

CNS hypersomnias and progress in understanding narcolepsy

THOMAS SCAMMELL, MD

HARVARD MEDICAL SCHOOL

BETH ISRAEL DEACONESS MEDICAL CENTER

Disclosures

Consulting: Avadel, Axsome, Consynance, Eisai, Harmony Biosciences, Idorsia, Jazz Pharmaceuticals, Merck, Takeda, and Woolsey Pharmaceuticals.

Grant support: Jazz Pharmaceuticals, Harmony Biosciences, Takeda.

CNS Hypersomnias

Narcolepsy Type 1

- Chronic sleepiness
- Cataplexy: brief, emotionally-triggered episodes of muscle weakness
- Other REM sleep-like phenomena
 - Sleep paralysis
 - Hypnagogic and hypnopompic hallucinations
- Fragmented sleep

Idiopathic hypersomnia

- Chronic sleepiness
- Long sleep times (>11 hrs)
- Severe sleep inertia

Narcolepsy Type 2

- Chronic sleepiness
- Other REM sleep-like phenomena
 - Sleep paralysis
 - Hypnagogic and hypnopompic hallucinations
- Fragmented sleep

Kleine-Levin Syndrome

- Episodes of long sleep times (12-20 hrs) lasting ~1 wk
- Psychologically abnormal during episodes
- Sometimes hyperphagia, hypersexuality
- Normal between episodes

