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High levels of a specific enzyme in fetuses linked to anxiety

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Mouse embryos with the human enzyme CYP2C19 in the brain develop a smaller hippocampus and anxiety-like behaviour as adults. The results of this new study, which is published in the journal *Molecular Psychiatry*, agree in principle with earlier genetic findings in humans, and can improve science's understanding of the genetic factors behind depression and anxiety disorders and contribute to the development of new anti-anxiety drugs.

Scientists have long been searching for the genetic reasons for the great differences in sensitivity that people show towards depression and anxiety disorders. Now, researchers at Karolinska Institutet have taken a closer look at the CYP2C19 enzyme, which plays an important part in the liver metabolism of psychoactive substances, such as antidepressants (e.g. SSRI drugs). CYP2C19 also operates on endogenous substances that affect the central nervous system. Interestingly, there is a genetic variation between humans, since mutations of the CYP2C19 gene leave people with no, low, normal or high levels of the enzyme.

The present study was conducted on transgenic mice, which had copies of the human CYP2C19 gene inserted into their DNA so that the researchers could examine if the expression of CYP2C19 affected brain function and behaviour. It was discovered that the enzyme was found in the brain of the mouse fetus, which developed differently to that of normal mice. The behaviour of the mice was then examined using a battery of four behavioural tests.

"We found behavioural changes indicating anxiety and a higher stress sensitivity," says research group leader Magnus Ingelman-Sundberg from the Department of Physiology and Pharmacology. "These findings can tell us more about the genetic determinants of anxiety and the transgenic mice can hopefully be used to develop new anxiolytic drugs."

The expression of CYP2C19 in the fetus produced adult mice that had a smaller, stress-hypersensitive hippocampus, an area of the brain essential to learning and memory, adaption and sensitivity to stress and emotional response. A dysfunctional hippocampus in humans is thought to play an important part in the development of both depression and anxiety disorders.

In an earlier study on twins conducted with epidemiologists from Karolinska Institutet, the group observed that individuals lacking the CYP2C19 enzyme display a less depressed base state, a finding that is supported in principle by the present study on mice. The researchers now plan to study what effects genetic variations of CYP2C19 have on the development of the human brain.

"If we can see similar changes in humans, it would improve our understanding of how changes in the developing fetal brain can increase the risk of depression and anxiety disorders later in life," says Anna Persson, in whose doctoral project the study is included.

More information: "Decreased hippocampal volume and increased anxiety in a transgenic mouse model expressing the human CYP2C19 gene " *Molecular Psychiatry*, online 23 July 2013

Provided by Karolinska Institutet