Study Provides Insight Into How the Brain Loses Plasticity of Youth

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A protein once thought to play a role only in the immune system could hold a clue to one of the great puzzles of neuroscience: how do the highly malleable and plastic brains of youth settle down into a relatively stable adult set of neuronal connections? Harvard Medical School researchers report in the August 17 *Science Express* that adult mice lacking the immune system protein paired-immunoglobulin like receptor-B (PirB) had brains that retained the plasticity of much younger brains, suggesting that PirB inhibits such plasticity.

Intriguingly, brains of immature PirB-deprived mice also exhibited greater plasticity than brains endowed with the protein. Taken together, the results have important implications for the future study and repair of the brain. “Our study of mutant mice lacking PirB function reveals that at all ages, even during critical periods when circuits are prone to change, there are active molecular mechanisms that function to limit synaptic plasticity,” said Josh Syken, HMS instructor in neurobiology and lead author of the study.

One way to promote new connections in brains damaged by disease or injury might be to target PirB. “The implications here should attract broad interest outside the field of developmental neuroscience because molecules and mechanisms that oppose neuronal plasticity represent new targets for therapy to re-establish damaged connections following spinal cord injury, head injury or stroke,” said Syken, who carried out the study with Carla Shatz, Nathan Marsh Pusey professor of neurobiology at HMS, and colleagues.

Plasticity, the ability of functional brain circuits to change in response to experience-dependent neuronal activity, is largely restricted to critical periods of development. In their classic Nobel-prize winning experiments, David Hubel and Torsten Weisel showed that visual areas of the brain are responsive to environmental cues during a discrete period early in life, after which they do not change. Researchers have successfully identified proteins that promote such critical periods of plasticity but less is known about the proteins that stabilize neuronal connections.

Several years ago, Shatz and colleagues made the surprising discovery that MHC Class I genes are turned on in neurons by neuronal activity and in fact are required for normal synaptic plasticity. In the immune system, MHC Class I proteins teach immune cells which cells to attack. They do this by interacting with a large number of receptors found on the surface of immune cells. Syken, Shatz and colleagues wondered whether such receptors might also be expressed in neurons and involved in MHC Class I-mediated synaptic plasticity.

Using a method called in situ hybridization, they found that the MHC Class I receptor PirB is expressed widely throughout the brain and at all ages. To see how PirB was functioning, they generated a mouse deficient in PirB. At first sight, the mutant's brain appeared normal. To get a better sense of how PirB might be affecting plasticity, they decided to focus on the visual cortex.

In their earlier work, Hubel and Weisel showed that suturing or removing one eye causes projections from the remaining eye to invade the area that normally represents the blocked eye. This shift is strictly limited to a critical period of development early in life. Syken and his colleagues sutured one eye in their adult mutant mice, and also in controls, for several days. They exposed the open eye to light and, using the activity-sensitive gene Arc as their guide, looked to see which

neurons in the cortex were activated. The PirB mutant adults exhibited a robust expansion of the area in visual cortex that responds to the open eye, suggesting that new connections representing the open eye had formed. They repeated the experiment with younger mice and found, somewhat unexpectedly, that plasticity was enhanced even during the immature period.

“Other factors have been shown to restrict plasticity after the critical period, but we believe that this is one of the first proteins shown to act in this way throughout life,” Syken said. “Our discovery implies that there are mechanisms that enable, and also those that oppose synaptic plasticity in a push-pull fashion.”

“Our discovery underscores further the fascinating and common molecular parallels between the nervous system and the immune system, where PirB was first studied. The discovery of a neuronal receptor for MHC Class I opens up a completely new avenue for thinking about broader roles for this family of molecules beyond the immune system,” he said.

Source: Harvard Medical School