NEWS

Prenatal antibodies boost brain stem cells in mice

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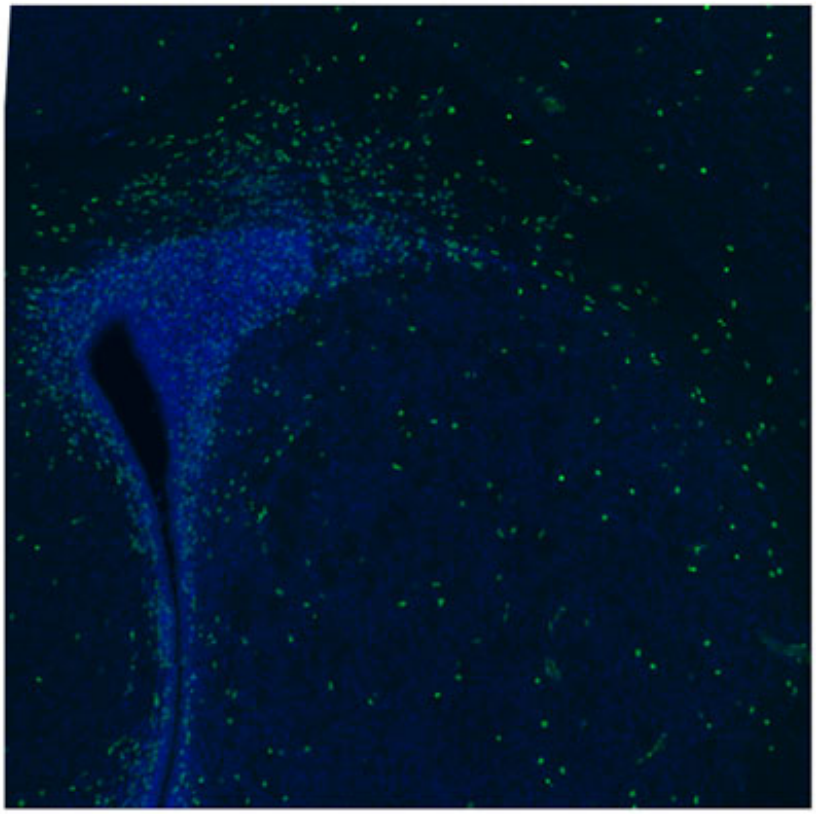

