HUMAN NARCOLEPSY IS LINKED TO REDUCED NUMBER, SIZE AND SYNAPTIC BOUTON DENSITY IN HYPOCRETIN-2 LABELED NEURONS.

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Recent work has shown that canine and murine narcolepsy can be caused by genetic mutations of the hypocretin (Hcrt) system. In contrast to these disease models, most human narcolepsy does not run in families, is discordant in identical twins and has not been linked to mutations. The hypothalamus of six human brains, three from narcoleptics with cataplexy and three from neurologically normal individuals were immunostained with an antibody to the hypocretin (Hcrt)-2 peptide. Three distinct abnormalities were identified. The number of Hcrt neurons and labeled axons in narcoleptics was only 5 percent of the number seen in age and sex matched controls ($P<.02$, t test). The size of the remaining Hcrt neurons was significantly smaller in the narcoleptics ($P<.05$, t test). The density of terminal boutons per micron of labeled axon was reduced in the narcoleptics ($P<.008$, t test). The greatly reduced numbers of Hcrt neurons and terminals can explain the reduced levels of Hcrt reported in the cerebrospinal fluid of narcoleptics (Nishino et al, 2000). The loss of Hcrt excitation of aminergic and cholinergic neurons can explain the deficits in muscle tone control (cataplexy) and sleepiness that define the disorder. The reduced numbers of Hcrt neurons in narcoleptics may result from a failure of development in the Hcrt system or from degenerative processes. If Hcrt cell loss is the underlying problem in most human narcoleptics, administration of Hcrt agonists may be an effective treatment for the disease.

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