BDNF overexpression in hippocampal astrocytes elicits neurogenesis-dependent and -independent anxiolytic-like activity

G. Quesseveur 1, DJ. David 1, TH. Nguyen 1, M-C. Gaillard 2, P. Pla 3,4,5, G. Auregan 2, V. Nicolas 6, I. David 7, A. Dranovski 7, M. Wu 7, F. Saudou 3,4,5, R. Hen 7, N. Déglon 2, AM. Gardier 1, BP. Guiard 1
1 Université Paris-Sud, EA3544, Laboratoire Neuropharmacologie, Faculté de Pharmacie, F-92296 Châtenay-Malabry Cedex, France
2 CEA, Institute of Biomedical Imaging, Molecular Imaging Research Center, F-92265 Fontenay-aux-Roses, France.
3 Institut Curie, 4 CNRS UMR 3306, 5 INSERM U1005, Orsay F-91405, France.
6 Université Paris-Sud, Plateforme Imagerie Cellulaire, Faculté de Pharmacie, F-92296 Châtenay-Malabry Cedex, France.
7 Departments of Psychiatry and Neuroscience, Columbia University, New York, NY 10032, USA
New York State Psychiatric Institute, New York, NY 10032 USA.

The therapeutic activity of selective serotonin (5-HT) reuptake inhibitors (SSRIs) relies on long-term adaptation at pre- and post-synaptic levels. The sustained administration of SSRIs increases the serotonergic neurotransmission in various brain regions involved in mood. In the hippocampus, the enhancement of 5-HT availability increases Brain Derived Neurotrophic Factor (BDNF) synthesis and signaling, a major event in the stimulation of adult neurogenesis. In physiological conditions, BDNF would be expressed at functionally relevant levels in neurons. However, the recent observation that SSRIs upregulate BDNF mRNA in primary cultures of astrocytes strongly suggest that the therapeutic activity of antidepressant drugs might result from an increase in BDNF synthesis in this cell type. In this study, by overexpressing BDNF in astrocytes, we balanced the ratio between astrocytic and neuronal BDNF raising the possibility that such manipulation could positively reverberate on anxiolytic-/-antidepressant-like activities in treated mice. In this prospect, we used a novel BDNF-gene transfer strategy to shift the tropism of lentiviral vectors towards astrocytes coupled to a detargeting method with miRNA to eliminate residual BDNF expression in neurons.

Our results indicate that BDNF overexpression in hippocampal astrocytes produced anxiolytic-/-antidepressant-like activity in the novelty suppressed feeding in relation with the stimulation of hippocampal neurogenesis whereas it did not potentiate the effects of the SSRI fluoxetine on these parameters. Moreover, overexpressing BDNF revealed the anxiolytic-like activity of fluoxetine in the elevated plus maze while attenuating 5-HT neurotransmission in the hippocampus.

These results emphasize an original role of hippocampal astrocytes in the synthesis of BDNF, which can act through neurogenesis-dependent and -independent mechanisms to regulate different facets of anxiolytic-/-antidepressant-like responses.

We are currently investigating the impact of such a BDNF overexpression in hippocampal astrocytes on anxiolytic-/-antidepressant-like responses in a mouse model of depression based on chronic administration of corticosterone in the drinking water.

Together, our results illustrate the concept of the tripartite synapse in which astrocytes are essential for serotonergic neuronal activity and their reactive response may contribute to the regulation of mood and anxiolytic-/-antidepressant-like activities.