NARCOLEPSY AND AUTOIMMUNITY IN MICE

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NARCOLEPSY

- Sleep/Wake Dysregulation
- Daytime Sleepiness
- Sudden onset cataplexy (loss of muscle tone)
  - 50% of patients
- Attacks are often triggered by emotion or exertion
- Affects 25-50 people per 100,000
- A difficult condition to live with
# SLEEP CYCLE

## Awake State

<table>
<thead>
<tr>
<th>Brain Activity</th>
<th>Skeletal Muscles</th>
</tr>
</thead>
<tbody>
<tr>
<td>NON REM</td>
<td>↓</td>
</tr>
<tr>
<td>REM</td>
<td>↑</td>
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</tbody>
</table>

- Rapid Eye movement

SLEEP CYCLE

**Normal sleep pattern**
- Wakefulness
- Light non-REM
- Deep non-REM
- REM

**Narcoleptic sleep pattern**
- Wakefulness
- Light non-REM
- Deep non-REM
- REM
ETIOLOGY

- Not completely understood
  - Low levels of Orexin in the CSF

- Orexins are produced in hypothalamus
  - Orexins have stimulatory effect over the mono-aminergic neurons
  - Control release of neurotransmissors associated with alert states.

- Loss of orexin (hypocretin) neurons

The main issue in narcolepsy is the loss of orexin neurons

**Autoimmunity?**

AUTOIMMUNE DISEASES

- Disease where the immune system attacks one's body.
- Develops in predisposed individuals.
WHY NARCOLEPSY?

- **Autoimmunity Hypothesis**
  - Several clues lead researchers to believe that the mechanism behind narcolepsy is autoimmunity

- **Genetics**
  - HLA-DQB1*0602 allele is present in 82-99% of narcoleptic patients

- **Environmental**
  - Evidence of cases of Narcolepsy with Cataplexy after vaccination against H1N1.
  - Streptococcus infections (antibodies against Strep, found in patients with recent onset narcolepsy)

Autoantibody anti Tribbles homologue 2 (Trib2) has recently been found in the serum of afflicted individuals.

26.1% of Japanese patients suffering from narcolepsy had higher levels of anti-Trib2 compared to 2.3% of healthy controls.

Witebsky’s Postulates

Criteria to establish a causal link between an autoantibody and a disease:

1. Identification of the autoantigen
2. Reproduction of the disease
3. Active immunization with the autoantigen
4. Passive transfer of T cells or autoantibodies

AIM of Study at The Zabludowicz Center for autoimmune diseases

- The aim of this study is to further confirm the theory that narcolepsy is an autoimmune disorder.

- Induction of narcolepsy in mice through passive transfer of total-IgG (including Trib2 autoantibodies) purified from patients with narcolepsy.
METHODS

- Evaluate the effect of injecting total-IgG from narcoleptic patients to mice brain.

- Mice evaluated for:
  - Sleep behavior
  - Neurocognitive behavior
  - Brain histology
INJECTION OF MICE

1. Mice are anesthetized
2. Skull exposed
3. Injection given in lateral vetricle by entering 2mm anterior and lateral to lambda suture
The sleep behavior is analyzed by looking for freezing events by using EthoVision software®.

Freezing events defined as an abrupt transition from an obvious motor activity, with the resumption of obvious purposeful motor activity.
SLEEP PATTERN

- Sleep pattern changes have been observed in some mice
- Patterns are still being analyzed
NEUROCOGNITIVE TESTS

- Staircase Test
- Assesses the level of anxiety (rears) and exploratory activity (stairs) of each mouse
- Total number of rears and stairs climbed are counted
NEUROCOGNITIVE TESTS

- Novel Object Recognition (NOR)
  - Evaluates any long-term memory deficits
NEUROCOGNITIVE TESTS

- Y-maze
  - Evaluates spatial short-term memory
RESULTS

Staircase Test

- Narcoleptic IgG injected mice were slightly less active than normal IgG injected mice.
- Narcoleptic mice less anxious

\[ p = 0.02 \]

\[ p = 0.07 \]
RESULTS

- **NOR**
  - No difference between Narcolepsy IgG injected mice and Control IgG injected mice.
  - Normal time spent with novel objects is >50%. ($p=0.3$)
RESULTS

- **Y-maze**
  - No difference between Narcolepsy IgG injected mice and Control IgG injected mice.
  - Normal time spent with new arm is >50%. *(p=0.07)*
CONCLUSION

- Autoimmunity may be involved in the pathophysiology of Narcolepsy.

- Research is being done to prove this so that treatment can be better understood and developed in the future.
REFERENCES


