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Balancing the brain

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Neuroscientists at Children's Hospital Boston have identified the first known "master switch" in brain cells to orchestrate the formation and maintenance of inhibitory synapses, essential for proper brain function. The factor, called Npas4, regulates more than 200 genes that act in various ways to calm down over-excited cells, restoring a balance that is thought to go askew in some neurologic disorders. The findings appear in the September 24 advance online edition of the journal *Nature*.

Synapses, the connections between brain cells, can be excitatory or inhibitory in nature. At birth, the rapidly developing brain teems with excitatory synapses, which tend to make nerve cells "fire" and stimulate their neighbors. But if the excitation isn't eventually balanced, it can lead to epilepsy, and diseases like autism and schizophrenia have been associated with an imbalance of excitation and inhibition. The creation of inhibitory connections is also necessary to launch critical periods -- windows of rapid learning during early childhood and adolescence, when the brain is very "plastic" and able to rewire itself.

Npas4 is a transcription factor, a switch that activates or represses other genes. The researchers, led by Michael Greenberg, PhD, director of the Neurobiology Program at Children's, demonstrated that the activity of as many as 270 genes changes when Npas4 activity is blocked in a cell, and that Npas4 activation is associated with an increased number of inhibitory synapses on the cell's surface.

The team further showed that Npas4 is activated by excitatory synaptic activity. "Excitation turns on a program that says, 'this cell is getting

excited, we need to balance that with inhibition,'" explains Greenberg, who now also chairs the Department of Neurobiology at Harvard Medical School.

Finally, the researchers bred live mice that lacked Npas4, and found evidence of neurologic problems – the mice appeared anxious and hyperactive and were prone to seizures.

Greenberg and colleagues are now trying to learn more about the wide variety of genes that Npas4 regulates, each of which could give clues to synapse development and reveal new treatment possibilities for neurologic disorders. "If you have your hand on a transcription factor such as Npas4, new genome-wide technology allows you to essentially identify every target of the transcription factor," says Greenberg. One such target is neurotrophic factor (BDNF), which Greenberg and colleagues previously showed to regulate the maturation and function of inhibitory synapses.

Citation: Lin Y; et al. Activity-dependent regulation of GABAergic synapse development by Npas4. Nature Sep 24, 2008 [advance online publication]. The article can be viewed at dx.doi.org/10.1038/nature07319 .

Source: Children's Hospital Boston