral administration	Humans	Sleep latency↓ Sleep efficiency↑
	DORA-22	Oral administration	Rats	Sleep ↑
			Rhesus monkeys	Cognition is not impaired
Cell transplantation	Posterior hypothalamic cells		Rats	Orexin-immunoreactive neurons↑

↑, increased; ↓, decreased; IV, intravenous injection; IP, intraperitoneal injection; DORA, dual orexin receptor antagonist.

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Thank You