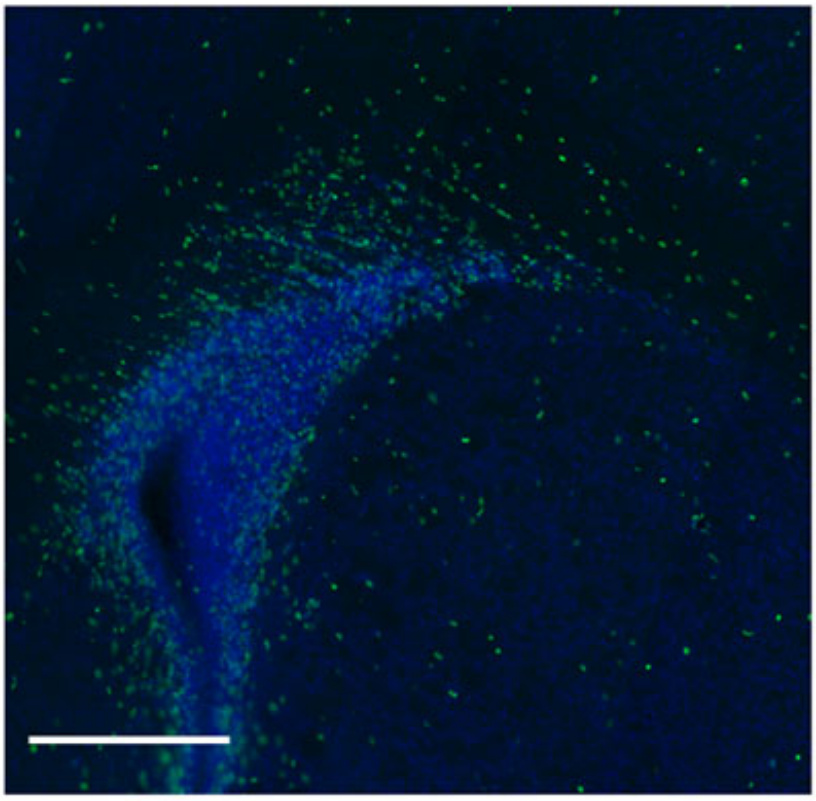

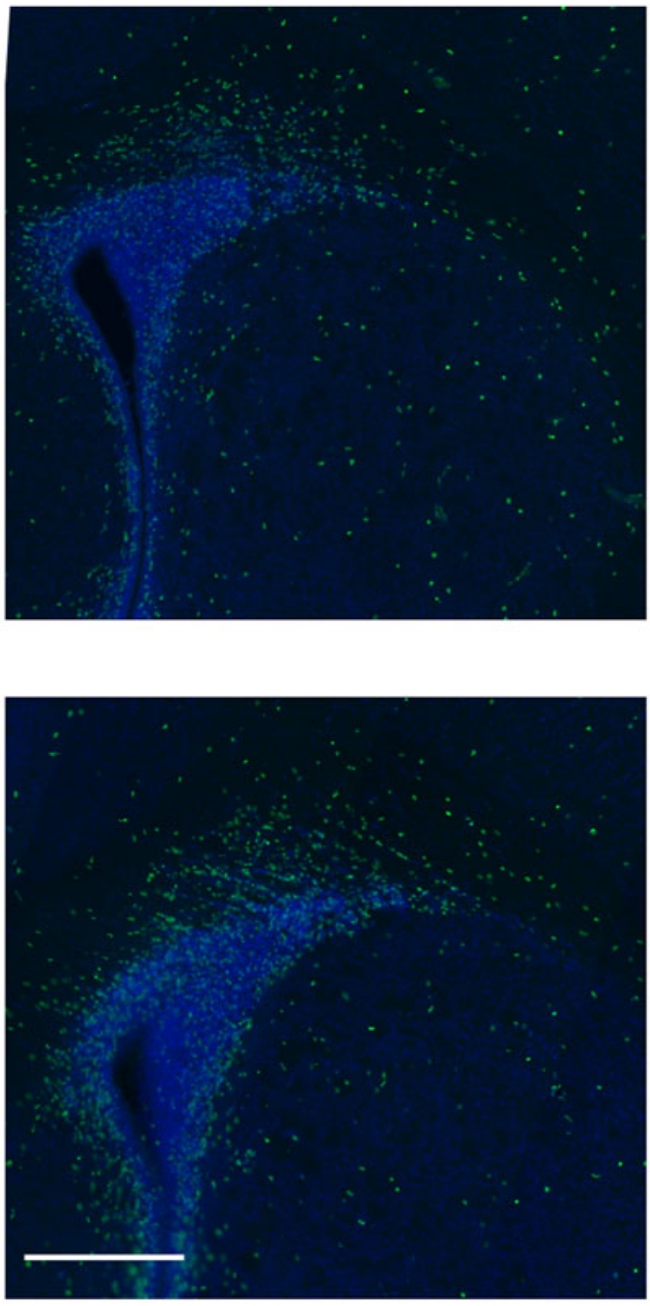

Growth spurt: In mice, prenatal exposure to autism-linked antibodies (bottom) increases the number of neural progenitor cells (green) compared with controls (top).

Prenatal exposure to antibodies collected from the mothers of children with autism boosts stem cell proliferation in the brains of mice, according to two studies presented at the **2012 Society for Neuroscience annual meeting** in New Orleans.

One study found that mice exposed to the autism-linked antibodies have higher levels of neural progenitor cells — an intermediate stage between neural stem cells and fully developed neurons and other brain cells — than those exposed to control antibodies.

