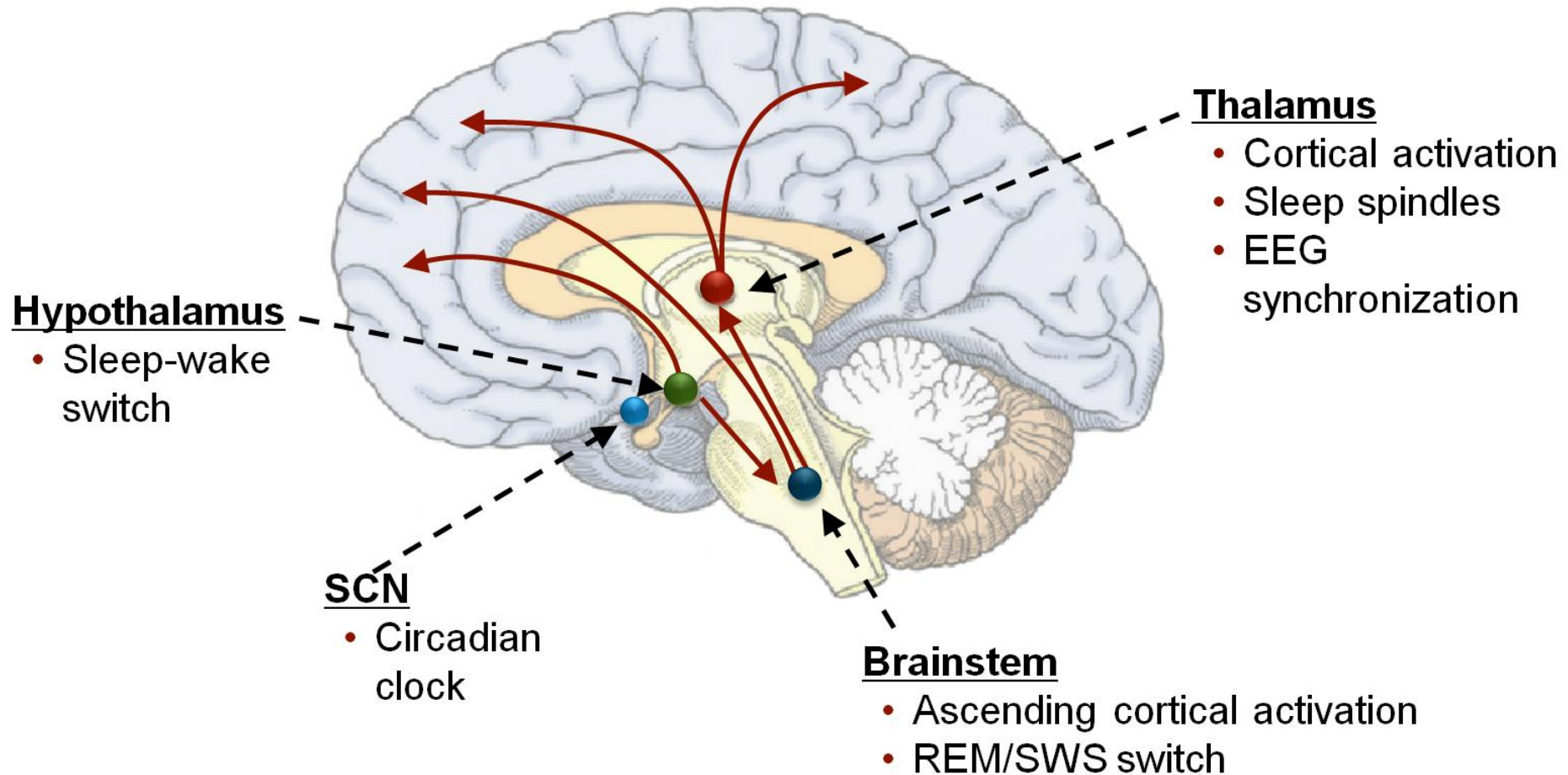


# **CAUSES OF HYPERSOMNIA NARCOLEPSY**

**M.V. PADMA SRIVASTAVA MD, DM, FAMS, F.N.A.Sc**  
**PROFESSOR**  
**DEPT. OF NEUROLOGY**  
**AIIMS, NEW DELHI.**

# Wakefulness/Sleep: Neurophysiology



# Narcolepsy Introduction

- What is it?
- A neurologic disorder causing daytime sleepiness
- A disorder involving REM sleep that in many cases induces symptoms of:
  - Cataplexy
  - Sleep paralysis
  - Hypnagogic hallucinations
  - Disturbed and disordered sleep
- A disorder developing due to orexin/hypocretin deficiency

