Toward a Mechanistic Understanding of Narcolepsy with Cataplexy

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OVERVIEW OF THE OREXINS

- Figure 2: 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

- 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].

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 (HLA-DQB1*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.
- Refeys 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
- Advancements in microcerebroventricularly 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

REFERENCES