MedicalXpress

Drug reverses mental retardation caused by genetic disorder

June 22 2008

UCLA mouse study offers hope for correcting how autism disrupts brain

UCLA researchers discovered that an FDA-approved drug reverses the brain dysfunction inflicted by a genetic disease called tuberous sclerosis complex (TSC). Because half of TSC patients also suffer from autism, the findings offer new hope for addressing learning disorders due to autism. *Nature Medicine* publishes the findings in its online June 22 edition.

Using a mouse model for TSC, the scientists tested rapamycin, a drug approved by the FDA to fight tissue rejection following organ transplants. Rapamycin is well-known for targeting an enzyme involved in making proteins needed for memory. The UCLA team chose it because the same enzyme is also regulated by TSC proteins.

"This is the first study to demonstrate that the drug rapamycin can repair learning deficits related to a genetic mutation that causes autism in humans. The same mutation in animals produces learning disorders, which we were able to eliminate in adult mice," explained principal investigator Dr. Alcino Silva, professor of neurobiology and psychiatry at the David Geffen School of Medicine at UCLA. "Our work and other recent studies suggest that some forms of mental retardation can be reversed, even in the adult brain."

"These findings challenge the theory that abnormal brain development is to blame for mental impairment in tuberous sclerosis," added first author

Dan Ehninger, postgraduate researcher in neurobiology. "Our research shows that the disease's learning problems are caused by reversible changes in brain function -- not by permanent damage to the developing brain."

TSC is a devastating genetic disorder that disrupts how the brain works, often causing severe mental retardation. Even in mild cases, learning disabilities and short-term memory problems are common. Half of all TSC patients also suffer from autism and epilepsy. The disorder strikes one in 6,000 people, making it twice as common as Huntington's or Lou Gehrig's disease.

Silva and Ehninger studied mice bred with TSC and verified that the animals suffered from the same severe learning difficulties as human patients. Next, the UCLA team traced the source of the learning problems to biochemical changes sparking abnormal function of the hippocampus, a brain structure that plays a key role in memory.

"Memory is as much about discarding trivial details as it is about storing useful information," said Silva, a member of the UCLA Department of Psychology and UCLA Brain Research Institute. "Our findings suggest that mice with the mutation cannot distinguish between important and unimportant data. We suspect that their brains are filled with meaningless noise that interferes with learning."

"After only three days of treatment, the TSC mice learned as quickly as the healthy mice," said Ehninger. "The rapamycin corrected the biochemistry, reversed the learning deficits and restored normal hippocampal function, allowing the mice's brains to store memories properly."

In January, Silva presented his study at the National Institute of Neurological Disorders and Stroke meeting, where he was approached

by Dr. Petrus de Vries, who studies TSC patients and leads rapamycin clinical trials at the University of Cambridge. After discussing their respective findings, the two researchers began collaborating on a clinical trial currently taking place at Cambridge to examine whether rapamycin can restore short-term memory in TSC patients.

"The United States spends roughly $90 billion a year on remedial programs to address learning disorders," noted Silva. "Our research offers hope to patients affected by tuberous sclerosis and to their families. The new findings suggest that rapamycin could provide therapeutic value in treating similar symptoms in people affected by the disorder."'

Source: University of California - Los Angeles