Writing Assignment #4

Found in both animals and humans, Narcolepsy is a debilitating neurological sleep disorder associated with symptoms of excessive daytime sleepiness (EDS), a prominent shift between wakefulness and rapid eye movement (REM) sleep, and cataplexy.[1] Sleep is broken down into REM sleep and non-REM sleep, with both being detrimental to survival. Characterizations of REM sleep are atonia of muscles, vivid dreams, REM, and electroencephalogram (EEG) activity; while non-REM sleep characterizations are partial atonia of muscles, synchronous EEG activity, and fewer dreams.[1] It is the circadian and homeostatic processes that are said to regulate the ability of one to sleep or stay awake; with the generation of circadian processes on a genetic level occurring in the hypothalamus's suprachiasmatic nucleus.[1] While significant knowledge has been acquired in the field about circadian rhythm generation at a neuroanatomical and molecular level, there is still very little understanding when it pertains to the generation of sleep at a molecular level. It is with hopes that by studying the sleep disorder narcolepsy, to gain a better understanding of sleep generation molecularly; as it is the only neurological disorder to specifically impact both the generation and organization of sleep.[1]

More than 0.05% of Americans suffer from the disabling neurological sleep disorder called Narcolepsy. Symptoms of the disorder consist of EDS, cataplexy, fragmented sleep, hypnagogic hallucinations, and sleep paralysis.[1] Narcolepsy is found in both humans and animals, with rigorous studies having occurred mainly with canine models. Through many studies over decades, a striking resemblance has been shown between human and canine narcolepsy, including symptoms.[1] While the majority of narcolepsy cases occur at random, some have been reported as occurring within a family. The particular HLA-DQ allele named HLA-DQB1*0602 has been identified as a genetic factor of predisposition; and due to the connection to HLA, it has been proposed that the human disorder could be autoimmune.[1] In the case of Doberman pinschers, however, the disorder is said to be an individual autosomal recessive trait. Researchers of the study, using the narcolepsy gene in canines, completed positional cloning to help potentially identify the cause of the neurological disorder.[1]

Knowledge gained in the study led researchers to propose that insertion of the short interspersed nucleotide element (SINE) in canines could have relocated the branchpoint sequence out of splicing rangeability.[1] To further test the prediction, analysis of PCR primers in control and narcoleptic canines took place. Results indicated the exact insertion of SINE was present in all narcoleptic Dobermans tested; while not being found in any of the control dogs.[1] The findings led researchers to conclude that the cause of narcolepsy in Doberman pinschers was the mutation of SINE insertion. Providing possible support of their finding, it was included that the cause of human narcolepsy has been reported as mutations of comparable retrotransposon insertion.[1] Due to not observing the mutation of SINE insertion in all narcoleptic dog breeds tested (Labrador retrievers and Dachshunds), this made researchers think there was a possibility of other Hcrtr2 gene mutations involved in the disease.[1] Test were run to identify if there was any truth to their suspicions. Results indicated that in narcoleptic animals, transcripts of Hcrtr2 produced are incredibly irregular molecules of mRNA. They went on to state that these likely impact membrane localization as well as conserved protein to experience loss of function.[1] With narcolepsy in the dog breeds occurring through autosomal recessive transmission, mutations observed were documented as being consistent.[1]

It is due to all the striking similarities shared between humans and canines with narcolepsy that give researchers hope that progress in one area also means progress in the other. Better understanding the cause of narcolepsy in dogs and pathways used can provide a specific area to investigate when studying the neurological disorder in humans.

References

[1] Lin, L. et al. The sleep disorder canine narcolepsy is caused by mutation in hypocretin (orexin) receptor 2 gene. *Cell* **98**, 365–376 (1999).