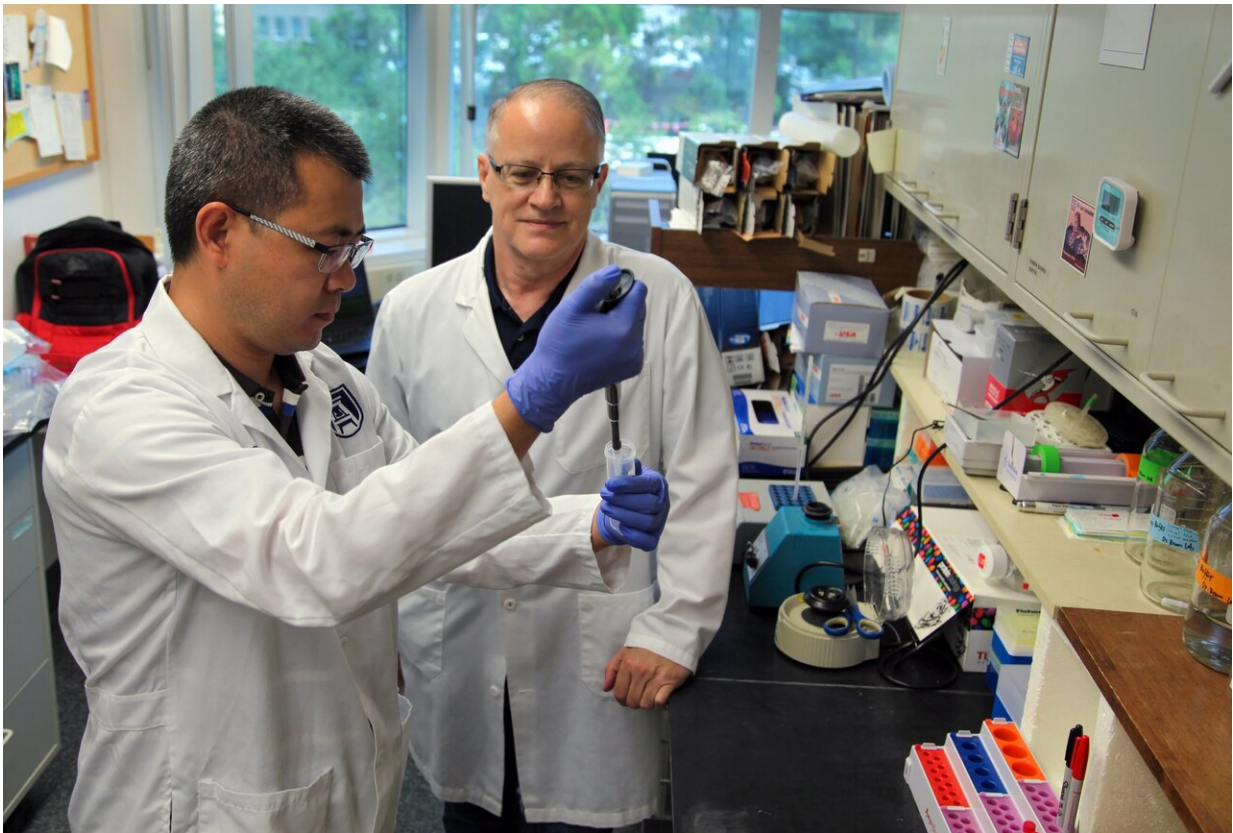


Brain estrogen is key to brain protection when oxygen is low

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Dr. Darrell Brann and Dr. Yujiao Lu from Medical College of Georgia at Augusta University. Credit: Phil Jones, Senior Photographer, Augusta University

When the brain isn't getting enough oxygen, estrogen produced by neurons in both males and females hyperactivates another brain cell type

called astrocytes to step up their usual support and protect brain function.

In the face of low [brain](#) oxygen that can occur with stroke or other [brain injury](#), these astrocytes, star-shaped [brain cells](#) that help give the brain its shape and regularly provide fuel and other support to [neurons](#), should become "highly reactive," increasing cell signaling, releasing neuroprotective factors and clearing neurotoxins, scientists report in *The Journal of Neuroscience*.

Astrocytes also should start producing protective estrogen, but it's neurons' producing estrogen that is critical to the protective cascade, they report.

"Astrocytes are always there and hovering and supporting," says Dr. Darrell W. Brann, neuroscientist and Virendra B. Mahesh Distinguished Chair in Neuroscience in the Department of Neuroscience and Regenerative Medicine at the Medical College of Georgia at Augusta University.

"When something bad happens, they are supposed to go into overdrive, get big and pushy, but this work suggests that you have to have neural estrogen for that to happen," Brann says.

The scientists say that theirs appears to be the first report demonstrating that neuron-derived estrogen is critical to astrocyte activation following an ischemic injury like a stroke. They reason that by understanding how estrogen is controlled, it will unlock therapeutic targets to one day help regulate the hormone's protection in the brain in the face of these maladies, as well as potentially normal aging.

Brann and Dr. Ratna Vadlamudi, molecular biologist and professor of obstetrics and gynecology at the University of Texas Health, San

Antonio, are co-corresponding authors on the study and co-principal investigators on the National Institute of Neurological Disorders and Stroke grant that helped fund it.

