Medical Xpress

Neuroscientists discover new estrogen activity in the brain

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Research by University of Massachusetts Amherst neuroscientist Luke Remage-Healey and colleagues has for the first time provided direct evidence that estrogens are produced in the brain's nerve cell terminals on demand, very quickly and precisely where needed. "This is an incredibly precise control mechanism and it solidifies a new role for estrogens in the brain," says Remage-Healey.

Estrogens like estradiol are crucial in modulating neural circuits that govern such behaviors as feeding and reproduction, memory, cognition and neuroplasticity in animals and humans. In a series of experiments with zebra finches, Remage-Healey and neuroendocrinologists from the University of California Los Angeles (UCLA) provide a new picture of neuron-produced estradiol suggesting that it acts remarkably like a classic neurotransmitter controlled by electrochemical events, in addition to its role as a hormone in the bloodstream, he adds.

"The fact that the brain synthesizes estradiol at the synapse in a very rapid, targeted way makes it almost a different beast than the estradiol we knew before. So we now know the brain can produce its own supply of estrogens that are not really acting like hormones anymore, but more like neurotransmitters. It's the exact same molecule in birds, fish, dogs and humans. It's the same molecule as is produced in the human ovary. But now we know that neurons can control the release of estrogens onto other neurons, in a way similar to the way neurotransmitters are controlled."

These new findings also support the idea that neuroestrogens modulate information flow in the brain's cortex in seconds to minutes, in contrast to the hours and days it takes for hormones circulating in the blood stream to have an effect. This work supported by the National Institutes of Health is described in a July issue of the *Journal of Neuroscience*.

"It's clear now that neurons are producing estrogens in presynaptic terminals, the hand-shake zone where a signal between neurons is transmitted," says Remage-Healey. He adds that these findings are extremely exciting because "presynaptic terminals are the interface between neurons. When that connection is strengthened in the presence of estradiol, it could lead to enhanced learning and plasticity."

For these experiments, the UMass Amherst and UCLA researchers developed a microdialysis probe to conduct *in vivo* real-time testing in the forebrains of active, alert zebra finches. These robust little birds are awake and flying, singing, eating and drinking with a tiny micron-diameter probe implanted in their forebrains. The probe not only allows researchers to measure estradiol levels but to alter local potassium and calcium levels, chemicals that activate or inhibit neural activity.

In a clever twist, Remage-Healey and colleagues also use conotoxin, a very specific toxin produced by the cone snail. It targets only presynaptic nerve terminals that use a voltage-gated calcium channel. The researchers pump minute amounts of the toxin through the probe to precisely inhibit calcium channels in individual nerve terminals. In this way, they established that estradiol is calcium-dependent, is synthesized very rapidly in response to stimuli in the presynaptic terminal, but not in the neuronal cell body.

In a typical experiment, Remage-Healey and colleagues infuse artificial cerebrospinal fluid through the probe continuously over a 30-minute period. They receive back dialysate, from which they measure local estradiol concentration. Results challenge the traditional view that the brain is responding to estrogens produced elsewhere.

The UMass Amherst neuroestrogen expert adds, "In other experiments using this new technology we've shown that estradiol is changing in this same brain area when the animal hears a sound. This shows that estradiol is fluctuating much faster and in a more specific way than we understood before. Estrogens could therefore target their actions to certain neurons, synapse by synapse."

Overall, the new findings could open the path to investigate more precisely the role of estrogens in learning, and perhaps reveal a way to deliver estradiol directly to neurons to enhance cognitive abilities without systemic side effects such as increased heart disease risk.

Provided by University of Massachusetts Amherst