Songbird brain synapses and glial cells capable of synthesizing estrogen

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Colin Saldanha, a biology professor at American University in Washington, D.C., has always been intrigued by the hormone estrogen. Specifically, how the hormone that does so much (for example, it promotes sexual behavior in women but can also increase susceptibility to seizures) does not cause major cross circuit meltdowns.

"In the extreme case, once every 28 days, women should be having seizures—and when they do, it's a condition called Catamenial Epilepsy—but that's obviously not the norm and there's the mystery," Saldanha said. "Somehow, the vertebrate body has figured out a way to produce and provide estrogen to precisely the right part of the body at precisely the right time."

To attempt to find out how the bodies of animals and humans can do this, Saldanha has been studying the brains of songbirds—specifically, adult male zebra finches. Why adult male zebra finches? Male zebra finches sing, but the females do not. During the spring—mating season, when males court prospective mates with their songs—parts of the male birds' brains nearly double in size only to shrink back to normal size in the fall when mating season has ended. Estrogen is behind the phenomenon.

Discovery Leads to a New Term

Previous research on hormone synthesis outlines three ways the body

makes and delivers estrogen to different parts:

- Endocrine signaling (estrogen produced in the ovaries and made available to the entire body through the bloodstream);
- Paracrine signaling (estrogen made in the brain but stays local/ in the area where it was made);
- And autocrine signaling (estrogen made in an individual cell for use in that cell).

Recently, Saldanha and colleagues from the University of Massachussetts—Amherst and the University of California—Los Angeles, published research that introduced a fourth and new method of estrogen synthesis to the scientific community: synaptocrine signaling, or at the synapse.

Synapses are junctions in the brain across which neurons (cells traditionally viewed as the most important in the central nervous system) use electrical or chemical signals to communicate with another cell downstream.

Saldanha and his colleagues originally discovered synaptocrine estrogen synthesis and signaling in 2005. They used a special protein they developed that detects aromatase, a complex enzyme key to estrogen synthesis, and an electron microscope to figure out which specific cells of the songbirds' brains were capable of making estrogen.

When they saw the protein marking the synapses, they were surprised.

"This was startling. There wasn't even a name for this in the literature. We had to come up with one to describe it. We called it synaptocrine signaling," said Saldanha, whose research into the synaptic localization of aromatase and estrogen synthesis has been funded since 2002 by more

than $3 million in grants from the National Institutes of Health.

Synaptocrine signaling is a highly specific form of neuro and hormonal communication. A specific target (a particular neuron) can create and feed high levels of estrogen to another, specific neuron with which it needs to communicate—and here is the key part—to the exclusion of other neighboring cells around the "target" neuron.

To make sure their findings were valid, Saldanha and his colleagues did the experiment again and even had someone else conduct it. When all of the experiments ended with the same results, Saldanha and his colleagues submitted their paper to Endocrine Reviews, the Endocrine Society's research journal, where it was published.

An Earlier Discovery

Through earlier research, Saldanha uncovered yet another way songbird brains can synthesize estrogen and it presents important implications for research into degenerative brain diseases and conditions in humans such as Alzheimer's and Parkinson's diseases, and strokes.

This is research Saldanha and colleagues began in 2000. *The Journal of Neuroinflammation* recently published their coauthored article. Saldanha and his fellow researcher found that glial cells, the most abundant cells in the central nervous system but mistakenly long considered less important than neurons, are also capable of synthesizing estrogen in the brain under certain conditions—specifically, inflammation.

Saldanha first noticed this in response to a specific injury to a songbird's brain. The injury occurred in a part of the brain where cells do not normally express aromatase.

"There were no cells that made estrogen on that side of the brain,"

Saldanha said. "But 24 hours later, I realized these cells [the cells in the injured part of the brain] were making aromatase."

In addition, Saldanha found that the estrogen seemed to prevent further damage to the brain. He discovered this by introducing to the injured area a drug to inhibit estrogen production, after which the amount of damage increased.

Saldanha and his colleague reasoned that the injury prompted an inflammatory response and that this inflammatory response—not the actual injury—prompted the glial cells to begin to produce estrogen. They tested the hypothesis by inducing inflammation without injury and saw the same response.

"It's very much like what happens when you get a paper cut," Saldanha said. "You cut your skin and expose your insides to the nasty toxins of the environment. Your immune cells are attracted to the area to protect it. In this case, these songbirds have the ability to respond to an inflammatory event rapidly by prompting cells that do not make estrogen to suddenly begin producing it."

Do Songbirds Have Strokes?

We don't know if songbirds have strokes. But humans do and the results can be devastating and at times, fatal. Does the ability of songbird brain cells to rapidly make estrogen in response to inflammation and thereby ostensibly protect the brain from secondary damage have anything to do with that? Saldanha thinks the answer could be yes.

"Most humans will have minor strokes in their lifetimes—such as a blood vessel bursting— and they are no big deal," Saldanha said. "How do we know they happen and are no big deal? We have autopsies of elderly patients who have never had symptoms of stroke, but we look at

their brains and there are all of these tiny lesions."

But every once in a while, a lesion becomes bad enough that the person exhibits signs of stroke such as losing the ability to speak or motor skills on a particular side of the body.

"When that happens, it means two things. One, the actual primary damage probably occurred 24 hours in advance because what results is a cascade of cell death around the primary site of damage," Saldanha said. "And two, the symptoms we see are actually the spreading of secondary damage. By the time we see the symptoms, the damage has already been done. It is too late to stop it."

The next phase of Saldnha's research will focus in part on confirming whether the estrogen produced in songbird brains does indeed prevent secondary brain damage. It is one part of his greater effort to more clearly understand the mysteries of estrogen production and provision.

"The research tells us something fundamentally new about hormonal signaling, I believe," Saldanha said. "Right now, I am convinced that what we're looking at is real and it has taken about seven years for me to be convinced that it is real. I can make up a good story about why it's a good thing to parcel out and specifically provide estradiol [estrogen] to specific targets at the right time, but it would be nice to have a handle on the exact function of that synaptic estrogen provision. And that is the next cycle."

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