Johns Hopkins neuroscientists discover a critical early step of memory formation

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Researchers at the Johns Hopkins University School of Medicine report in the July issue of *Neuron* how nerve cells in the brain ensure that Arc, a protein critical for memory formation, is made instantly after nerve stimulation. Paradoxically, its manufacture involves two other proteins — including one linked to mental retardation — that typically prevent proteins from being made.

Previous research already established that long-term memory formation depends on Arc protein, but scientists did not know the mechanism that turned on this process.

To find it, they surveyed proteins in mouse brains that change or are activated after a nerve is stimulated and identified eEF2K (short for eukaryotic elongation factor 2 kinase) as a player. When turned on, eEF2K inhibits an important step of protein translation.

"This seemed strange, because it suggested that nerve cells might make Arc protein by using pathways typically thought to turn off protein manufacture," says Paul Worley, M.D., a professor of neuroscience in the Johns Hopkins University School of Medicine.

Further examination of mouse brain slices lacking eEF2K in their nerve cells showed that when stimulated, such cells fail to make the usual pools of Arc protein, demonstrating that eEF2K is required for making Arc.

What it didn't tell them was whether eEF2K specifically was responsible,

or whether some other pathway is also involved, so researchers next treated the brain slices from normal mice with a chemical that inhibits protein manufacture by the same mechanism as eEF2K. At the same time that general protein synthesis was turned down, Arc translation actually increased, making it clear eEF2K, through its ability to turn down protein manufacture, somehow enabled a nerve cell to make Arc in response to nerve stimulation.

Meanwhile, Worley's team proceeded to build on research showing that a protein linked to a form of mental retardation passed on by an abnormal "fragile X" chromosome also represses the manufacture of some proteins. The researchers looked at Arc protein levels in nerve cells lacking the fragile X mental retardation protein and found stable levels of Arc protein all the time, before, during, after and even without stimulation of the nerve cells. They concluded that without fragile X protein, the presumed "brakes" on the system, the manufacture of Arc goes unregulated.

"It's sort of a seesaw relationship," Worley says. When nerve cells are stimulated, eEF2K is activated to suppress protein manufacture generally, thereby allowing for the rapid manufacture of Arc, and, at the same time, fragile X mental retardation protein is stimulated to let Arc protein get made.

"By defining a mechanism that is associated with fragile X syndrome — the most common inherited cause of mental retardation and autism — it may help others to identify potential therapeutic targets to help with the disease," Worley says.

Source: Johns Hopkins Medical Institutions