

## Recent Developments in Narcolepsy Research, An Explanation for Patients and the General Public

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Narcolepsy is no longer a mysterious disease. In work reported this September, our group at UCLA and Mignot's group at Stanford independently identified abnormalities in human brains that pinpoint the cause of most human narcolepsy. We were able to acquire four brains of deceased people who had had narcolepsy, and our work was based on a comparison of these brains with the brains of twelve neurologically normal deceased people. There are many different kinds of cells in the brain, with each kind containing different chemicals. In our work, we found that the number of brain cells containing the chemical named hypocretin (also called orexin) was reduced by 85-95% in people with narcolepsy. We found that neurologically normal individuals have about 70,000 hypocretin containing cells, whereas the narcoleptic individuals have between 3,000 and 10,000 of these cells. The brain region where hypocretin cells are located is called the hypothalamus and is located at the base of the brain. We found that scar tissue (also called gliosis) was present in regions of the hypothalamus where hypocretin brain cells used to be. This indicates that the cells were present at birth and died later. It is likely that they died at or shortly before the time of symptom onset.

The cause of the death of the hypocretin cells is not entirely clear, but there are two possibilities. One is that a specific "poison" produced by the body or absorbed through the environment kills these cells. Parkinson's disease, another neurological disease caused by the loss of specific brain cells, can be triggered by ingested toxins, for instance. The second and more likely possibility is that the hypocretin cells are killed by the immune system, which confuses these cells with an infectious agent such as a virus. Other cells near where the hypocretin cells should have been appear to be normal; this indicates that whatever the cause of the cell loss, the hypocretin cells are targeted very specifically.

There are some differences between the findings of the two studies. Mignot's group concluded that all the hypocretin cells were absent in the hypothalamus of the two brains they examined, but we saw cells that had survived in all four of the brains we studied. Mignot's group also counted only 15-20,000 hypocretin cells in the normal brains they studied, compared to the 70,000 we saw. In addition, Mignot's group did not see scar tissue in the narcoleptic brains. However, we observed this scar tissue in all of the narcoleptic brains we examined. These differences are probably due to differences in the sensitivities of the techniques used in each laboratory. However, both groups are in basic agreement that hypocretin cell loss causes narcolepsy in humans. One problem that both of our groups faced, however, is that very few narcoleptic brains are available for study. Although animal work has been vital in unraveling the mystery of narcolepsy, we now must now have more human brains to study to progress further in our understanding of narcolepsy in humans. People

with narcolepsy who will their brains to science can greatly contribute to our understanding of this disorder.

What does finding the cause of narcolepsy mean for people with narcolepsy? This discovery ends the 120-year search for the cause of this debilitating disease. It also has important implications for people with narcolepsy:

1. We have clearly shown that narcolepsy is a neurological disease not a psychiatric one. The problem is not "in your mind," but rather is caused by damage to your brain, specifically to the hypothalamus. Many persons with narcolepsy have not only had to suffer from the disease but also from family members, friends and even physicians, who thought of narcolepsy as a motivational problem. Only the ignorant will now consider narcolepsy a psychological problem.
2. It is clear that most human narcolepsy is caused by the cell loss we have identified. However, we know that certain genetic mutations affecting the hypocretin system can cause the disease in animals. Although most people's narcolepsy is not caused by genetic mutations in the hypocretin system, mutations and other neurological and/or genetic problems may account for a small percent of the cases of human narcolepsy.
3. Further research is necessary to determine why symptoms vary between people with narcolepsy. For example, we do not yet know why some individuals have severe cataplexy and others only rarely have cataplexy. In our recently published paper we found that even people with narcolepsy with rare or no cataplexy have a profound loss of hypocretin neurons.
4. New diagnostic techniques may be developed as a result of this discovery. This will enable much earlier and more accurate identification of the disorder.
5. We can now begin to think about how to treat the cause of narcolepsy, rather than the symptoms. Prior work in our laboratory identified some of the brain systems whose malfunction causes the symptoms of narcolepsy. We now understand that current treatments with stimulants and antidepressants work because they activate these systems, and in this way replace the missing hypocretin containing brain cells.
6. Our group found that all the narcoleptic brains we examined had some surviving hypocretin cells. It may be possible to boost the function of these cells and thereby reduce symptoms of narcolepsy.
7. Basic research has recently shown that certain kinds of cells called "stem cells" can be transformed into a variety of brain cells. In the distant future this may allow a "cure" for narcolepsy by permitting the replacement of the lost hypocretin cells. However because of the complexity of the brain's wiring and the danger of implanting cells with current techniques, which would require delicate brain surgery, a cure using this technique is very far away.
8. We have begun experimenting with injecting hypocretin into the veins of narcoleptic dogs. If a deficiency in the response to this chemical is causing the disorder in the dogs, as we reasoned, giving extra hypocretin to the dogs might reverse their symptoms. This is just what happened. Hypocretin administration reduced daytime sleepiness, increased sleep continuity at night and

reduced or eliminated cataplexy (see <http://www.bol.ucla.edu/~jsiegel/> for the text of this paper and other work in our laboratory). This finding is very encouraging. First, it suggests that administration of hypocretin to persons with narcolepsy might be a uniquely effective treatment for all of the symptoms of narcolepsy. Second, it suggests that hypocretin administered intravenously can get to the brain to reverse the problems of narcolepsy. Third, it indicates that exposing the entire body to hypocretin does not cause any obvious distress. Many individuals with narcolepsy have contacted me to volunteer for clinical trials of this procedure. However, we are not yet ready for this big step. Even though hypocretin is a naturally occurring substance, it may well have side effects when administered to the entire body or over long periods of time. We are working as rapidly as possible to conduct animal tests on the effectiveness and safety of this treatment before beginning any human use. But there is reason to expect that much better treatments are on the way as a result of our new understanding of narcolepsy.