MedicalXpress

New Down syndrome treatment suggested by study in mice

November 18 2009

At birth, children with Down syndrome aren't developmentally delayed. But as they age, these kids fall behind. Memory deficits inherent in Down syndrome hinder learning, making it hard for the brain to collect experiences needed for normal cognitive development.

Now, findings from the Stanford University School of Medicine and Lucile Packard Children's Hospital shed light on the neural basis of memory defects in Down syndrome and suggest a new strategy for treating the defects with medication. The study, which was conducted in mice, is the first to show that boosting norepinephrine signaling in the brains of mice genetically engineered to mimic Down syndrome improves their cognition. Norepinephrine is a neurotransmitter that nerve cells use to communicate.

"If you intervene early enough, you will be able to help kids with Down syndrome to collect and modulate information," said Ahmad Salehi, MD, PhD, the primary author of the study, which will be published Nov. 18 in *Science Translational Medicine*. "Theoretically, that could lead to an improvement in cognitive functions in these kids." Salehi, a research health science specialist at the Veterans Affairs Palo Alto Health Care System, was a senior scientist at the School of Medicine when the study was conducted.

Down syndrome is a genetic disorder caused by an extra copy of chromosome 21. Using a mouse model, Salehi and his colleagues are examining exactly how the brain malfunctions in Down syndrome.

"Cognition doesn't fail in every aspect; it's failing in a structure-dependent fashion," he said.

For instance, people with Down syndrome struggle to use spatial and contextual information to form new memories, a function that depends on the hippocampus part of the brain. As a result, they have trouble with learning to navigate complex environments such as a new neighborhood or a shopping mall. But they're much better at remembering information linked to colors, sounds or other sensory cues because such sensory memories are coordinated by a different brain structure, the amygdala.

Salehi and his colleagues looked at what could be causing the problems in the hippocampus. Normally, as contextual or relational memories are formed, hippocampal neurons receive norepinephrine from neurons in another part of the brain, the locus coeruleus. The researchers showed that, like humans with Down syndrome, the mice in their experiments experienced early degeneration of the locus coeruleus.

When the locus coeruleus broke down in the study's mice, the animals failed at simple cognitive tests that required them to be aware of changes in the milieu: For instance, the genetically engineered mice, when placed in the strange environment of an unknown cage, did not build nests. That contrasts with normal mice, which typically build nests in such circumstances.

However, by giving norepinephrine precursors to the mice with the Down-syndrome-like condition, the researchers could fix the problem. Only a few hours after they got the drugs, which were converted to norepinephrine in the brain, these mice were just as good at nest-building and related cognitive tests as normal mice. Direct examination of neurons in the hippocampus of the genetically altered mice showed that these cells responded well to norepinephrine.

"We were very surprised to see that, wow, it worked so fast," Salehi said. The drugs' effect also wore off relatively quickly, he added.

Enhancement of norepinephrine signaling has been explored for other neurological conditions. Some of the drugs already on the market for depression and attention deficit hyperactivity disorder target the norepinephrine system; Salehi hopes the new results will spur tests of these drugs for Down syndrome.

Other studies of drug therapies for Down syndrome have targeted a different neurotransmitter, acetylcholine, which also acts at the hippocampus. Based on his team's new findings, Salehi said the ideal medication regimen for improving cognition in Down syndrome will likely improve both norepinephrine and acetylcholine signals.

The new study also provides the first direct link between locus coeruleus breakdown in Down syndrome and a specific gene. People with Down syndrome have an extra copy of a gene called APP on their extra chromosome 21. Other researchers have linked APP to Alzheimer's disease, another disorder in which spatial orientation and memory formation go awry. Salehi and colleagues previously linked APP to the breakdown of neurons that make acetylcholine in these mice.

Salehi's results give "a ray of hope and optimism for the Down syndrome community for the future," said Melanie Manning, MD, director of the Center for Down Syndrome at Lucile Packard Children's Hospital. Manning was not a part of Salehi's research team. "It's very exciting," she said. "We still have a long way to go, but these are very interesting results."

Source: Stanford University Medical Center (news : web)