"The hallmark of activation is astrocytes get very large, hypertrophic, their volume increases tremendously," says Brann, often more than doubling in size, he says, although he has no evidence they increase in number.

To try to understand how astrocytes take on this enhanced role, they knocked out the enzyme aromatase, which is critical to estrogen production, in neurons in the forebrain, the largest region of the human brain, in their animal model.

They found that one way estrogen made by neurons is protective in ischemia is by suppressing signaling of the fibroblast growth factor, FGF2, which is also made by neurons and known to suppress astrocyte activation, Brann and his colleagues write. Normally neurons use this FGF2 brake to help keep astrocyte response from getting out of control.

In this scenario, when they used a neutralizing antibody to block FGF2, astrocytes became more active and neuron damage was decreased. "The astrocyte activation came back and we saw the protective growth factors that they make," Brann says. Giving more estrogen produced similar benefits, including improving cognition after ischemia.

But without the ability to make aromatase, and consequently estrogen, in the male and female neurons, they found activation of astrocytes was significantly reduced, brain estrogen levels were decreased and the results included worse damage to neurons and cognitive dysfunction following a period of ischemia. When they looked closer, they found changes in pathways and genes associated with astrocyte activation, brain inflammation and oxidative stress in the aromatase knockouts.

They also saw less of known neuroprotective growth factors, like brain derived neurotrophic factor and insulin-like growth factor 1, which astrocytes normally release at an increased rate in response to a stressor like ischemia, and more suppressive substances like the brake FGF2.

The findings are more evidence that decreased activation of astrocytes has functional consequences to astrocytes' role in neuroprotection, Brann says.

"We know estrogen can just go right out of the astrocyte to the neuron and help regulate neuron protection," he says. It also can help regulate microglia, another type of glial cell in the brain—astrocytes also are glial cells—that instead releases inflammatory factors that can exacerbate damage.

Activated astrocytes also help clear glutamate, the brain's most abundant excitatory neurotransmitter that normally helps neurons communicate. But without estrogen from the neurons, the glutamate transporter, GLT-1, which removes about 90% of the glutamate, is significantly decreased and the chemical can accumulate at toxic levels in the brain and become a major cause of neuron destruction. "Glutamate is essential for [brain function](#), but if it's overproduced, it's brain toxic," Brann says.

When all is going well in the brain, only neurons appear to be a local estrogen source, but with a stressor like ischemia, aromatase and the estrogen it enables are known to increase significantly in the astrocytes as well, if they are activated.

"We know that you have to have [astrocyte](#) activation to have the aromatase activated," Brann says. "We only see aromatase in astrocytes when they are activated after an injury, after a stress," Brann says. When aromatase goes up, is when they can start making estrogen, he says of the star-shaped supporter cells. That just did not happen in their knockouts.

Now they want to learn more about why astrocytes typically don't produce aromatase and resulting estrogen routinely, and exactly why they do in ischemia. They think those answers will provide even more direction for possible intervention, again for males and females, with oxygen challenges to the brain. Brann notes there are research compounds that produce estrogen in the brain they will be working with in the lab moving forward, which may be a good option since there are health concerns, including for the breast and uterus, about increasing estrogen bodywide, Brann says.

Brann's lab reported last year in *The Journal of Neuroscience* that estrogen in the brain is important to neurons communicating and making memories and that when male and female neurons don't make estrogen, they have less dense spines and synapses, key communication points for neurons. At the time, Brann said it was direct evidence that neuron-derived estrogen is a critical messenger for these.

While the neuroprotection afforded in these studies was essentially equal between males and females—they removed the ovaries in the females to remove peripheral estrogen from the equation—Brann's lab and others have evidence of gender differences in areas like the impact on memory. For example, they have found a more significant impact in females, about 90% versus 60%, in the molecular basis of memory, called long-term potentiation, when neurons could not produce estrogen, suggesting that brain-derived estrogen may have a bigger regulatory role in females, Brann says.

Brann also has some evidence that estrogen in the brain also has ongoing roles in both male and female brains. "When you have a challenge is when you see that role very clearly," he says.

There is no evidence that without estrogen, astrocytes turn on the neurons they typically support, rather they no longer can provide their

usual protection, Brann notes. There also is no evidence that estrogen produced by the neurons themselves goes up in response to low oxygen.

Dr. Yujiao Lu, a recent Ph.D. graduate in neuroscience from The Graduate School at AU who is now a postdoctoral fellow with Brann, is the study's first author. Collaborators also include Drs. Gangadhara R. Sareddy, Uday P. Pratap and Rajeshwar R Tekmal from the Department of Obstetrics and Gynecology at the University of Texas Health, San Antonio.

Ischemic strokes account for 87% strokes, according to the American Heart Association. Like circulating estrogen levels in females, brain-derived [estrogen](#) also decreases with age in both sexes.

More information: Yujiao Lu et al. Neuron-Derived Estrogen is Critical for Astrocyte Activation and Neuroprotection of the Ischemic Brain, *The Journal of Neuroscience* (2020). [DOI: 10.1523/JNEUROSCI.0115-20.2020](#)

Provided by Medical College of Georgia at Augusta University

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