Early perspectives on narcolepsy



Westphal



Gélineau

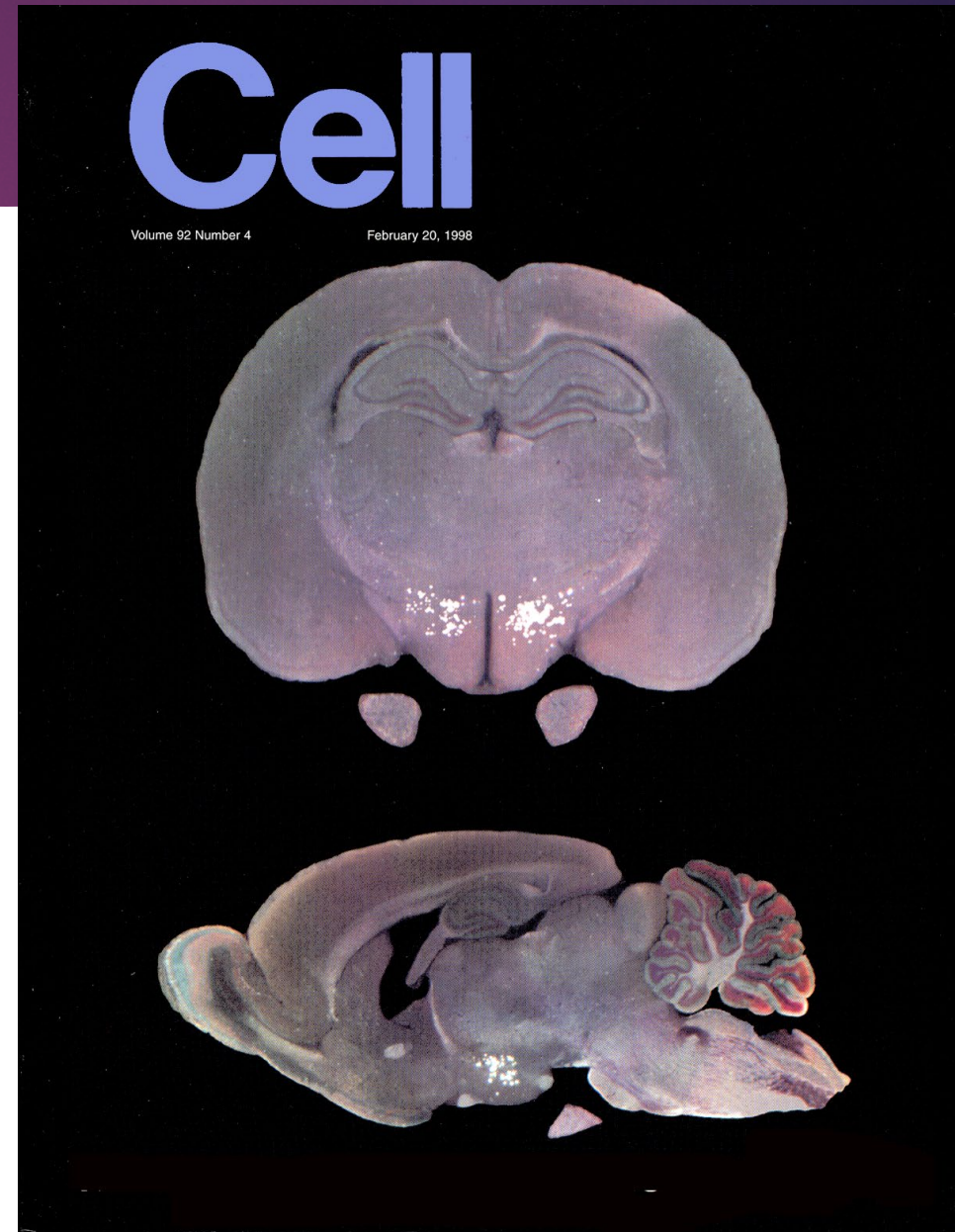
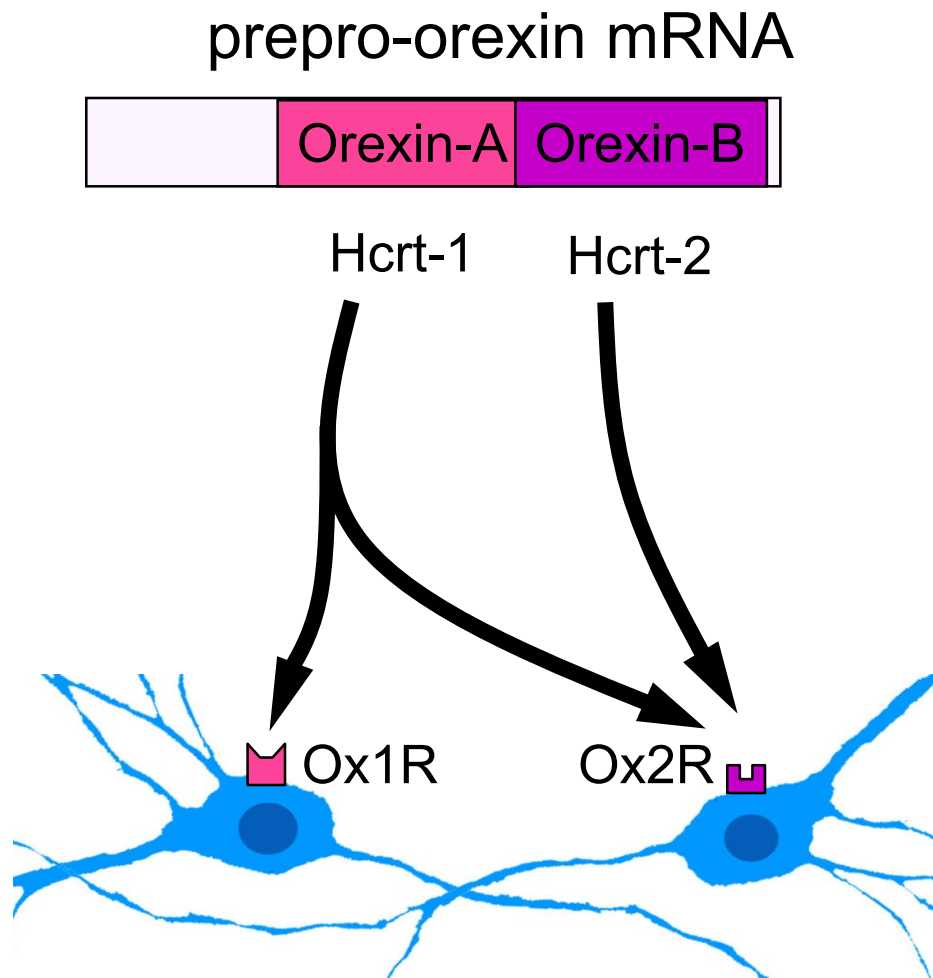


