

# Canadians open door to learning-disorder drug

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An eight-year effort by Canadian scientists has connected a crucial brain protein with the power to learn, raising the possibility that learning disabilities could be corrected with a drug.

A Toronto research team discovered that this single protein, which helps brain cells talk to one another, results in learning impairments when it is missing or malfunctions. And in a remarkable one-two punch, the scientists have also found that a medication, now being tested in Alzheimer's patients, may fix the problem.

“Neurologists and neuroscientists have always tended to think that if the brain is abnormal at birth, nothing can be done to improve intellectual function, and that special education was virtually the only assistance available,” said senior investigator Roderick McInnes, a leading geneticist at the Hospital for Sick Children. “It is no longer a fantasy to think that drug treatment might, in the future, be available for such patients.”

It's estimated that roughly 10 per cent of the population suffers from a learning disability, although it is not known how many of those might carry a defective form of this protein, known as Neto1. Still, advocates for people with learning disabilities say the work is promising.

“It probably is the first indication that learning disabilities might be treatable [with medication],” said Barbara McElgunn, health policy adviser to the Learning Disabilities Association of Canada. “It sounds very positive and hopeful for kids with learning disabilities, even though, of course, this is in its early days.”

The work, published in the current issue of PLoS Biology, a peer-reviewed online scientific journal, does come with caveats. For one, the Toronto group conducted its studies with mice, and research is still under way to determine how faithfully the results will translate into humans.

As well, while the Alzheimer's drug in question has passed phase-one safety trials run by a U.S. biotech firm and has moved into larger phase-two trials to test its efficacy, it remains unknown when, or if, any researchers will try it in people with learning disabilities.

Dr. McInnes, who holds the Anne and Max Tanenbaum Chair in Molecular Medicine at the University of Toronto, said, “We're very concerned that every child and adult with a learning disability will want to take these drugs, when this is very early days [in the research].”

He said he would be particularly worried about trying such drugs on the developing brain of a child, since it could result in “disordered thinking or emotional disturbances, which can't be fully evaluated in an animal model.”

Still, the Toronto work is part of a growing body of evidence – most of it coming from animal studies – that, through the lifelong ability to make new brain cells and advances in genetics, it may be possible to reverse neuro-developmental disorders once thought beyond the reach of medicine.

Dr. McInnes, who specializes in genetic eye diseases, had been hunting genes involved in eye development in 2000 when he and his postdoctoral fellow David Ng came across the gene that makes Neto1. Eventually, research from his lab proved the protein to be very active in the brain – particularly in sending messages between cells in the hippocampus, the seahorse-shaped brain region heavily involved in memory and learning.

They discovered all sorts of species – from flies to people – carry versions of Neto1. “This suggests it has been strongly conserved [through evolution] and so it must be important,” Dr. McInnes explained.

To nail down precisely how Neto1 might affect behaviour, the researchers specially bred mice who were missing the gene that makes it. The “knock-out” mutants had no obvious physical or behavioural anomalies, but they did fare poorly on both electrophysiological measurements of brain activity and cognitive tests compared to normal, wild-type mice.

John Roder, at the Samuel Lunenfeld Research Institute at Mount Sinai Hospital found that mice missing Neto1 failed a water maze test in which they had to recall the location of a hidden safety platform. Normal mice swimming through the water maze were able to find the platform faster with each effort, but the Neto1 knock-out rodents got lost each time.

Michael Salter, head of the neuroscience and mental health program at Sick Kids and one of the research team leaders, found the knock-out mice were only able to generate electrical signals between brain cells at half the strength of normal mice.

The researchers conclude that mice missing the Neto1 gene have fewer so-called NMDA receptors on their brain cells. NMDA receptors, known to be crucial for forming memories and learning, are like windows into a brain cell that open and close, allowing electro-chemical signals to pass through.

They are different from AMPA receptors which are more involved in activities we do unconsciously, such as when “we talk, walk or breathe,” Dr. Salter said.

But AMPA receptors have to be activated and open first for an NMDA receptor to open. For this reason, Sinai's Dr. Roder wondered if new drugs known as ampakines might boost the learning abilities of the knock-out mice.

AMPA receptors usually fire open in flashes of a couple of milliseconds, but the drugs help them stay open longer and, in turn, researchers found this indirectly helped the fewer NMDA receptors in the mutant function better. With the drugs, the strength of their brain cell connections returned to normal and they performed cognitive tests as well as the wild mice. “The effects,” Dr. Salter said, “were almost immediate.”

“This is further evidence that as we come to know more about the molecular biology of the brain, the more hope there is that we can design therapies to correct cognitive disorders.”