Study hints that antidepressants could help slow reproductive aging

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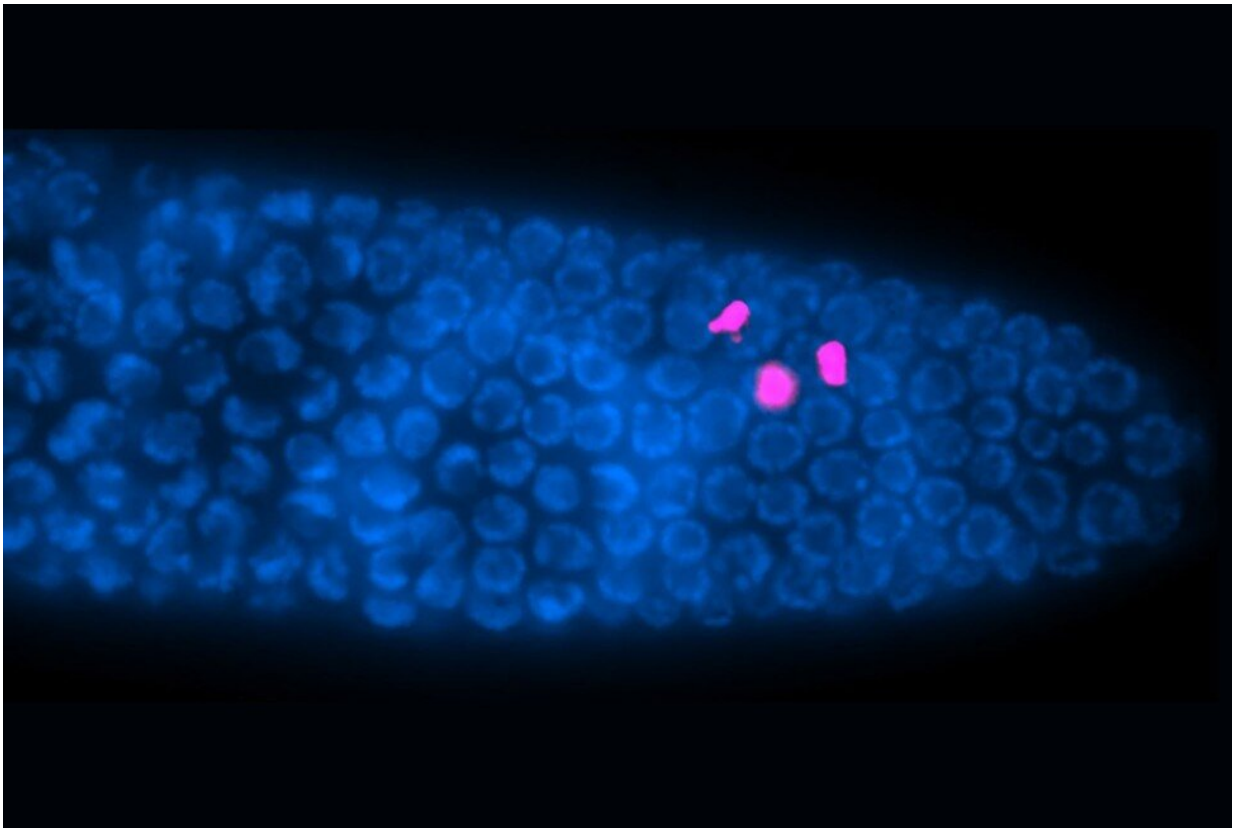

Egg precursor cells (blue) inside the gonad of a female roundworm. Prozac increases the division of precursor cells (magenta). Credit: Ilya Ruvinsky

Worms might not be depressed, per se. But that doesn't mean they can't benefit from antidepressants.

In a new study, Northwestern University researchers exposed roundworms (a well-established model organism in biological research) to selective serotonin reuptake inhibitors (SSRIs), a class of drugs used for treating depression and anxiety. Surprisingly, this treatment improved the quality of aging females' egg cells.

