Brain-derived neurotrophic factor and glucocorticoids

Influence on serotonin 2A receptors and relation to major depression

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ABSTRACT

This study has been conduced at Copenhagen University Hospital, Rigshospitalet.

Major depression is associated with dysregulation of the hypothalamic pituitary adrenal (HPA) axis and serotonergic deficiency, not the least of the 5-HT_{2A} serotonin receptor. There is also accumulative evidence that brain-derived neurotrophic factor (BDNF) is involved in the pathophysiology of major depression. However, whether the changes in 5-HT_{2A} receptor levels are a direct effect of a hyperactive HPA axis the reduced BDNF levels seen in depression are unknown. Furthermore, if the altered BDNF level is a state or a trait marker of depression remains unclear.

The aims of this thesis were to study the effects of a dysregulatory HPA axis, namely high corticosterone levels and altered glucocorticoid receptor (GR) signalling, and the effects of BDNF and TrkB on 5-HT_{2A} receptor protein levels. For this we used organotypic hippocampal cultures and mice models under- and over-expressing GR (GR+/-, YGR), BDNF (BDNF+/-) and TrkB (TrkB TK). We also investigated whole blood BDNF levels as trait or state marker of depression in unaffected twins discordant for affective disorder.

The results show that increased GR signalling, by high corticosterone levels or high GR expression, leads to increased hippocampal 5-HT_{2A} receptor levels. The increase in 5-HT_{2A} receptor levels was counteracted by specific blockers for GR and mineralocorticoid receptor. Decreased GR signalling, by contrast, decreased 5-HT_{2A} receptor levels, indicating that a dysfunction in HPA axis regulates 5-HT_{2A} receptor levels. BDNF also had an effect on the 5-HT_{2A} receptor; high levels of BDNF decreased hippocampal 5-HT_{2A} receptor levels and BDNF+/- mice displayed increased hippocampal 5-HT_{2A} receptor levels. That the BDNF-induced alterations in 5-HT_{2A} receptor levels might be dependent on TrkB levels was shown by TrkB TK mice having increased frontal cortex and hippocampal 5-HT_{2A} receptor levels. Furthermore, organotypic cultures exposed to BDNF for seven days also had decreased TrkB levels.

The methodological investigations established that whole blood BDNF levels are measured with accuracy and high reproducibility and that female gender is associated with higher whole blood BDNF levels, adding important information on what considerations should be given when measuring blood BDNF. Furthermore, the combination of genetic risk, female gender and number of recent stressful life events decreased whole blood BDNF levels, indicating that low blood BDNF levels are a trait marker of depression.

In conclusion, this thesis sheds light on how BDNF and glucocorticoids regulate 5-HT_{2A} receptor levels, and it associates whole blood BDNF levels to in vivo brain 5-HT_{2A} receptor binding levels and to risk factors for development of depression.