# NARCOLEPSY

- Frequency: 0.09% Prevalence
- Genetic Predisposition +
- M:F=1.64:1
- Age Of Onset: 3-72 Years
- Peaks in Teens & Early 30s

# Milestones in Clinical and Basic Research in Narcolepsy

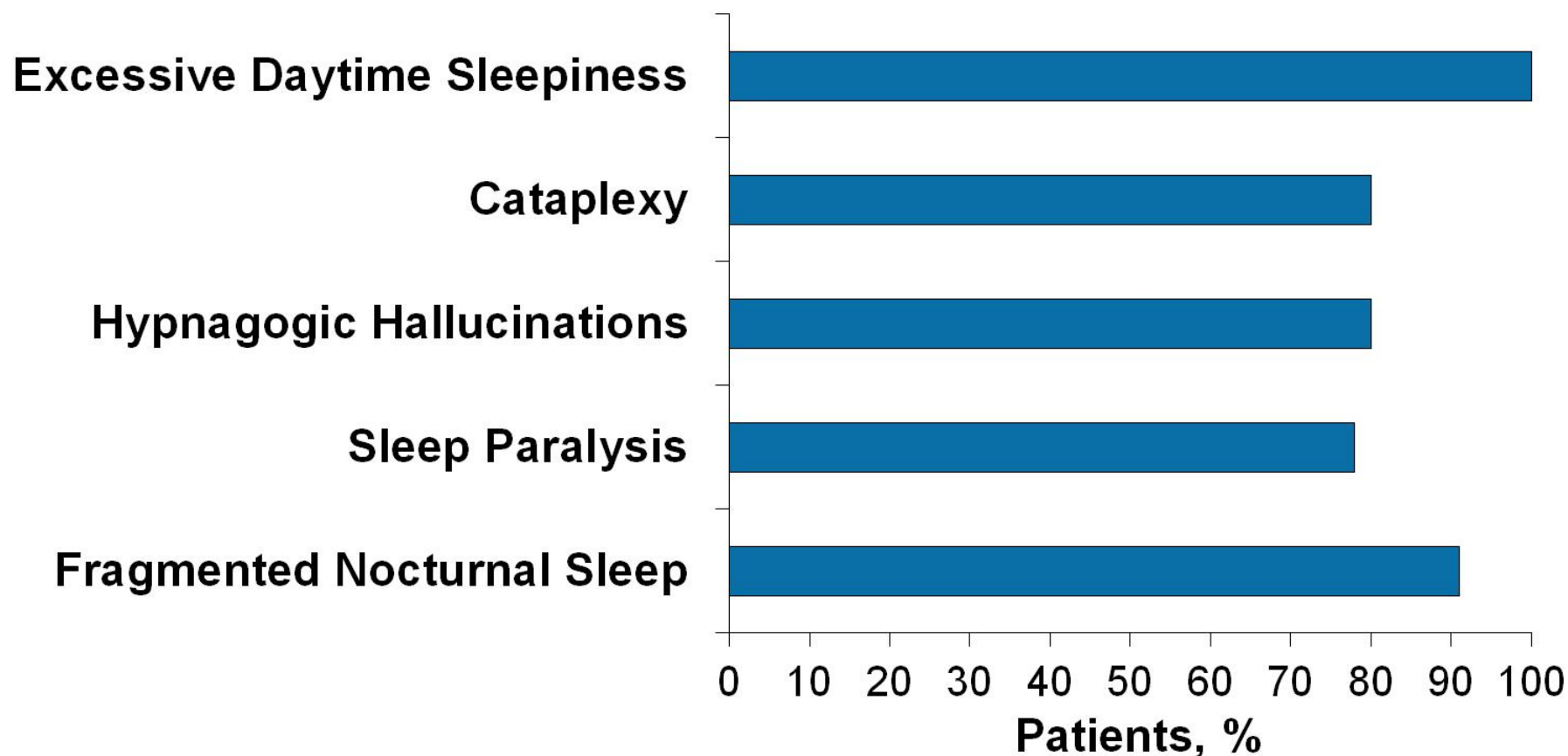
- 1877 First description in medical literature (Westphal)
- 1880 Gelineau called the disorder "narcolepsy"
- 1902 Loewenfeld coined the term "cataplexy"
- 1920 Anatomic substrate for symptoms of narcolepsy (von Economo)
- 1935 Amphetamines for the treatment of narcolepsy
- 1960 Tricyclics as anticataplectic medications
- 1960 Sleep-onset REM periods in narcoleptic subjects<sup>a</sup>
- 1970 Discovery of narcoleptic dogs<sup>b</sup>
- 1983 Association of narcolepsy with HLA-DR2<sup>c</sup>
- 1999/2000 Discovery of hypocretin involvement in animal and human narcolepsy<sup>d</sup>

