Loss of enzyme reduces neural activity in Angelman syndrome

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Angelman Syndrome is a rare but serious genetic disorder that causes a constellation of developmental problems in affected children, including mental retardation, lack of speech, and in some cases, autism. Over a decade ago, researchers found that AS was caused by mutation in a single gene, but no one had been able to explain how this defect resulted in the debilitating neurological symptoms of the disease.

New work from Michael Greenberg, chair of the department of neurobiology at Harvard Medical School (HMS), provides insight into the mystery by showing that the lost enzyme, Ube3A, interacts with a key neuronal protein in order to control how environmental input shapes synaptic connections. In other words, loss of Ube3A interferes with the brain's ability to use environmental experience to fine-tune neuronal circuits, which could explain the devastating developmental deficits that occur in AS. This suggests new targets for treating Angelman syndrome. Currently, doctors can manage some AS symptoms, but there is no treatment for the core features.

What's more, the Ube3A gene is also mutated in some cases of autism, raising the possibility that these findings may also explain some of the problems that occur in autism spectrum disorders, which are 100 times more common than AS.

"With this work, we've gone from a place where we could only imagine how Ube3A might work, to being able to think about possibilities for therapeutic intervention in a disorder where until very recently there was

little that could be done," says Greenberg, Nathan Marsh Pusey professor of neurobiology at HMS.

These findings will be published in the March 5 issue of *Cell*.

During the first few years of life, brain activity is "rewired" by external stimuli . This tweaking of neuronal connections is critical to establish normal neurological function, and is thought to go awry in a number of developmental disorders that lead to mental retardation or other cognitive problems. The new work suggests that Ube3A is a key regulator in this process, and ties the loss of Ube3A to a specific change in synaptic function.

Under normal conditions, the Ube3A enzyme tags cellular proteins for destruction. Co-ead author Paul Greer, a postdoctoral fellow in Greenberg's lab identified the synaptic protein Arc as one of Ube3A's targets. Arc's primary function is to decrease neuronal signaling. However, with a mutated Ube3A, Arc accumulates to higher than normal levels, which causes an abnormal lowering of neuronal signaling, leading to impaired neuronal communication and synaptic development.

The Arc connection has revealed surprising links to other disorders, Greenberg says. In Fragile X syndrome, a major form of inherited mental retardation, neurons also have an over-abundance of Arc protein. Although the excess Arc occurs through a different mechanism independent of Ube3A, the two diseases seem to converge on a common synaptic defect. That means new treatments now under study for Fragile X may someday be useful for Angelman Syndrome, Greenberg says.

The work may also suggest additional therapeutic targets for AS. As part of the study, the researchers identified several proteins regulated by Ube3A in addition to Arc, some of which might be involved in creating the complex features of AS. "It could be that affecting Arc levels may be

useful for some of the symptoms of AS, while modulating other targets will be useful for others," Greer says. "We are hoping to identify many substrates upon which Ube3a is acting, and one can imagine doing targeted therapeutics on several of them."

More information: "The Angelman Syndrome-associated ubiquitin ligase Ube3A regulates synapse development by ubiquitinating Arc", *Cell*, March 5, 2010, Vol 140, No. 5

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