The Frustrating and Mostly Fruitless Search for an Autoimmune Cause of Narcolepsy


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MORE THAN 20 YEARS AGO, YUTAKA HONDA AND COLLEAGUES SHOWED THAT NARCOLEPSY IS STRONGLY LINKED TO THE HUMAN LEUKOCYTE ANTIGEN (HLA) DR2. Many subsequent studies have shown that DQB1*0602, a DQ1 subtype allele, is found in more than 90% of narcoleptics with cataplexy, whereas it occurs in fewer than 25% of Caucasian American controls. This remarkable association has led many researchers to hypothesize that narcolepsy is caused by an autoimmune process. Specifically, DQB1*0602 and probably other genes may provide some genetic susceptibility to narcolepsy, so that a viral infection or other insult can trigger an immune response that destroys the hypocretin-orexin-producing neurons of the lateral hypothalamus.

Certainly, an autoimmune process is capable of destroying the hypocretin neurons. Anti-Ma2 paraneoplastic encephalitis often produces hypothalamic inflammation that can result in narcolepsy with cataplexy, low hypocretin levels in the cerebrospinal fluid (CSF), and other signs of neurologic dysfunction. Still, there is remarkably little evidence to prove that idiopathic narcolepsy is caused by an autoimmune process. As in multiple sclerosis and type 1 diabetes mellitus, the cell loss in narcolepsy with cataplexy is very selective, apparently targeting only the hypocretin-producing neurons. The number of astrocytes in the hypothalamic field or in regions with hypocretin terminals may be increased, suggesting some local inflammation, but this finding is nonspecific and controversial. Tumor necrosis factor-α and interleukin-6 are increased in the serum of people with narcolepsy.

In addition, the crystal structure of DQB1*0602 suggests that it could present hypocretin fragments or other peptides to the immune system, and a recent study suggests that antibodies in the CSF of narcoleptics may bind to homogenized rat hypothalamus. In one study, intravenous immunoglobulins reduced cataplexy in a small number of patients, but their sleepiness and low CSF hypocretin levels failed to improve, so it’s hard to conclude that the immunoglobulins really altered immune function. Clearly, more direct evidence is needed to prove that an autoimmune process causes narcolepsy.

In this issue of Sleep, Tanaka et al report on their ambitious and important attempt to detect autoantibodies in narcolepsy. They hypothesized that narcolepsy might be caused by an antibody-mediated attack on hypocretin or the two hypocretin receptors. Using a radioligand binding assay, they detected autoantibodies in the sera of 8 of 171 (5%) narcoleptics with cataplexy compared with 3 of 91 (3%) healthy control subjects, a difference that was not statistically significant. Autoantibodies were also detected in 1 of 10 narcoleptics without cataplexy but not in subjects with other hypersomnias. The mean titers of autoantibodies did not differ between groups, and, overall, this study failed to find evidence of an antibody-mediated attack on the key hypocretin-signaling molecules.

Despite these results, a humoral attack on the hypocretin system remains possible. Tanaka correctly notes that because their assay used radiolabeled hypocretin receptors that were produced in a cell-free system, the final conformation of the receptors might differ from their shape on the surface of neurons. In addition, serum was collected from narcolepsy patients with an average age of 45, and most of these subjects probably developed narcolepsy 20 to 30 years prior. In type 1 diabetes mellitus, islet-cell antibodies are abundant around disease onset, but 5 to 10 years later, titers are much lower. Because the symptoms of narcolepsy usually stabilize within the first few years, it’s likely that any autoimmune process settles down over time. Perhaps, the prevalence of serum autoantibodies would be much higher around disease onset. In addition, CSF might contain a higher concentration of relevant autoantibodies.

Other researchers have found similarly negative results using different approaches. Black and colleagues found no serum autoantibodies against hypocretin or its cleavage products using immunoprecipitation assays, enzyme-linked immunosorbent assays, immunofluorescence microscopy, and Western blots. Using a technique often effective with paraneoplastic syndromes, Overeem et al examined whether serum from narcoleptics binds to cells in human hypothalamus. They found immunostaining of hypothalamic neurons with serum from 2 of 76 narcoleptics but also with serum from 2 of 63 controls. Last year, Smith and colleagues reported that inoculation of mice with immunoglobulin from people with narcolepsy seemed to alter cholinergic signaling; this treatment increased the sensitivity of bladder smooth muscle to cholinergic stimulation and appeared to produce cata-plexy-like behavior. These passive-transfer experiments need to be replicated, but, overall, these studies provide little support for a humoral immune mechanism in narcolepsy.

Several other approaches have failed to demonstrate that immune system dysfunction causes narcolepsy. Unlike many autoimmune diseases, narcolepsy is not associated with other autoimmune diseases. Microglia and tumor necrosis factor-α mRNA were not increased in the hypothalami of 2 narcoleptics in 1 study, though the brains were examined decades after the onset of symptoms. No gross changes in immune function have been identified; the CSF of narcoleptics lacks increased protein or oligoglial bands, and their serum lacks the antibodies seen in many autoimmune diseases. These largely negative results do not

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disprove the autoimmune hypothesis, but they certainly highlight the need to develop new approaches.

Just because narcolepsy is linked to an HLA marker does not mean that it is caused by an autoimmune process—DQB1*0602 might play a different role. For example, DQB1*0602 may make the expression of narcolepsy more apparent. Normal subjects who are DQB1*0602 positive have shorter latencies to rapid eye movement (REM) sleep, suggesting that this marker somehow enables quicker transitions to REM sleep. DQB1*0602 may also affect the severity of narcolepsy because DQB1*0602-positive narcoleptics have longer episodes of cataplexy, more nocturnal sleep disruption, and more daytime sleepiness. Currently, it remains unknown whether DQB1*0602 binds hypocretin in vivo or directly affects the function of CNS neurons.

Lastly, the hypocretin neurons might succumb to other processes. Maybe the hypocretin cells are directly destroyed by a neurotropic virus with an affinity for these particular neurons. Some people have developed narcolepsy after a period of shift work or insufficient sleep, and perhaps the hypocretin neurons are uniquely vulnerable to this stress, selectively dying off like the motor neurons in amyotrophic lateral sclerosis. There is little evidence for these alternative mechanisms, but, in the absence of strong support for autoimmunity, we should keep an open mind.

Our ignorance about the cause of narcolepsy remains encyclopedic, and much more work is needed to support the autoimmunity hypothesis. The new study by Tanaka and colleagues suggests that hypocretin and its receptors are not the target of a humoral attack, and we should broaden our search for other antigens produced by the hypocretin neurons. The target of an autoimmune process may be an antigen always expressed on hypocretin neurons or a cryptic antigen exposed to the immune system only after some injury or stress. T cells are a fundamental part of many autoimmune diseases, and cellular immune mechanisms also should be examined in people with narcolepsy. Most importantly, it will be essential to study serum and CSF very soon after disease onset, presumably when the narcolepsy is still developing and any inflammation is ongoing. Identifying the mechanism that kills the hypocretin neurons will take substantial effort, but that discovery may enable us to identify and stop narcolepsy at a preclinical stage.

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REFERENCES