a. Vogel G, et al. *Pharmacol Biochem Behav.* 1988;31:103-106<sup>[5]</sup>; b. Mitler MM, et al. *Exp Neurol.* 1974;45:332-340<sup>[6]</sup>; c. Honda Y. *HLA in Narcolepsy.* 1988:24-57<sup>[7]</sup>; d. Lin L, et al. *Cell.* 1999;98:365-376.<sup>[8]</sup>

# **SIGNS & SYMPTOMS**

- EDS
- Cataplexy
- Hypnagogic Hallucinations
- Sleep Paralysis

# Narcolepsy: Symptom Prevalence (Upper Range)



Guilleminault and Cao. Narcolepsy: diagnosis and management. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 5th ed. St Louis, MO: Saunders; 1994<sup>[15]</sup>; Scammel TE. *Ann Neurol*. 2003;53:154-166<sup>[16]</sup>; Overeem S, et al. *J Clin Neurophysiol*. 2001;18:78-105<sup>[17]</sup>; Nishino and Mignot. *Prog Neurobiol*. 1997;52:27-78.<sup>[18]</sup>

# Sleep Disorders Frequently Found Concomitant With Narcolepsy

- Obstructive sleep apnea
- Periodic limb movement syndrome
- REM sleep behavior disorder
- Fragmented sleep



# EDS

- Sleep interludes
- Impaired attention
- ↓ Apparent memory

# Common Causes of EDS

- Chronic behavioral/circadian sleep deprivation
- Sedating medications
- OSA
- Mood disorders and depression

# CATAPLEXY

- 65%-70% of patients
- If severe & generalized → fall
- Partial loss of tone
- Respiratory & extra ocular movements are preserved
- Triggered by emotions

# SLEEP PARALYSIS

- 60% of patients
- Patient is unable to move on awakening
- Less commonly, unable to move on falling asleep
- Hallucinations
- Respiratory & extra ocular muscles are spared
- Paralysis occurs less frequently when the person sleeps in an uncomfortable position.
- Relieved by sensory stimuli.

# HALLUCINATIONS

- 15%-50% of cases
- Hypnagogic or Hypnopompic
- Vivid & frightening
- May be accompanied by paralysis

# OTHER COMMON FEATURES

- Tendency to take short & refreshing naps during the day
- Trouble sleeping at night
- Nocturnal compulsive behavior
- Obesity

# FEATURES OF NARCOLEPSY IN CHILDREN

- Restlessness & motor over activity
- Academic deterioration, inattentiveness, emotional lability
- Wide range of motor disturbance at onset
- Hypotonia and Hypertonia
- Motor disturbance resolve factor

# Narcolepsy: Burden of Disease

## Profound individual and socioeconomic burden

- ↓ Performance: school and workplace
- ↑ Interpersonal difficulty (relationships)
- ↓ Social interaction
- ↑ Accidents/injury: automobile and workplace
- ↑ Depression and anxiety
- ↓ Self-esteem



# Burden of Narcolepsy Disease (BOND) Study

- Results of the BOND study (funded by Jazz Pharmaceuticals) were presented at SLEEP 2013 and have not yet been published in a peer-review journal
- Insurance database survey of 9312 narcolepsy patients with 46,559 matched controls continuously insured from 2006 to 2010
- People with narcolepsy, with or without cataplexy (muscle weakness), were more likely to have an increased rate of comorbidities, including mental illness, endocrine disorders, digestive disorders, and cardiovascular disease when compared with the general population
  - 51.4% had OSA
  - 35.8% had depressive disorders
- People with narcolepsy have significantly higher health and medical costs compared with the general population.
  - Mean annual medical costs 2 × as high (\$8346 vs \$4147)
  - Employed subjects had almost 2 × as many disability days (7.6 vs 3.0)

# How to Identify the Patient With Narcolepsy?

- Unexplained EDS
- Do not have OSA
- Not taking sedating medications
- Onset in adolescence
- Sleepiness affects their daytime functioning

