Trigger for brain plasticity identified

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Researchers have long sought a factor that can trigger the brain's ability to learn – and perhaps recapture the "sponge-like" quality of childhood. In the August 8 issue of the journal *Cell*, neuroscientists at Children's Hospital Boston report that they've identified such a factor, a protein called Otx 2.

Otx2 helps a key type of cell in the cortex to mature, initiating a critical period -- a window of heightened brain plasticity, when the brain can readily make new connections.

The work was done in a mouse model of the visual system, a classic model for understanding how the brain sets up its wiring in response to input from the outside world. But Takao Hensch, PhD, of the Neurobiology Program and Department of Neurology at Children's, the study's senior investigator, speculates that there may be similar factors from the auditory, olfactory and other sensory systems that help time critical periods. Timing is important, because the brain needs to rewire itself at the right moment -- when it's getting the optimal sensory input.

"If the timing is off, the brain won't set up its circuits properly," Hensch says.

Being able to control the timing of critical periods in different parts of the brain could possibly ameliorate developmental disorders such as autism, in which researchers believe critical periods may be inappropriately accelerated or delayed. Retriggering a critical period might also help people learn more readily after childhood – acquiring a

new language, developing musical abilities or recovering from stroke or brain injury, for example.

Interestingly, Hensch and colleagues found that the brain cells that switch on critical periods in the visual system (parvalbumin cells) don't actually make Otx2 themselves. Instead, Otx2 is sent by the retina. In essence, the eye is telling the brain, "The eyes are ready and seeing properly -- you can rewire now."

"The eye is telling the brain when to become plastic, rather than the brain developing on its own clock," says Hensch, who is also a professor at Harvard Medical School and at Harvard University's Department of Molecular & Cellular Biology. "The idea that this class of molecular messenger is passed from cell to cell is considered unorthodox in cell biology." This idea, however, has long been advocated by Dr. Alain Prochiantz of the Ecole Normale Superieure (Paris) and College de France, Hensch's collaborator and a coauthor on the study.

It was previously known that when parvalbumin cells mature, they set up inhibitory circuits in the cortex, balancing the existing excitatory circuits. Hensch and others have shown that setting up inhibitory circuits is key in launching critical periods. "Early excitatory input is important to make first contacts between neurons," Hensch explains. "But then, at the next stage, you need inhibition."

In the current study, Hensch and colleagues demonstrated that when mice are reared in the dark, thus getting no visual input, Otx2 remains in the retina. Only when the mice received full visual input did Otx2 begin to appear in the cortex, and only then did parvalbumin cells start to mature.

In other experiments, the researchers injected Otx2 directly into the cortex. The parvalbumin cells matured, even when the mice were kept in

the dark. Finally, when Otx2 synthesis was blocked in the eye, parvalbumin cell functions failed to mature.

Otx2 has an unusual derivation: it is originally produced during embryonic development; without it, mice don't develop heads. Production then stops, but some days after birth, it reappears in parvalbumin cells. "The nervous system is recycling an embryonic factor to induce brain plasticity," says Hensch.

Hensch, who last fall won the highly competitive NIH Director's Pioneer Award, is also interested in the transport mechanism that propagates Otx2 from the retina to the cortex. He speculates that Otx2 itself could be a carrier for factors you'd want to deliver to the brain, envisioning eye drops for brain disorders such as schizophrenia, in which parvalbumin cells don't properly mature.

Source: Children's Hospital Boston