Genetic discovery could increase understanding of ADHD

November 28 2013

(Medical Xpress)—Scientists at Trinity College Dublin have discovered that a mutation in a single gene involved in the functioning of the brain's nervous system can lead to hyperactivity symptoms that are characteristic of Attention-Deficit Hyperactivity Disorder (ADHD).

Getting the nervous system wired up properly is a big job. The brain contains billions of different types of nerve cells, which all have to be connected in a very precise fashion. This circuitry self-assembles as an embryo grows, based on a developmental programme involving the actions of thousands of different genes.

The scientists discovered that a mutation in a single mouse gene, 'Elfn1', can have a big effect. Their new findings give impetus to discover whether mutations in Elfn1 in humans can give rise to similar symptoms and whether they might play a part in some patients with epilepsy and ADHD. These two conditions occur together far more often than expected by chance.

In an article just published in the international journal, *PLOS ONE*, Associate Professor in Genetics at Trinity, Kevin Mitchell, and Research Technical Officer, Dr Jackie Dolan, investigated the importance of the function played by Elfn1 and the protein it produces when expressed. They did this by experimentally removing it from some mice and comparing the effects against those seen in mice with the normal gene.

Although overall brain anatomy and patterns of connectivity remained

normal, there was clear evidence of disturbance in brain function in individuals without Elfn1. Seizures occurred in some, and these became more common over time and were easily triggered by human interaction. Secondly, hyperactivity was observed, and this showed an unusual response to the stimulant, amphetamine.

Amphetamine normally causes hyperactivity in animals that have Elfn1 present, as it does in most humans. Here, it reduced the hyperactivity of the mice without the gene. This is similar to the situation in patients with ADHD, where amphetamine and related drugs have a paradoxical, calming effect. "These findings clearly show that removal of the Elfn1 gene affects brain circuits with multiple consequences for behaviour," said Dr Dolan.

The seizures likely relate to the function of Elfn1 in dampening the response of the nervous system to strong stimuli in key brain structures called the cortex and hippocampus. However, the development of ADHD-like hyperactivity focused on a different brain structure, known as the habenula. This structure is part of a system that integrates information from multiple regions of the brain and regulates the activity of nerve cells that produce mood-regulating chemicals such as dopamine and serotonin.

Professor Mitchell said: "We are at the beginning of this process of figuring out how this gene works and understanding the consequences when it is mutated. But, these animals provide a unique model to investigate how subtle changes in brain development can ultimately result in aberrant brain function".

Elfn1 was first discovered by Dr Dolan, Professor Mitchell and colleagues in 2007. The protein it produces when expressed allows communication from one nerve cell to another. In a study published in Science last year, Emily Sylwestrak and Anirvan Ghosh, of the

University of California, San Diego, showed that the Elfn1 protein determined what kind of connection was made onto those nerve cells.

More information: dx.plos.org/10.1371/journal.pone.008049

Provided by Trinity College Dublin