Research advances understanding of autism

November 7 2012

(Medical Xpress)—Research by scientists from the Centre for Brain Research at the University of Auckland has uncovered new information about the mechanisms underlying autism spectrum disorders (ASDs), to be published in the next issue of the prestigious *Journal of Neuroscience*.

Principal investigator, Dr Johanna Montgomery, says the findings are highly significant: "We're moving beyond simply what happens in ASDs and starting to understand how it happens."

The behavioural manifestations of ASDs are well documented and include impaired communication and socialisation, learning difficulties, and repetitive or stereotyped behaviours. These behavioural characteristics are in turn associated with a wide range of gene mutations. Many of these mutated genes are responsible for the production of specific proteins in the neurons of the brain.
Dr Montgomery and her team took a close look at parts of these neurons – the synapses, which are the structures that enable brain cells to communicate with each other. This cell to cell communication is vital for a healthy brain, and underlies how we learn, remember, move and sense.

In a complex cascade of chemical and electrical signalling, information is transmitted from one neuron to another at the synapses. This process is mediated by several families of protein, some of which form the bedrock of the synapse on the 'listening' side. Dr Montgomery's team chose to investigate one of these proteins, known as Shank3, because it has been identified as vital to the communication process between two

neurons, and because it is known to be mutated in ASDs.

Usually, the more two neurons "talk" to one another, the larger and more efficient the synapse becomes - in the same way that exercising your muscles helps make them bigger and stronger. However, Dr Montgomery and her team found that in neurons carrying ASD mutations in the Shank3 protein, not only was cell to cell communication weaker than usual, but that repetition did not strengthen or stabilise the synaptic connection.

Further investigation revealed that Shank3, when healthy, forms complexes with two other types of protein known as neurexin and neuroligin (also frequently mutated in ASDs). These complexes act to physically bridge the synaptic gap and can transmit information from the receiving or "listening" side of the synapse to the transmitting side. This "backward" flow of information completes a feedback loop between the two neurons which is likely to be responsible for the strengthening of the connection.

Dr Montgomery and her team theorise that the Shank3/neurexin/neuroligin complex is critical to the ability of neurons to effectively transfer information across the synapse so as to ensure the correct messages get through at the appropriate strength. This complex of proteins helps both sides of the synapse to co-ordinate to improve the efficacy of messaging, and this in turn increases the likelihood of successful transmission in future. Therefore, ASD mutations are preventing this efficient transfer of information between neurons, which likely underlies the behavioural and cognitive changes that occur in people with ASDs.

Intriguingly, the opposite occurs when neurons express multiple copies of the Shank3 gene, as is known to occur in Aspergers Syndrome. In this case the communication between neurons gets much stronger, increasing

their efficacy and providing a possible mechanism for the enhanced cognitive function that is associated with this syndrome.

"This is really exciting stuff", says Dr Montgomery. "Now we have identified the problems that these mutated proteins cause, we have a focus for developing treatments to offset the synaptic deficits that result. That's the next step."

Autism NZ Chief Executive Alison Molloy says, "It is great that this research is happening in New Zealand. For those on the autism spectrum, and their families, it means we can look forward to a time when the characteristics of Autism can be managed, making living and communicating considerably less stressful for them."

Provided by University of Auckland