Not only did exposure to SSRIs decrease embryonic death by more than twofold, it also decreased chromosomal abnormalities in surviving offspring by more than twofold. Under the microscope, egg cells also looked younger and healthier, appearing round and plump rather than tiny and misshapen, which is common with aging.

Astounded by the results, the researchers replicated the experiment in fruit flies—another common model organism—and the SSRIs demonstrated the same effect.

Although much more work is needed, the researchers say these findings provide new opportunities to explore pharmacological interventions that might combat infertility issues in humans by improving egg quality and by delaying the onset of reproductive aging.

The study is be published in the journal *Developmental Biology*.

"There is still a great distance between this new finding and the fertility clinic," said Northwestern's Ilya Ruvinsky, who led the study. "But the more we study the reproductive system, the better we understand it and the more opportunities we have for developing practical interventions."

Ruvinsky is an associate research professor at Northwestern's Weinberg College of Arts and Sciences. Erin Aprison, a research associate in Ruvinsky's laboratory, is the paper's first author. Svetlana Dzitoyeva, a postdoctoral researcher in Ruvinsky's laboratory, co-authored the paper.

Cutting out the middleman

Previously, Ruvinsky's team discovered that male pheromones slowed the aging of females' egg cells. Published in the *Proceedings of the National Academy of Sciences* in May 2022, the previous study exposed female roundworms to male pheromones, which resulted in healthier offspring.

When female roundworms sensed the male pheromones, they shifted their energy and resources away from their overall body health and toward increasing reproductive health. "The pheromone coaxes the female into sending help to her eggs and shortchanging the rest of her body," Ruvinsky said. "It's not all or nothing; it's shifting the balance."

In the new study, Ruvinsky and his team decided to remove male pheromones from the equation entirely.

"The neurons that signal the body to shift its resources rely on serotonin as the messenger," he said. "We identified those neurons in previous work and wondered if we could tap directly into that system. Maybe we could stimulate the serotonin system with pharmaceuticals, bypassing the need for male pheromones. Lo and behold, we saw better eggs by every measure."

Delaying decline

To conduct the study, the team added a low dose of SSRIs to aging roundworms' food. The researchers primarily explored the effects of fluoxetine (Prozac) but also tested citalopram (Celexa) and zimelidine.

Researchers continuously exposed the aging worms to SSRIs at concentrations comparable to those used to treat anxiety and depression

in humans. Although egg quality typically drops precipitously as the worms age, worms treated with fluoxetine managed to stave off the decline.

"When we only delivered a temporary regimen of the drug and then withdrew it, the egg quality stayed high for a while but then quickly decreased," Ruvinsky said. "We think it's because they need a continuous signal."

Ruvinsky and his team also found that, when exposed to fluoxetine, roundworms produced more egg cell precursors. But, in a seemingly counterproductive twist, more of these cells died. However, this, too, is another advantage.

"How do you get the components to make higher-quality eggs? You take components from other eggs," Ruvinsky explained. "Many eggs die and get sent to the 'salvage yard.' You break up the parts and use those for the few eggs that survive."

Shared signaling

Wondering whether or not the finding was exclusive to worms, Ruvinsky's team replicated the study in fruit flies. Yet again, exposure to fluoxetine improved the quality of eggs for older female flies.

Although worms, flies and humans might seem very different, they have more in common than most people realize.

"This neuronal system does more or less the same thing in various animals," Ruvinsky said. "More serotonin in the brain causes animals to focus on food instead of exploring their surroundings. That's true for mammals, flies and worms. We might not be able to widen the fertility window to 60 years. But even if we could add a year or two to a person's

fertility window, that would make a big difference."

More information: Erin Z. Aprison et al, Serotonergic signaling plays a deeply conserved role in improving oocyte quality, *Developmental Biology* (2023). DOI: 10.1016/j.ydbio.2023.04.008

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