# Assessing for Narcolepsy

## Tools/Questionnaires

- Sleepiness scales
  - eg, Epworth
- Sleep history
- Sleep diary

## EDS History

- Familial
- Age of onset

# DIAGNOSIS

## DSM-5 criteria

- Episodes of irrepressible need to sleep at least 3 times/week for 3 months +
- Episodes of cataplexy- few times/ months
- Hypocretin deficiency
- REM sleep latency <15 mins or a mean sleep latency <8 mins. & 2 or more SOREMPs

# SUBTYPES

- Narcolepsy with out cataplexy with hypocretin deficiency
- Narcolepsy with cataplexy without hypocretin deficiency
- AD cerebellar ataxia, deafness & Narcolepsy
- AD narcolepsy, obesity & type 2 DM
- Narcolepsy secondary to another medical condition

# DIAGNOSIS

- PSG + MSLT
- MSLT= <8 min of sleep latency  
2 or more SOREMPs.
- CSF Hypocretin <110 pg/ml
- No better explanation including neurologic, mental, medical disease or drug/ substance use.

# Testing

## Multiple Sleep Latency Testing

- Positive study for narcolepsy has:
  - > 2 sleep-onset REM periods
  - mean sleep latency < 8 min
- False-negative results can occur in individuals taking REM-suppressant medications such as antidepressants or benzodiazepines
- False-positive results can occur in individuals with PTSD, mood disorders, and in sleep-deprived patients
- Both sedating and activating medications can alter sleep latency
- Serial MSLTs are sometimes required for diagnosis

# DSM-5 Diagnostic Criteria for Narcolepsy

- A. EDS at least 3 times per week over the past 3 months.
- B. Presence of at least 1 of the following:
  - 1. Episodes of cataplexy, defined as either (a) or (b):
    - a. In individuals with long-standing disease, brief (seconds to minutes) episodes of sudden bilateral loss of muscle tone with maintained consciousness that are precipitated by laughter or joking.
    - b. In children or in individuals within 6 months of onset, spontaneous grimaces or jaw-opening episodes with tongue thrusting or a global hypotonia, without any obvious emotional triggers.



# DSM-5 Diagnostic Criteria for Narcolepsy

2. Low CSF levels of hypocretin-1 must not be observed in the context of acute brain injury, inflammation, or infection.
3. Nocturnal PSG showing REM sleep latency  $\leq 15$  min, or MSLT showing a mean sleep latency  $\leq 8$  min and 2 or more sleep-onset REM periods.

# Proposed New ICSD-3 Definitions of Narcolepsy<sup>a</sup>

## Narcolepsy Type 1 (Narcolepsy with cataplexy)

- EDS for at least 3 months.
- One of the following:
  - Definite cataplexy and positive MSLT result\*
    - If narcolepsy type 1 is strongly suspected clinically but MSLT criteria are not met, repeat the MSLT
  - Low CSF hypocretin-1 ( $\leq 110$  pg/mL or  $< 1/3$  of normal)

## Narcolepsy Type 2 (Narcolepsy without cataplexy)

- EDS for at least 3 months.
- Cataplexy is absent
- Positive MSLT\*
- Normal CSF hypocretin-1 ( $> 110$  pg/mL or  $\geq 1/3$  of normal) or not measured.

\*Positive MSLT: mean sleep latency of  $\leq 8$  min and  $\geq 2$  SOREMPs. A SOREMP on the preceding nocturnal PSG may replace one of the SOREMPs on the MSLT.

a. TE Scammell, personal communication.

# Differential Diagnosis

- Behavioral and circadian disturbance in adolescence
  - Sleep history
  - Assessing a sleep diary
- Sedating medications
- Cataplexy versus absence seizures

# PATHOPHYSIOLOGY

- Genetic predisposition
- Abnormal neurotransmitter functioning & sensitivity
- Abnormal immune modulation

