Enzyme research provides a new picture of depression

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Depression is the predominant mental disease and constitutes the most common cause of morbidity in developed countries. Now researchers at Karolinska Institutet have managed to find a connection between development of depression and the existence of an enzyme in the brain of the fetus.

Despite the fact that more than four percent of the world's population suffer from depression, and even though approximately 1,500 individuals commit suicide each year in Sweden, the understanding of the pathophysiology of depression remains unclear and only a few new discoveries of mechanisms behind it have been made in recent years. New approved pharmacological interventions are mainly absent, despite intensive research on the subject.

Researchers at Karolinska Institutet have characterized the role of the enzyme CYP2C19 in depression and functional and morphological changes in the brain. The enzyme is responsible for the metabolism of many neuroactive compounds, including antidepressants, and is located in the fetal brain and adult liver.

"We previously found that the CYP2C19 gene is expressed not only in the liver, but also in fetal brain. We described that transgenic mice that overexpress the human CYP2C19 in fetal life, in adult life have smaller hippocampus as well as an altered composition of nerve cells in the hippocampus and suffer from a higher level of anxiety- and depression-like behavior as compared to the wild type mice", says Magnus Ingelman-

Sundberg, who has been leader of the study together with Marin Jukic.

Altered structure and function of the hippocampus was the starting point

The hippocampus is a central part of the brain for control of emotions and stress, and the finding of altered structure and function of the hippocampus following overexpression of CYP2C19 was in the starting point for the new study. The researchers now have examined to what extent these findings in mice can be extrapolated to humans.

Such analysis was facilitated by the fact that four percent of the population lacks the CYP2C19 enzyme, while thirty percent have increased expression of the same enzyme. By analysis of MRI-based measurements of the hippocampal volume and by analyzing epidemiological statistics for suicide as well as by evaluating tests of depressive mood from thousands of people, researchers found that the absence of the enzyme was associated with a larger volume of the hippocampus.

"These persons showed a lesser degree of depressed mode. Conversely, we found that increased activity of CYP2C19 was associated with higher suicidal incidences in depressed patients", Marin Jukic says.

The results, presented in the international publication *Molecular Psychology*, show that the propensity for depression and hippocampal function in part is programmed in fetal life. Fetuses lacking CYP2C19 enzyme have a lower risk of depression and have larger hippocampi in adulthood.

"These findings form the basis for the identification of new biomarkers for depressive phenotypes and strengthen the fact that our CYP2C19

depression mice model can be used to understand new mechanisms for the basis of depression and for preclinical screening of new drug candidates for anti-depressant effect, in particular for those that affect the serotonergic neurotransmission", Magnus Ingelman-Sundberg concludes.

More information: M M Jukić et al, Elevated CYP2C19 expression is associated with depressive symptoms and hippocampal homeostasis impairment, *Molecular Psychiatry* (2016). DOI: 10.1038/mp.2016.204

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