Alterations in the neurosteroid biosynthetic pathways in the human prefrontal cortex in mood disorders: a postmortem study

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Research question and background

Altered concentrations of neurosteroids have been reported in the brain, the cerebral spinal fluid and plasma of patients with mood disorders. Neuroimaging studies have reported both functional and structural abnormalities in the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) in such disorders.

Methods and tissues used

In order to determine whether the endogenous production of neurosteroids is altered in the ACC and DLPFC of patients with major depressive disorder (MDD) or bipolar disorder (BPD), quantitative real-time PCR was used to detect mRNA expression levels of the key enzymes in the neurosteroid biosynthetic pathways in the postmortem grey matter from the dorsolateral prefrontal cortex and the anterior cingulate cortex from Netherlands Brain Bank. Immunohistochemistry of SULT2A and CYP17A1 in the postmortem ACC was also performed.

Results and conclusion

In the ACC of MDD patients, a significant decrease was observed in the mRNA level of cytochrome P450 17A1 (CYP17A1, synthesizing C19 ketosteroids) and a trend for an increase in that of hydroxysteroid sulfotransferase 2A (SULT2A, catalizing the sulphate conjugation of dehydroepiandrosterone (DHEA)), suggesting alterations in DHEA and its sulfate metabolite DHEA-S levels. Interestingly, we found a significant positive correlation between CYP17A1 and tyrosine-related kinase B (TrkB) full length isoform as well as a negative correlation between SULT2A and TrkB truncated isoform 1 in the ACC of MDD subgroup, indicating a close relationship between neurosteroid and neurotrophic factor pathways in depression. Furthermore, in the DLPFC, a significant increase in SULT2A and a trend for an increase in steroidogenic acute regulatory protein (StAR, facilitating the shuttle of cholesterol through the intermembrane space) mRNA levels were observed in the MDD and BPD subgroup, respectively. Higher mRNA level of 11β-hydroxysteroid dehydrogenase 1 (HSD11B1, reducing cortisol to the active hormone cortisol) showed a trend in the MDD and the pooled depressed patients, suggesting higher endogenous cortisol production. Immunohistochemistry showed expression of SULT2A and CYP17A1 in both neurons and glia-cells in human ACC. In conclusion, this study suggests the presence of a disturbance in the endogenous synthesis of DHEA, DHEAS and cortisol in mood disorders.

Publication

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