

Cell death in sparrow brains may provide clues in age-related human diseases

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A remarkable change takes place in the brains of tiny songbirds every year, and some day the mechanism controlling that change may help researchers develop treatments for age-related degenerative diseases of the brain such as Parkinson's and dementia.

Writing in today's *Proceedings of the National Academy of Sciences*, researchers from the University of Washington and the University of California, Berkeley, report a striking shrinkage in the size of the brain regions that control singing behavior of Gambel's white-crowned sparrows. This transformation is triggered by the withdrawal of testosterone, a naturally occurring steroid hormone, and is apparent within 12 hours. The study is the first to report such rapid regression of brain nuclei caused by the withdrawal of a hormone and a change in daylight conditions in adult animals.

"The changes are substantial," said Christopher Thompson, lead author of the study and a UW doctoral student in neurobiology and behavior. "First, the volume of a song-control region called the HVC collapses 12 hours after testosterone is removed from circulation. Then, by four days, thousands of HVC neurons are lost. We have good reason to believe that they are killed by a cell suicide program call apoptosis."

Co-authors of the study are Eliot Brenowitz, a UW professor of psychology and biology, and George Bentley, a former UW postdoctoral researcher who is now a UC Berkeley assistant professor of integrative biology.

The research mimicked the natural seasonal changes that occur in the brains of the sparrows. Their song-control regions expand in the spring and summer leading up to the breeding season, as they use songs to establish territories and attract mates in Alaska. Later in the summer, as the birds get ready to migrate back to California, the same brain regions shrink.

"We've seen seasonal changes in the brains of fish, reptiles, amphibians, birds and mammals such as gerbils, mice, and even in humans," said Brenowitz. "However, the magnitude of changes in birds far exceeds that seen in other animals."

To better understand what happens in the sparrows' brain, the researchers received federal and state permits to capture 25 of the migrating male birds in Eastern Washington. Next, they housed the birds for 12 weeks before exposing them to 20 days of long-day conditions comparable to the natural lighting the sparrows would experience in Alaska during the breeding season. The birds were also implanted with testosterone.

At the end of 20 days, six of the birds were euthanized and the remaining 19 were castrated and testosterone implants were removed so there would not be any circulating testosterone in their systems. After 12 hours five more birds were euthanized and the remainder were euthanized at 2, 4, 7 and 20 days. These procedures were done with the approval of the UW's Institutional Animal Care and Use Committee and the National Institute of Mental Health. The latter funded the research.

The researchers found that the size of the HVC region decreased 22 percent within 12 hours after the withdrawal of testosterone and that the number of neurons in this song-control region fell by 26 percent after four days. In addition, the size of two other song-control regions called Area X and the RA significantly regressed after 7 and 20 days,

respectively.

Thompson said there are a number of potential medical implications relating to age-related degenerative diseases and conditions marked by declining mental abilities from this study.

"Having an animal model system with such robust neurodegeneration could be very useful in uncovering the mechanisms that underlie these kinds of diseases," he said. "We will be looking at the molecular mechanisms of what happens when testosterone is removed. As men age, circulating levels of testosterone decrease, and other researchers have shown that this decline may contribute to cognitive impairment, brain disorders and neuron death."

Brenowitz added: "There is no reason to think that these processes are restricted to birds. They are very similar to what happens in some mammals. This study shows that regions of the brain that are hormonally sensitive are going to regress without testosterone. The flip side is that hormones such as testosterone protect neurons, so perhaps some form of hormone therapy may provide protection. Steroids such as testosterone are very potent and have wide implications for effects on the brain."

Source: University of Washington

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