Von Economo

1877 - Narcolepsy first described

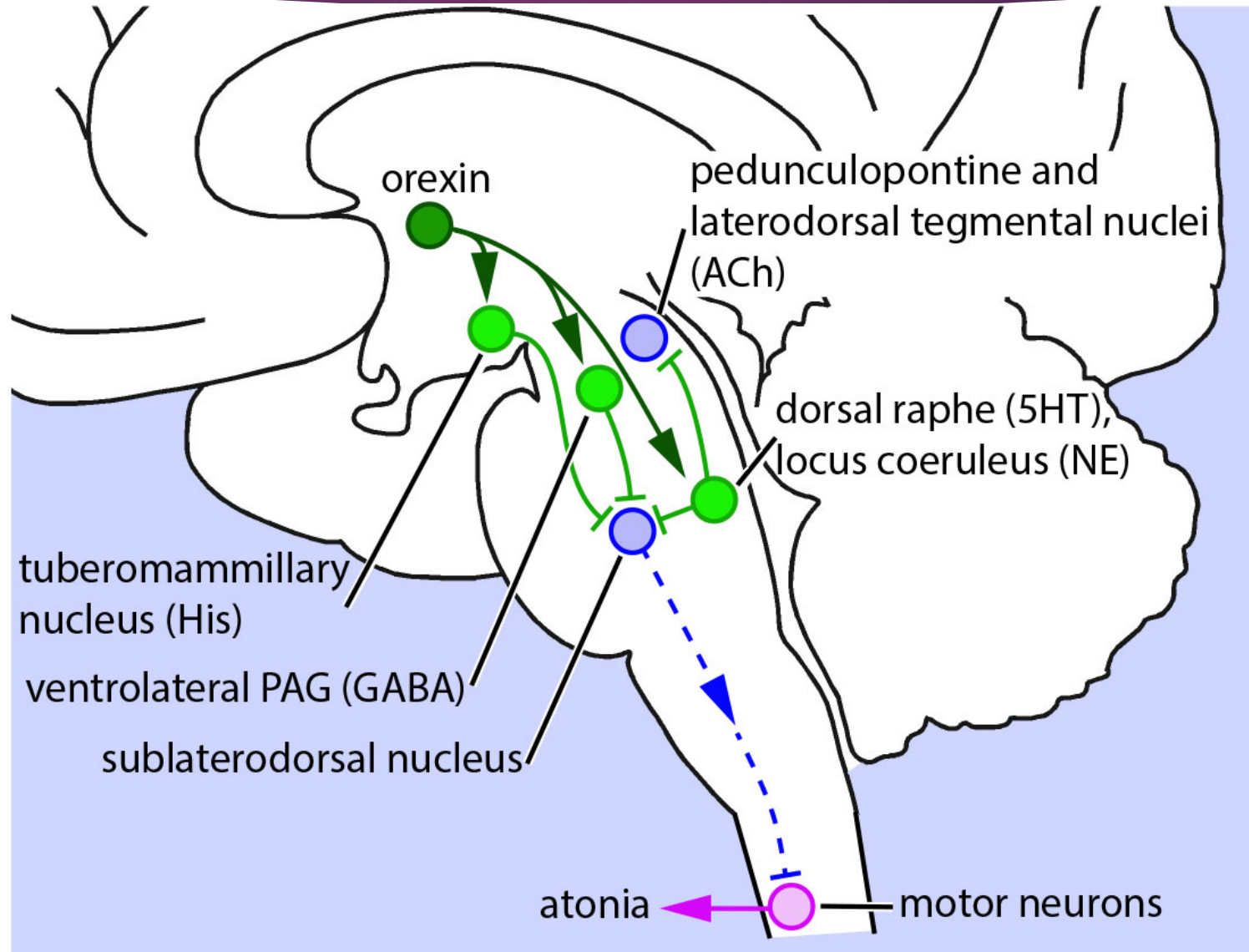
1918 – Hypothalamic injury hypothesized

