U.S. Department of Health and Human Services
NIH News
National Institutes of Health

National Institute on Drug Abuse
http://www.drugabuse.gov/

EMBARGOED FOR RELEASE
December 14, 2007

NIDA Contacts: Dorie Hightower or
Sara Rosario Wilson
301-443-6245
media@nida.nih.gov

Contacto en Español: 301-594-6145

Early fine-tuning of neural connections may turn destructive later in life

Mouse study implicates immune process in brain development as well as degenerative diseases

The immune system helps to prune excess connections between neurons in the developing brains of young mice, according to scientists funded by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health (NIH). The study, published in the December 14 issue of the journal *Cell,* sheds critical new light upon a fundamental process, while hinting at a likely mechanism behind neurodegenerative diseases like glaucoma and Alzheimer's disease.

Shortly after birth, the mammalian brain contains vast numbers of connections, or synapses, between neurons – many more than will be needed in adulthood. Scientists have known for years that the developing brain follows a use it or lose it rule: inactive connections are pruned away during childhood and adolescence. However, the molecular mechanism underlying this pruning process has remained one of the biggest mysteries in neurobiology. Now, Dr. Beth Stevens and Dr. Ben Barres of the Stanford University School of Medicine and their colleagues report that a protein used by the immune system to destroy bacteria is also needed by the young brain to target and destroy unwanted synapses.

"From the fetal period through early adulthood, the developing brain is constantly fine-tuning its synaptic connections. These results provide new insight into this vital process," said Dr. Nora Volkow, NIDA director. "Eventually, research like this, into the fundamental mechanisms of brain development, will help us understand why a child's brain is so vulnerable to environmental factors, including addictive drugs."

"The immune system's involvement in sculpting synapses was totally unexpected," added Dr. Barres. The immune protein C1q is among the body's first responders to injury or infection, attaching to dead cells or bacteria and triggering their destruction. Surprisingly, the researchers also found C1q attached to immature synapses in the brains and retinas of young mice. Unlike normal mice, mice missing C1q were unable to eliminate extra synapses as they aged, producing disorganized, abnormal connections in their visual systems.

In collaboration with Dr. Simon John of The Jackson Laboratory, the researchers asked whether diseases like glaucoma could trick C1q into targeting synapses in the adult. They found that although C1q is normally turned off in the nervous systems of mature mice, it reappears during the early stages of glaucoma, when retinal synapses begin to deteriorate. This discovery offers a tantalizing clue to how synapses might be lost in neurodegenerative diseases like Alzheimer's disease and ALS.

"It looks like as soon as something goes wrong, C1q is reactivated," said Dr. Barres. "In the mouse model of human glaucoma, C1q is the earliest sign of disease, appearing well before visible damage to synapses and neurons. We hope that if we block C1q and the immune cascade it triggers, we can block the disease before neurons start to die."

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