

Impaired brain plasticity linked to Angelman syndrome learning deficits

May 10 2009

How might disruption of a single gene in the brain cause the severe cognitive deficits associated with Angelman syndrome, a neurogenetic disorder? Researchers at the University of North Carolina at Chapel Hill School of Medicine and Duke University now believe they have the answer: impaired brain plasticity.

"When we have experiences, connections between brain cells are modified so that we can learn," said Benjamin Philpot, Ph.D., professor of cell and molecular physiology at UNC and senior author of the study published online May 10 in [Nature Neuroscience](#). "By strengthening and weakening appropriate connections between brain cells, a process termed 'synaptic plasticity', we are able to constantly learn and adapt to an ever-changing environment."

Angelman syndrome occurs in one in 15,000 live births. The most common [genetic defect](#) of the syndrome is the lack of expression of the gene UBE3A on [chromosome 15](#). The syndrome often is misdiagnosed as cerebral palsy or autism. Characteristics of the syndrome include intellectual and developmental delay, severe mental retardation lack of speech (minimal or no use of words), seizures, sleep disturbance, hand flapping and motor and balance disorders.

Philpot and his co-authors studied a mouse model of Angelman syndrome. In these mice, the gene UBE3A is functionally deficient. The study found that brain cells in the mice lacked the ability to appropriately strengthen or weaken their connections in the neocortex, a

region of the brain that is important for cognitive abilities.

"If brain cells were unable to modify their connections with new experiences, then we would have difficulty learning," said Michael Ehlers, M.D., Ph.D., professor of neurobiology at Duke and co-senior author of the study. "We have found that a specific form of brain plasticity is severely impaired in a mouse model of Angelman syndrome and this prevents [brain circuits](#) from encoding information provided by sensory experiences. In addition, an exciting possibility is that the defect we have found may be a more general feature of other disorders of brain development including autism."

The inability of brain cells to encode information from experiences in the Angelman syndrome model suggests that this is the basis for the learning difficulties in these patients.

"It is difficult to study how experiences lead to changes in the brain in models of mental retardation," said Koji Yashiro, PhD, a former graduate student in Philpot's lab and lead author of the study, now a scientist with Urogenix, Inc. in Research Triangle Park, North Carolina. "Instead of studying a complex learning model, we studied how connections between brain cells change in visual areas of mice exposed to light or kept in darkness. This approach revealed that brain cells in normal mice can modify their connections in response to changes in visual experiences, while the brain cells in Angelman syndrome model mice could not."

An unexpected finding was that the plasticity of the cellular connections could be restored in visual areas of the brain after brief periods of visual deprivation. Philpot said the observation that the brain defect could be reversed "is very encouraging, as it suggests that viable behavioral or pharmacological therapies are likely to exist."

"By showing that brain plasticity can be restored in Angelman syndrome model mice, our findings suggest that brain cells in Angelman syndrome patients maintain a latent ability to express plasticity. We are now collaborating to find a way to tap into this latent plasticity, as this could offer a treatment, or even a cure, for Angelman syndrome," said Philpot.

Philpot added, "This same experimental approach could also reveal how [brain cells](#) encode information from experiences in other related disorders, such as autism, and may provide a model to find cures for a variety of neurodevelopmental disorders."

Source: University of North Carolina School of Medicine

Citation: Impaired brain plasticity linked to Angelman syndrome learning deficits (2009, May 10) retrieved 20 November 2023 from <https://medicalxpress.com/news/2009-05-impaired-brain-plasticity-linked-angelman.html>

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