Orexins/Hypocretins

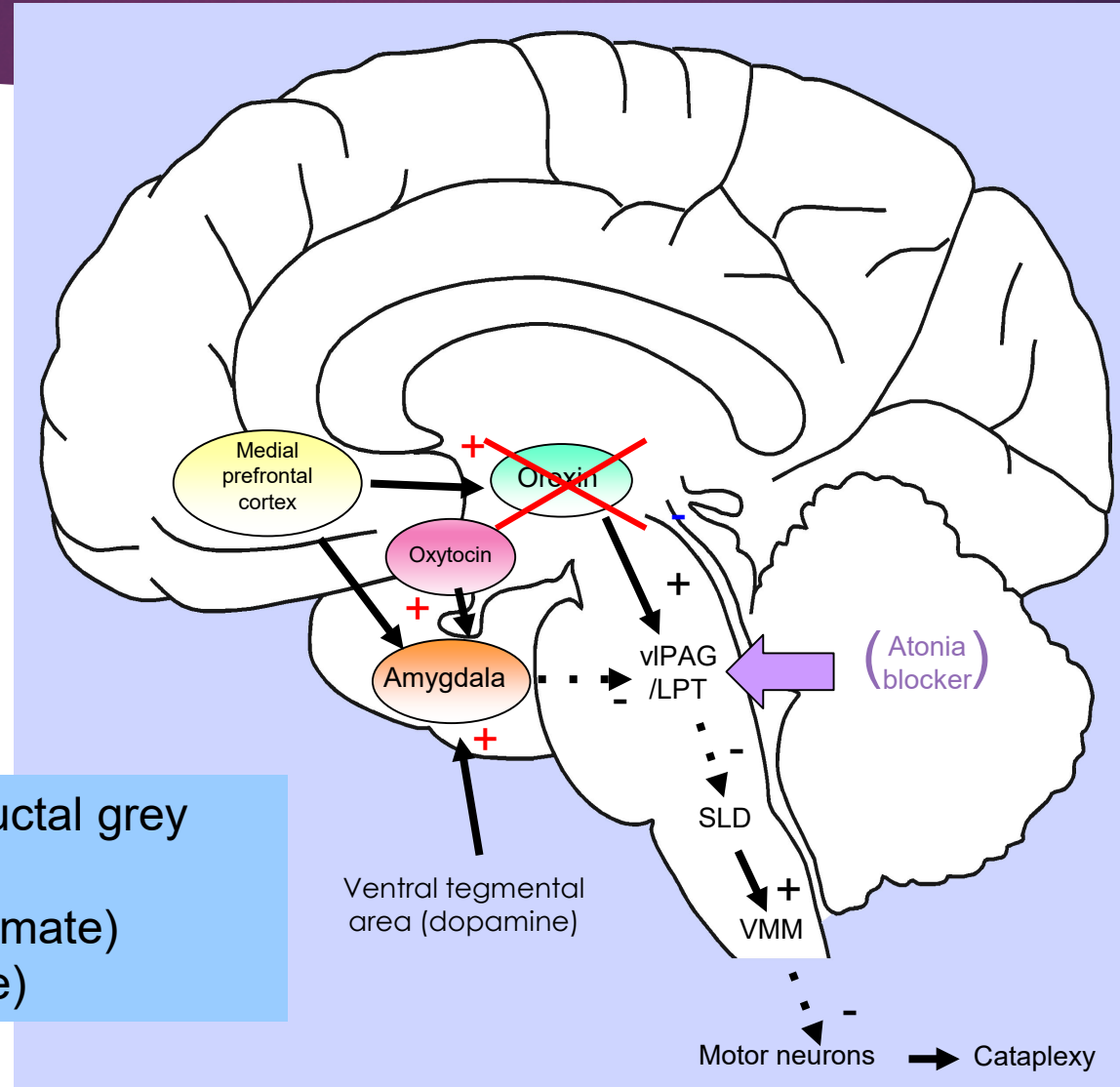


Sakurai, et al, 1998; de Lecea, et al, 1998

Orexins promote arousal and suppress REM sleep

