# Antidepressant harms baby neurons in lab-grown 'mini-brains'

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Researchers at Johns Hopkins Bloomberg School of Public Health have demonstrated the use of stem-cell-derived "mini-brains" to detect harmful side effects of a common drug on the developing brain. Mini-brains are miniature human brain models, developed with human cells and barely visible to the human eye, whose cellular mechanisms mimic

those of the developing human brain.

The scientists, who will publish their findings on February 21 in *Frontiers in Cellular Neuroscience*, used the mini-brains to determine that the common antidepressant paroxetine suppresses the growth of synapses, or connection points between neurons, and leads to significant decreases in an important support-cell population. Paroxetine is sold under the brand names Paxil and Seroxat, among others.

Paroxetine, which can cross the placenta in pregnant women, currently comes with a warning against use in early pregnancy, largely due to a known risk of heart and lung defects. Some epidemiological studies also have suggested that paroxetine raises the risk of autism. The new findings are likely to heighten concerns about the effects of this drug, and others in its class, on the developing brain.

The study authors say that the findings suggest that lab-grown mini-brains, which they call BrainSpheres, are a good alternative to traditional animal testing. In particular, they can reveal drugs and other chemicals that are harmful to young brains.

"There's a growing concern that we have an epidemic of neurodevelopmental disorders, including autism, and that these might be caused by exposures to common drugs or other chemicals. However, since traditional animal testing is so expensive, we haven't been able to properly investigate this question," says co-senior author Thomas Hartung, MD, the Doerenkamp-Zbinden Chair and Professor in the Department of Environmental Health and Engineering and director of the Center for Alternatives to Animal Testing at the Bloomberg School.

Hartung and colleagues developed the mini-brains to model early brain development. The tiny clumps of brain tissue are made by taking cells from adult humans, often from their skin, and transforming them into

stem cells, and then biochemically nudging the stem cells to develop into young brain cells. The mini-brains form a rudimentary brain-like organization over a period of a few months. Because they are made of human cells, they may be more likely to predict effects on the human brain—and because they can be mass-produced in the lab, they are much cheaper to work with than animals.

A set of animal toxicology tests for a single chemical costs about $1.4 million on average, the authors note, which explains why the vast majority of chemicals used in drugs and other consumer products have never been tested for toxicity. In contrast, toxicity testing using mini-brains costs only a few thousand dollars.

In the new study, the scientists used mini-brains to test for neurodevelopmental effects of paroxetine. It and other antidepressants in its class, known as SSRIs or selective serotonin reuptake inhibitors, are among the world's most commonly prescribed drugs, accounting for at least hundreds of millions of prescriptions annually.

The research team exposed mini-brains to two different concentrations of paroxetine over eight weeks as the clumps of tissue developed. Both concentrations were within the therapeutic range for blood levels of the drug in humans. In the experiments, the researchers also used two different sets of mini-brains, each derived from a different stem cell.

The scientists found that while paroxetine didn't seem to have a significant neuron-killing effect, at the higher concentration it reduced levels of a protein called synaptophysin, a key component and marker of synapses by up to 80 percent. Paroxetine reduced levels of two other synapse-related markers as well. Similarly, the team observed that paroxetine reduced the normal outgrowth of structures called neurites, which eventually develop into the output stalks and root-like input branches of mature neurons. Finally, the researchers noted that

paroxetine-exposed mini-brains developed with up to 75 percent fewer oligodendrocytes, the support cells that are crucial for the proper "wiring" of the brain, than controls.

These effects suggest that the drug might hinder the normal formation of interconnections among developing neurons—a result that could conceivably underlie autism or other disorders.

The study also shows the broader potential of mini-brains-based testing to detect adverse effects of drugs on the developing brain.

"In this report, we were able to show that testing with mini-brains can reveal relatively subtle neurodevelopmental effects, not just obvious effects, of a chemical," Hartung says. "Whether paroxetine causes autism has been a decade-long debate, which could not be settled with animal tests or epidemiological analyses. So we see mini-brains as technology for broader assessment of the risks of common drugs and chemicals, including those that might be contributing to the autism epidemic."

Hartung and colleagues recently received a grant from the U.S. Environmental Protection Agency to develop their technology as an alternative to animal testing.

**More information:** "Antidepressant Paroxetine exerts developmental neurotoxicity in an iPSC-derived 3D human brain model" *Frontiers in Cellular Neuroscience*, 2020.

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