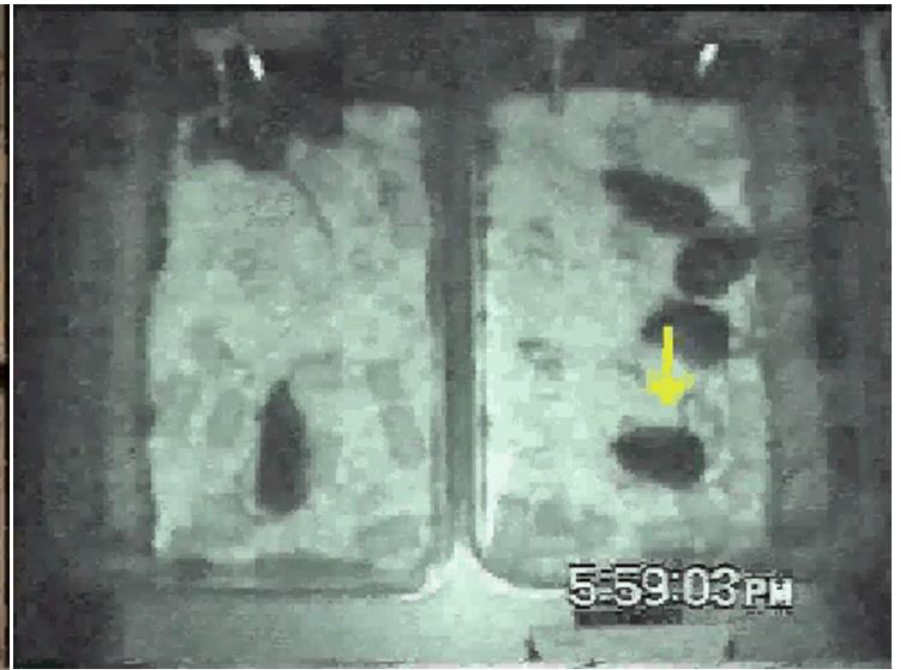
# ANIMAL MODELS

- Muscarinic cholinergic stimulation- ↑
- Cholinergic blockade - ↓
- Alpha-1- noradrenergic receptors- mediate
- Prazocin – worsens

## *HCRTR2* Mutation in Familial Canine Narcolepsy<sup>a</sup>



## Orexin/Hypocretin Gene Knockout Mice Display Narcolepsy<sup>b</sup>



Video used with permission of Dr. Seiji Nishino, Stanford University, Stanford, CA.

a. Lin L, et al. *Cell*. 1999;98:365-376<sup>[8]</sup>; b. Chemelli RM, et al. *Cell*. 1999;98:437-451.<sup>[9]</sup>

# NEURO- ANATOMIC SITES

- Pons
- Mesocorticolimbic dopaminergic system

# ABNORMAL IMMUNE- MODULATION

- Vaccine against H<sub>1</sub>N<sub>1</sub> using potent ASO<sub>3</sub> adjuvant.
- HLA DQB\*0602 allele



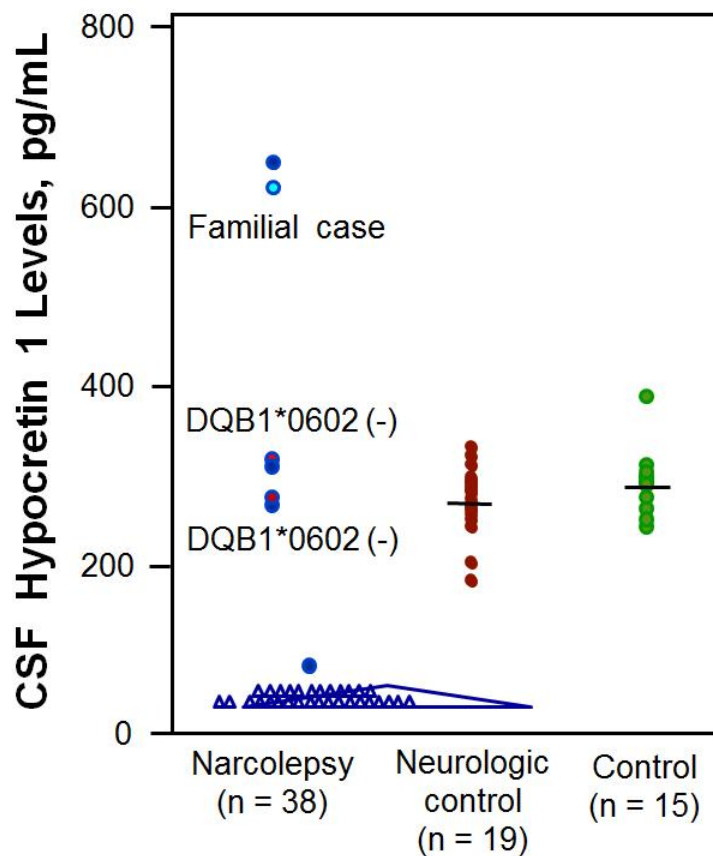
# REM SLEEP

- Dysfunction & inappropriate regulation
- Neuro-anatomic control → Pontine RAS
- REM –on cells – cholinergic
- REM –off cells – noradrenergic/serotonergic
- ? Defective monoamine- dependent inhibition of REM – on cells