The second study also found higher numbers of neural progenitor cells, as well as larger neurons in adults, in mice exposed to the autism-linked antibodies compared with controls.

The fact that two studies using antibodies isolated from different pools of women show similar effects is promising, says **Shilpa Kadam**, lead investigator on one of the studies and an instructor at the Kennedy Krieger Institute in Baltimore.

Mothers of children with autism are **five times more likely** to have antibodies that can bind to the fetal brain than controls are, and about 10 to 15 percent of such mothers carry them. These maternal antibodies may cross the placenta and increase risk for autism in the fetus.

The offspring of both mice and monkeys exposed to autism-linked maternal antibodies from humans have more social deficits and other autism-like symptoms than do those exposed to control antibodies[1,2]. “But we don’t know the mechanism that results in these altered behaviors,” says Kadam.

The researchers focused on two parts of the brain populated by neural progenitor cells: the subventricular zone, which supplies cells to the cortex and other brain areas, and the subgranular zone, which generates neurons in the hippocampus, a brain area essential for learning and memory.

A cell is born:

During a mouse’s first week of life, the progenitor cells give rise to neurons and other cells, which then migrate to their final location in the brain. By 7 days of age, roughly equivalent to humans at birth, most mouse neurons have reached their final destination. But they don’t fully integrate into the brain for several weeks.

In the first study, Kadam and her collaborators used immunoglobin G, or IgG, antibodies collected from 66 mothers of children with autism and 63 control mothers.

The researchers injected pregnant mice with either the autism-linked or control antibodies, and after birth gave the babies a chemical to label dividing cells in the brain.

They gave one set of mice the label when the mice were just 1 day old, and studied their brains a week later. They gave a second set of mice the label at 1 week old, and analyzed their brains just two hours later. This allowed the researchers to look at differences in the cells' proliferation.

In the mice labeled on day 1, the researchers saw fewer labeled cells in the cortex compared with mice exposed to control antibodies. "That means the cells either died during migration or during maturation," says Kadam. "We now plan to tease that apart."

In the mice labeled on day 7, the researchers saw higher cell proliferation in both of the neural progenitor zones compared with controls. "That might be a response to more cells dying in the cortex at an earlier age," says Kadam.

The researchers also saw hints of differences in the number of astrocytes, cells that support neurons. Astrocytes have also been **implicated in some forms of autism**.

They next plan to label both neurons and astrocytes and to look at the brain at later ages.

In the second study, **Verónica Martínez Cerdeño** and her collaborators injected autism-linked maternal antibodies directly into the brain ventricles of fetal mice, ensuring that the antibodies reach the brain. (Ventricles are fluid-filled cavities in the brain.)

The researchers then analyzed the number of stem cells in the animals' brains, in some cases soon after the injection, and in others as adults.

They found that before birth, fetal mice exposed to autism-linked antibodies have more neural progenitor cells in the subventricular zone than do those exposed to control antibodies. The biggest boost in cell growth occurs two days after antibody injection, says Cerdeño, assistant professor of pathology and medicine at the University of California, Davis Mind Institute.

In adult mice, the researchers don't see changes in the numbers of fully differentiated neurons or glia in the brain. But the neurons are bigger than in mice exposed to control antibodies. The adult animals also show deficits in social and **repetitive behaviors**.

Cerdeño says the peak proliferation period in the mice exposed to autism-linked antibodies may be shortened, so that there are more cells early on, but the total number remains the same.

If that's correct, it would mean that newly born neurons migrate through the cortex and reach their final destination too early, and therefore may not make the appropriate connections. Her team next plans to look at the morphology, or shape, of the adult neurons in mice exposed to autim-linked antibodies.

*For more reports from the 2012 Society for Neuroscience annual meeting, please **click here**.*

References:

1: Singer H.S. *et al*. *J. Neuroimmunol.* **211**, 39-48 (2009) **PubMed**

2: Martin L.A. *et al. Brain Behav. Immun.* **22**, 806-816 (2008) **PubMed**