

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

Qi^{1,2}, X.R., Zhao¹, J., Liu¹, J., Fang¹, H., Dick F. Swaab², D.F., Zhou^{1,*}, J.N.

¹ CAS Key Laboratory of Brain Function and Diseases, School of Life Sciences, University of Science and Technology of China, Hefei, Anhui, PR China;

² Netherlands Institute for Neuroscience, An Institute of the Royal Netherlands Academy of Arts and Sciences, Amsterdam, The Netherlands

* Corresponding author jnzhou@ustc.edu.cn

Xin-Rui Qi and Jun Zhao contributed equally to the work.

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 elderly depressed patients who did not die from suicide and their matched control subjects from the 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

Here we found that mRNA levels of key elements of retinoid signaling were significantly reduced in the postmortem dorsolateral prefrontal cortex/anterior cingulate cortex from the depressed patients obtained from the Netherlands Brain Bank. Decreased mRNA levels of BDNF and TrkB isoforms were also found in the same group of subjects. Similar alterations were observed in rats subjected to chronic unpredictable mild stress. Along with neurons immunopositive for both retinoic acid receptor- α (RAR 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 depressed patients. *In vitro* studies showed that RAR α was able to bind to and transactivate the TrkB promoter 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 mood disorders, and the transcriptional upregulation of TrkB by RAR α provide a possible mechanism for their interaction. The retinoid signaling pathway that may activate TrkB expression will be an alternative novel target for BDNF-based antidepressant treatment.