Toward a Mechanistic Understanding of Narcolepsy with Cataplexy

William McCurdy, McNair Scholar, Biology Major
Dr. Andrew Andres, McNair Mentor, School of Life Sciences

ABSTRACT

Narcolepsy (hypersomnolence) is a disorder that affects 1 in 2000 individuals in the United States and it is characterized by excessive daytime sleepiness (EDS) and cataplexy, which is a sudden loss of muscle tone. As of relatively recent date, the nature of these disorders has been a general consensus amongst the scientific community concerning the etiology of narcolepsy as numerous studies suggest that it is caused by the deficiency of neurotransmitters called orexin-A and orexin-B (or hypocretin-1 and hypocretin-2). Research suggests that deficiencies of these proteins are related to a mutation on chromosome 6 in the human leukocyte antigen (HLA) complex which is a locus that houses genes responsible for critical immune-related responses. At this point, an explanation describing the mechanism behind the mutation of the HLA complex and how such a mutation results in an orexin deficiency remains of topic of speculation, although mechanisms regarding the specific pathophysiology have been hypothesized. The primary purpose of this research is to distinctly discuss the hypothesized mechanisms behind the pathophysiology of narcolepsy-cataplexy by presenting a review that seeks to synthesize current literature. Additionally, new technologies responsible for contributing much of the information available on the subject including current and future treatments for narcolepsy will be discussed.

INTRODUCTION

- Narcolepsy with cataplexy (NC) is a complex neurologic disorder that is characterized by excessive daytime sleepiness (EDS), often accompanied by cataplexy
- Affects 0.02% - 0.07%, or 1 out of every 2000 individuals in the United States [1, 2].

**REFERENCES**


**OVERVIEW OF THE OREXINS**

- The structures of orexin-A and orexin-B have been elucidated.
- The mature 33 amino acid orexin-A and 28-amino acid orexin-B are produced upon cleavage of the proenzyme prepro-orexin [3].
- The primary structures of the orexins are highly conserved.
- When comparing mice and humans, the orexin-A sequences are identical and the orexin-B sequences only differ by 2 amino acids and thus the human and mouse orexin B sequences are 94% identical [4, 5].
- It has been described that 90% of NC patients show significantly decreased orexin-A levels in the cerebrospinal fluid (CSF) [6].

**DEPICTION OF THE PROTEOLYTIC CLEAVAGE OF THE 130-AMINO ACID PREPRO-OREXIN PRECURSOR PEPTIDE, SHOWN AS SOLUTION PHASE NMR STRUCTURES BASED ON X-RAY CRYSTALLOGRAPHY, INTO MATURE OREXIN-A AND OREXIN-B NEUROPEPTIDES**

**LITERATURE REVIEW**

**Etiology of Narcolepsy-Cataplexy**

- Research indicates that NC patients also exhibit an inherent degradation of orexin producing neurons because the patient’s immune system destroys its own neurons that it should ignore.
- The HLA allele most strongly associated with the NC phenotype (HLADQB1*0602) is seen in significant proportions in the general population [7, 8].
- Typical markers that suggest strong predisposition amongst multiple ethnic backgrounds are the HLA-DQB1*0602 allele (a MHC class II molecule) which is a mutation seen in 90% - 100% of symptomatic patients [9].
- Some alleles such as HLA-DQB1*0601 appear to offer protection against the NC phenotype as patients with this allele were asymptomatic [9].

**GENOME-WIDE ASSOCIATION STUDIES (GWAS)**

- GWAS is excellent for finding common DNA polymorphisms (SNPs) by surveying a large population.
- Does not use the typical familial-based linkage studies to examine gene variants correlated with NC. Instead, GWAS is an unbiased way to study complex genetic disorders that involve variants (SNPs) that can occur across a large population of unrelated individuals.
- Releys heavily on sampling methods and samples 500,000 to 1 million DNA polymorphisms (SNPs) to observe genetic trends [10].

**CURRENT TREATMENTS**

- Modafinil (Provigil), armodafinil (Nuvigil), methylphenidate (Ritalin), venlafaxine (Effexor), clonazepam (Klonopin), and sodium oxybate (Xyrem)

**FUTURE DEVELOPMENTS IN NARCOLEPSY-CATAPLEXY THERAPY**

- Additionally, from minicerebroventriculatrically of orexin-A to rats during the light period resulted in increased wakefulness time and decreased REM and non-REM sleep time [11].
- Pharmaceutical companies, currently developing intranasal spray that acts as an orexin receptor agonist.