Study of learning disabled mice shows balance in the brain is key

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A new study in the October 31st issue of *Cell*, a Cell Press journal, has revealed the molecular and cellular underpinnings of one of the most common, single gene causes for learning disability in humans. The findings made in learning disabled mice offer new insight into what happens in the brain when we learn and remember.

While most previous studies have focused on the role of brain cells that excite other brain cells in the process of learning, the current results suggest that inhibitory neurons and a careful balance between excitatory and inhibitory signals may be just as essential, according to the researchers. They liken the role of those inhibitory and excitatory signals in the brain to the role of red and green stoplights in directing traffic.

" The significance of these findings is two-fold," said Alcino Silva of the University of California, Los Angeles. "First, we have in great detail the exact mechanism for one of the most common single gene causes for learning disability known. It's also a beachhead in our understanding of the balance between excitation and inhibition critical for learning."

Learning disabilities are estimated to affect one in five people worldwide. "It's a huge problem and there is little known about their causes," Silva said.

To begin to chip away at those underlying causes for conditions that often have complex causes, Silva's team began a hunt several years ago to unravel the mechanisms responsible for a couple of single gene

disorders that lead to learning disability.

In the new study, they examined mice with learning disabilities resulting from a condition called neurofibromatosis type 1. The condition stems from a defect in the Nf1 gene encoding a protein called neurofibromin. Earlier studies showed that neurofibromin controls a "Ras/Erk" signal that is involved in long-term potentiation (LTP) and learning in mice. LTP is a process that strengthens the connections between neurons in the brain--the cellular basis for learning and memory.

Now, the researchers have found that the deficits in spatial learning experienced by mice with an abnormal version of the Nf1 gene stem from an increased release by inhibitory neurons of a chemical nerve messenger (or neurotransmitter) called GABA. GABA is the chief inhibitory neurotransmitter in the central nervous systems of mammals.

That rise in GABA leads to deficits in the plasticity of neurons required for learning and memory. Importantly, they also show that the learning deficits in the mice can be reversed with treatments that reign GABA levels back in. They also show that GABA levels normally swell when mice learn, suggesting that a balance of GABA is the key.

Silva's team notes another recent study implicating changes in GABA inhibition in the learning deficits exhibited by an animal model of Down's syndrome. Although learning disability—characterized by profound changes in one part of brain function—differs widely from mental retardation, that finding together with the new study suggest there may nevertheless be a common thread, Silva said.

Ultimately, these insights could lead to new ways to treat learning disabilities, although reaching that goal won't be a simple proposition.

" It won't be a single step from the mechanism to finding a drug," Silva

said. As with other complex disorders like cancer, he said, it will likely take years of exploration to turn scientific advances into medical applications. Nevertheless, "the more insight we have into the mechanisms responsible, the more likely it is that our treatment efforts will be effective. "

The new study is also representative of the exciting advances in the study of neuroscience more broadly.

" We are at the beginning of a wonderful journey into how the human mind works," Silva said. "We are developing a highly detailed view of what goes on in the brain when we learn and remember. There is nothing more inspiring; it's what makes us who we are."

Source: Cell Press