Confronting the side effects of a common anti-cancer treatment

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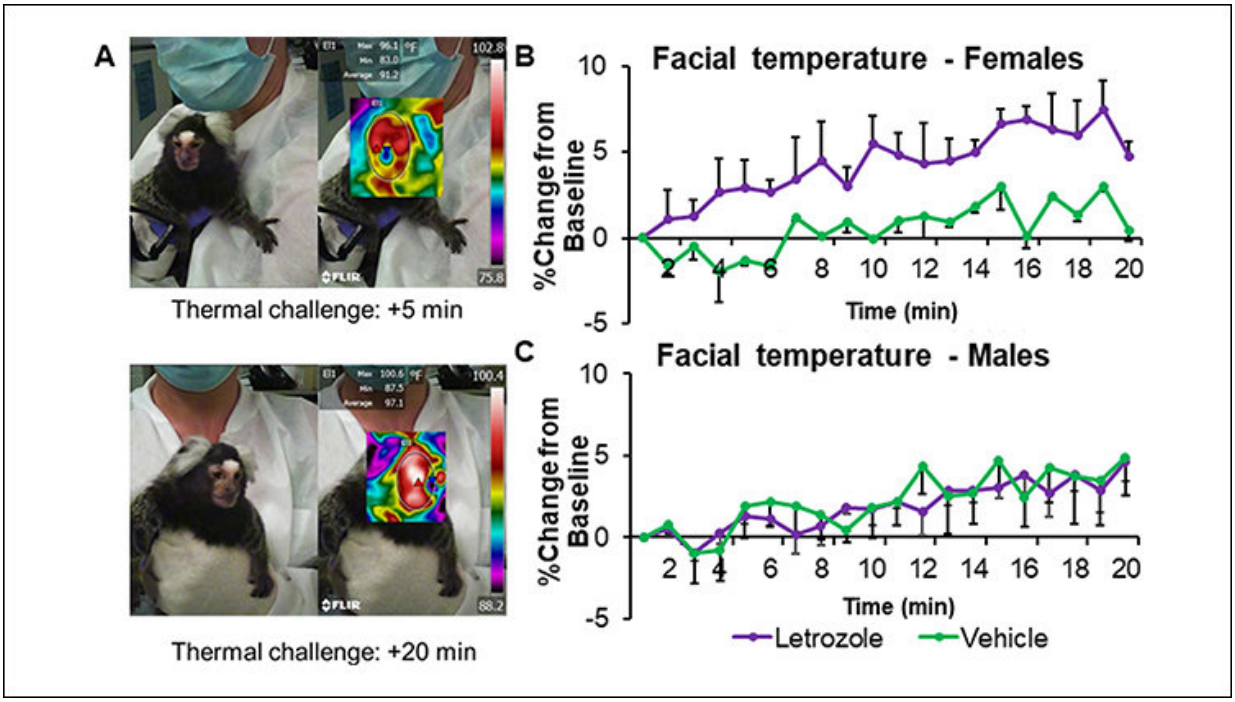

Letrozole (20 μg/day, p.o.) exerts sex-specific reduction in thermoregulation during thermal challenge. (A) Facial temperature was measured via thermal camera during a 20-min thermal challenge. Representative images obtained 5 min and 20 min into the challenge are shown, along with the temperature reading. Percent change in temperature (°F) from the first min of the thermal challenge was plotted over time for females (B; Vehicle: n = 2; Letrozole: n = 4) and males (C; Vehicle: n = 5, Letrozole: n = 4). Letrozole treatment resulted in greater elevation in temperature across time for females only (p JNeurosci (2018)

Results of a new study by neuroscientists at the University of Massachusetts Amherst and the University of Toronto suggest that a new treatment approach is needed—and how this may be possible—to address adverse effects of aromatase inhibitors, drugs commonly prescribed to both men and women to prevent recurrence of estrogen-positive breast cancer.

The current drug therapy is linked to such complaints as hot flashes, memory lapses, anxiety and depression, side effects so bothersome that some patients discontinue the life-saving treatment, the researchers point out. Their study found that aromatase inhibitors do indeed suppress estrogen synthesis in body tissues, but their unexpected findings in the brain could explain some of the negative effects and provide insight into more effective, less disruptive future therapies.

Neuroscientists Agnès Lacreuse, Luke Remage-Healey and their graduate students at UMass Amherst, collaborator Jessica Mong at the University of Maryland and first author Nicole Gervais worked together on this research. Gervais, who conducted the experiments as a postdoctoral researcher at UMass Amherst, is now at the University of Toronto. The authors studied a small group of aged male and female marmosets, non-human primates whose brains are much like humans' and which exhibit "complex behavior," senior author Lacreuse explains.

She adds, "This drug is given to prevent recurrent breast cancer in humans and it does save lives, but a lot of times, patients are not compliant because of unpleasant side effects that affect quality of life." Their study, showing changes in the animals consistent with some of the human complaints, allowed the researchers to assess cognitive behavior, thermal regulation and neuronal changes in drug-treated vs. control groups. Their findings appear this week in the *Journal of Neuroscience*.

As Gervais explains, studies in humans are hampered by confounders.

"The patients have had cancer, so it's hard to disentangle the stress of their disease and treatment from the drug effects." She adds, "We wanted to know if the symptoms while using the aromatase inhibitors can be reproduced in an animal model, and further explore the mechanisms to understand how they work and find alternative treatments."

In this work supported by the NIH's National Institute on Aging and National Institute of Neurological Disorders and Stroke, the researchers administered the estrogen-inhibiting drug orally "the way it's given to humans and at a similar dose," Gervais explains, for one month, and observed that it did indeed suppress estrogen production in the body. They then compared changes in behavior, memory, electrophysiology, and thermoregulation in the treated and control groups

Gervais says, "Sure enough, we found deficits in some aspects of memory and we also saw the most striking results in thermal regulation, a deficit in the ability to regulate body temperature when the ambient temperature increases, but only in females. It doesn't match hot flashes exactly but it's consistent with what we know about the regulation of hot flashes by estrogens in women. Females on the drug could not regulate their temperature as well as control females."

It was in the investigation of neurons that the researchers saw something quite surprising, says Remage-Healey. "In the hippocampus, which is thought to be critical for learning and memory functions, instead of reduced estrogen levels we found that the drug caused a paradoxical increase in estrogen levels."

Gervais adds, "We believe that the hippocampus may have synthesized its own estrogens to compensate for low levels it senses in peripheral tissues. According to our results, the mechanism for an adverse effect on memory may be due to an increase of estrogen synthesis in the

hippocampus. Perhaps, future treatments could find a way to block this increased synthesis, and maybe prevent some of the negative side effects."

Remage-Healey points out that "We were also able to follow the excitability of hippocampal neurons, which was compromised in the treatment but not control group. This is consistent with the occasional memory problems reported by patients. It seems the hippocampus is particularly sensitive to estrogens and their blockade. But we have a lot of work to do to understand the precise mechanism underlying these effects."

The authors state, "These findings suggest adverse effects of aromatase inhibitors on the primate brain and call for new therapies that effectively prevent breast cancer recurrence while minimizing side effects that further compromise quality of life."

More information: Adverse effects of aromatase inhibition on the brain and behavior in a nonhuman primate, *JNeurosci* (2018). www.jneurosci.org/lookup/doi/1 … EUROSCI.0353-18.2018

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