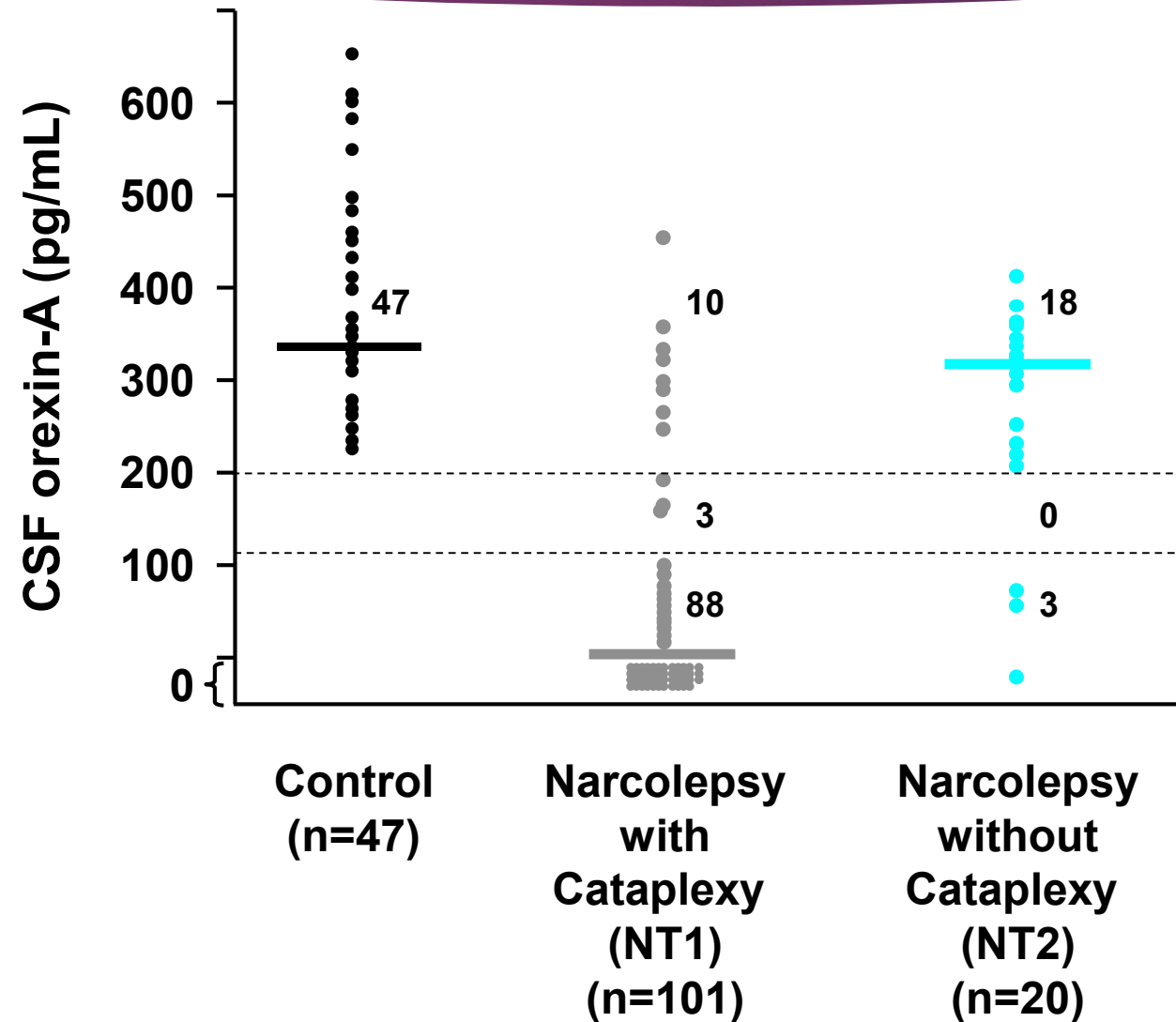


Proposed model for cataplexy

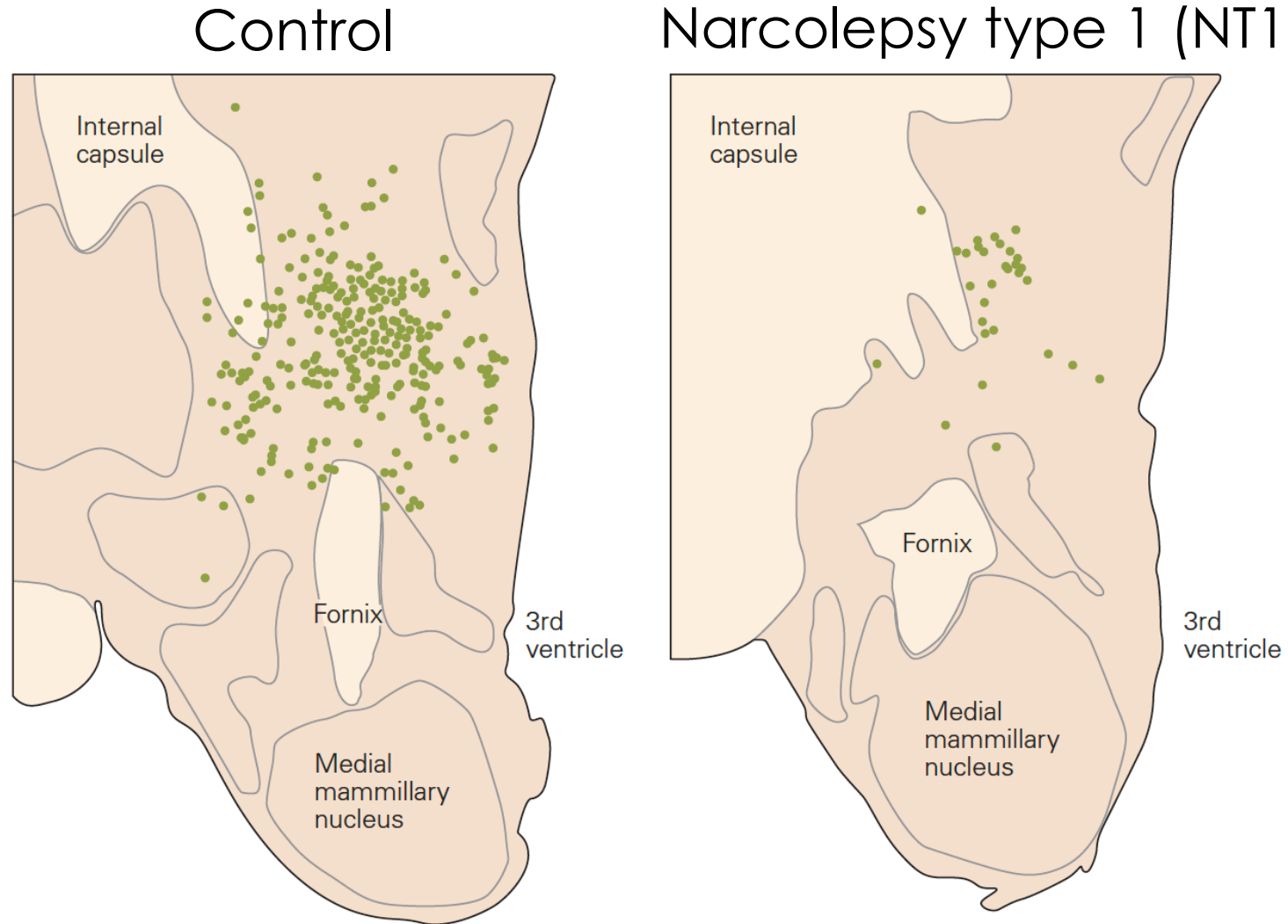


vIPAG/LPT: ventrolateral periaqueductal grey
and lateral pontine tegmentum
SLD: sublaterodorsal nucleus (glutamate)
VMM: ventromedial medulla (glycine)