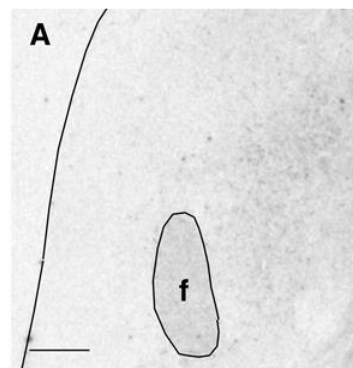
# HYPOCRETIN

- ↓ CSF level of hypocretin
- ↓ number of hypocretin neurons
- Instability of sleep/ wake states
- Hypocretin neurons → autoexcitatory

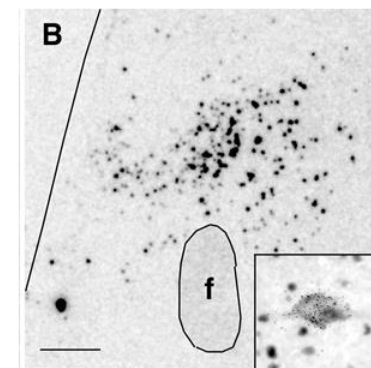
# Absence of Hypocretin Peptide and Signal in the CSF and the Hypothalamus of Narcoleptic Patients



A. Narcoleptic



B. Control



**Prepro-hypocretin messenger RNA in the lateral hypothalamic area**

# PROJECT FROM LATERAL HYPOTHALAMUS TO MAINTAIN WAKEFULNESS



# HISTAMINE

- Maintains wakefulness
- ↓ levels in CSF
- Also seen in “hypocretin normal” patients
- Idiopathic hypersomnia
- Normal in OSA
- ? Biomarker reflecting the degree of hypersomnia of central origin

# CNS NUCLEI FOR WAKEFULNESS

- Locus ceruleus — Norepinephrine
- Raphe nucleus — Serotonin
- Tubo mammillary nucleus — Histamine
- Ventral Tegmental area — Dopamine
- Basal forebrain — Acetylcholine

# ? AUTOIMMUNE PROCESS

- Auto antigen against Tribbles homolog 2 (Trib 2)
- ? Destruction of hypocretin- producing neurons
- ? IV Ig trails

# GENETIC FACTORS

- 40% risk in I<sup>o</sup> relatives
- 90% carry HCA DR 15 & HLA DQ gene
- Siblings have 60 fold<sup>↑</sup> risk.
- Associated with HLA DQA101:02 DQB1 06:02
- GWA studies : - Protective variants DQB1 06:03
- Association between SNP in the Tcell receptor alpha locus & narcolepsy
- SNP in the purigenic receptor subtype P2Y11 gene
- GWA study on 202 candidate genes in 222 patients / 380 controls

NFATC2, SCP2,  
CACNA1C, TCRA, POLE, & FAM2D



# MANAGEMENT

Non- pharmacologic

Sleep Hygiene

# PHARMACOLOGIC TREATMENT

- Methylphenidate
- Modafinil
- Dextroamphetamine
- Sodium oxybate, TCA, SSRIs

# Summary and Key Messages

- Untreated excessive daytime sleepiness is dangerous to self and others
- Narcolepsy is always a consideration in the adolescent and adult with unexplained daytime sleepiness
- Narcolepsy is a diagnosis with a common presentation and clear diagnostic criteria

# Summary and Key Messages (cont)

- Over the past few decades, we have had significant gains in the pathophysiology of narcolepsy (ie, hypocretin deficiency), and the findings have been incorporated to the nosology and diagnosis of narcolepsy.
- However, no pathophysiology-based treatments are still yet available.
- Similarly, the etiology of the disease is still unknown, and further research is essential for the prevention and radical treatments of the disease.

# Summary and Key Messages (cont)

- Narcolepsy is a disorder of wake and sleep state instability, resulting in excessive sleepiness and REM-related symptoms, including cataplexy.
- The instability appears to be related to injury or dysfunction in hypocretin-mediated signaling.
- The spectrum of patient-related symptoms, including the presence or absence of cataplexy, dictated a revision of the nosology (DSM-5 and ICSD-3).