**Abnormal retinoid and TrkB signaling in the prefrontal cortex in mood disorders**

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**Research question and background**

Multiple observations have shown that the prefrontal cortex is structurally and functionally altered in mood disorders. Retinoids as well as brain-derived neurotrophic factor and its receptor TrkB have been reported to be involved in depression.

**Methods and tissues used**

We performed quantitative real-time PCR to detect the mRNA expression levels of the major proteins involved in the retinoid signaling pathway, brain-derived neurotrophic factor and TrkB in the postmortem grey matter from the dorsolateral prefrontal cortex and the anterior cingulate cortex from Netherlands Brain Bank. The same genes were also detected in the frontal cortex of a chronic unpredictable mild stress rat model for depression. Immunohistochemistry for retinoic acid receptor-α and TrkB in human anterior cingulate cortex and in vitro studies were conducted to explore the relationship between the two receptors.

**Results and conclusion**

All the important elements in the retinoid signaling pathway were expressed in the postmortem dorsolateral prefrontal cortex/anterior cingulate cortex. Especially the mRNA levels of retinaldehyde dehydrogenase-1 and-3 -enzymes that synthesize retinoic acid-, retinoid x receptor α and β, and cytochrome P450 family 26C1 -an enzyme that metabolizes retinoic acid-, were significantly reduced in such areas of the elderly depressive patients that did not die from suicide. Furthermore, decreased mRNA levels of brain-derived neurotrophic factor and two TrkB isoforms were found. In the chronic unpredictable mild stress animal model, similar results were observed in the frontal cortex. Along with neurons immunopositive for both retinoic acid receptor-α and TrkB, a positive correlation between mRNA levels of the two receptors was found in the anterior cingulate cortex of control subjects but not of depressive subjects, suggesting that the close interaction between them was affected. In vitro studies showed that retinoic acid receptor-α was able to bind to and activate the TrkB promoter region via a putative retinoic acid response element within the TrkB promoter. In conclusion, the retinoid and BDNF-TrkB signaling in the prefrontal cortex are compromised in depression, and the transcriptional upregulation of TrkB by RARα provide a possible mechanism for their interaction. The retinoid signaling pathway which would rather activate TrkB expression will be an alternative novel target for BDNF-based antidepressant treatment.