Low orexin levels in narcolepsy type 1

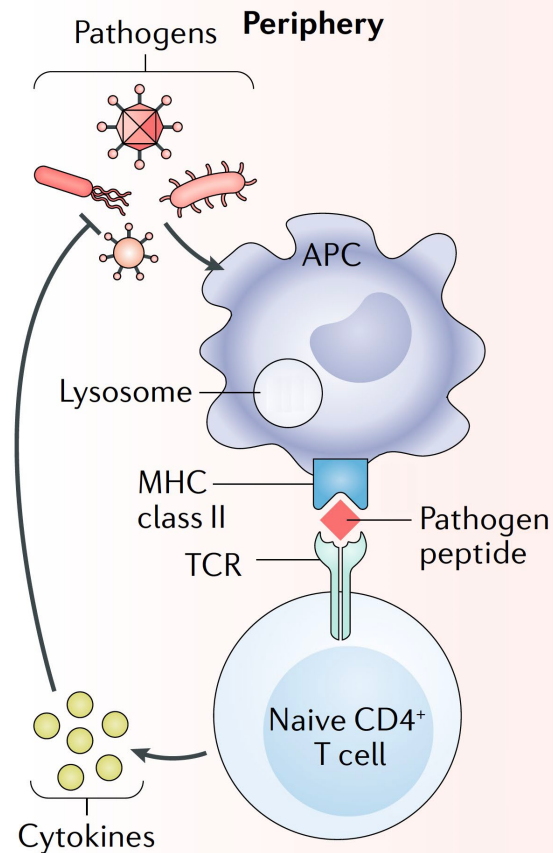


Loss of orexin neurons in narcolepsy type 1



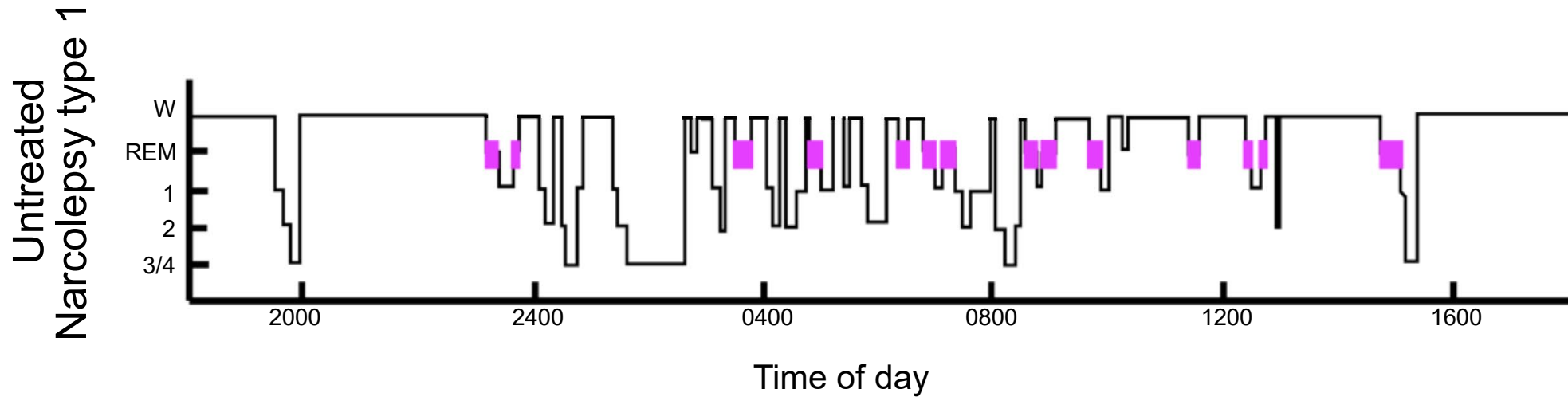
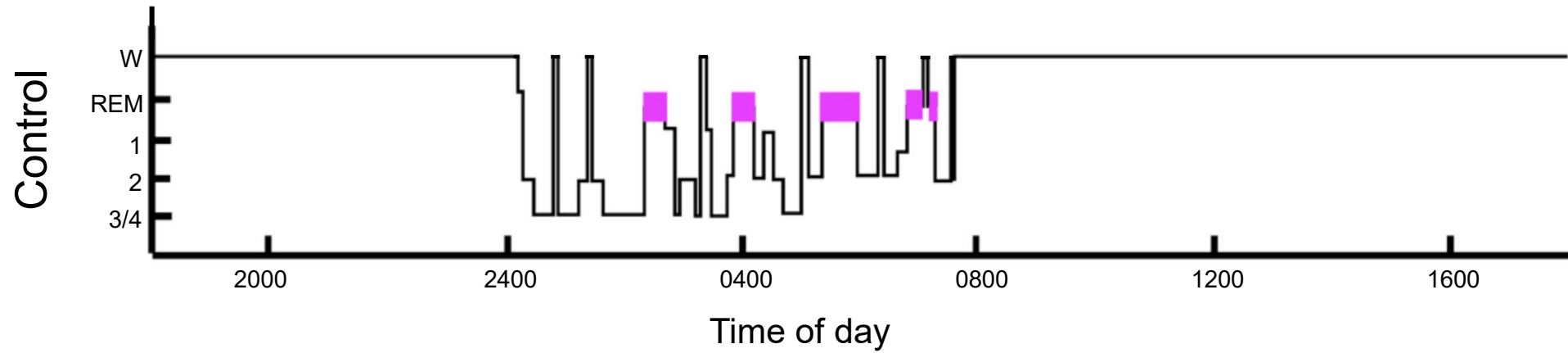
Peyron, et al 2000; Thannickal, et al, 2000; Crocker, et al, 2005; Valko, et al, 2013

Molecular mimicry and narcolepsy



NT1 patients often have T cells (CD4 and CD8) that are activated by prepro-orexin.
(Mignot, 2013; Latorre, et al 2018; Luo, et al, 2018; Cogswell, et al, 2019)

24 hour sleep recordings



Adapted from Rogers et al. *Sleep*. 1994;17:590.

Current medications for narcolepsy

▶ **Sleepiness**

- ▶ Amphetamines (methylphenidate, dextroamphetamine, etc.)
- ▶ Modafinil, armodafinil, solriamfetol, pitolisant
- ▶ Oxybates

▶ **Cataplexy**

- ▶ Antidepressants (venlafaxine, fluoxetine, clomipramine, etc.)
- ▶ Pitolisant
- ▶ Oxybates

▶ Limited efficacy of current “optimal” therapies

- ▶ Mental foginess, unintentional sleep, poor school and work performance, and car accidents are common.
- ▶ Maintenance of wakefulness test latencies are 50-70% of normal

▶ Side effects moderately common with current meds.

Progress and unanswered questions



- ▶ Can we stop the autoimmune destruction of the orexin neurons?
- ▶ What causes narcolepsy type 2? IH? KLS?
- ▶ What are the key neurons that mediate sleepiness and cataplexy, and can these be targeted therapeutically?
- ▶ We need more effective therapies with fewer side effects. Can we develop medications to restore orexin signaling?