- GENDER SPECIFIC IMPROVEMENT OF SYNAPTIC FUNCTION BY ACTIVATION OF RXR NUCLEAR RECEPTOR IS MEDIATED BY PPARALPHA

N. Pierrot [1] *L. Ris* [2] *I.C. Stancu* [3] *A. Doshina* [4] *F. Ribeiro* [5] *D. Tyteca* [6] *E. Baugé* [7] *F. Lalloyer* [8] *L. Malong* [9] *O. Schakman* [10] *K. Leroy* [11] *P. Kienlen-Campard* [12] *P. Gailly* [13] *J.P. Brion* [14] *I. Dewachter* [15] *B. Staels* [16] *J.N. Octave* [17]

[1]*Université catolique de Louvain, Institute of Neuroscience, Brussels, Belgium*
[2]*University of Mons, Laboratory of Neuroscience- Health Institute, Mons, Belgium*
[3]*Hasselt University, Biomedical Research Institute, Hasselt, Belgium*
[4]*Université catolique de Louvain, Institute of Neuroscience, Brussels, Belgium*
[5]*Université catolique de Louvain, Institute of Neuroscience, Brussels, Belgium*
[6]*Université catolique de Louvain, de Duve Institute, Brussels, Belgium*
[7]*Université de Lille, EGID- Inserm- CHU Lille- Institut Pasteur de Lille, Lille, France*
[8]*Université de Lille, EGID- Inserm- CHU Lille- Institut Pasteur de Lille, Lille, France*
[9]*Université catolique de Louvain, Institute of Neuroscience, Brussels, Belgium*
[10]*Université catolique de Louvain, Institute of Neuroscience, Brussels, Belgium*
[11]*Université libre de Bruxelles, Laboratory of Histology and Neuropathology, Brussels, Belgium*
[12]*Université catolique de Louvain, Institute of Neuroscience, Brussels, Belgium*
[13]*Université catolique de Louvain, Institute of Neuroscience, Brussels, Belgium*
[14]*Université libre de Bruxelles, Laboratory of Histology and Neuropathology, Brussels, Belgium*
[15]*Hasselt University, Biomedical Research Institute, Hasselt, Belgium*
[16]*Université de Lille, EGID- Inserm- CHU Lille- Institut Pasteur de Lille, Lille, France*
[17]*Université catolique de Louvain, Institute of Neuroscience, Brussels, Belgium*

Abstract body

Objectives: Nuclear receptors (NRs) are ligand-dependent transcription factors regulating gene expression. Among NRs, peroxisome proliferator-activated receptor (PPAR) forms permissive obligate heterodimers with retinoid X receptor (RXR). NRs activation with specific agonists leads to brain function improvement in mouse models of neurodegenerative diseases. However, the link between NRs activation and cognitive improvement is missing. Here, we analyzed how RXR activation improves synaptic plasticity and neuronal function and identified PPARalpha as a crucial player.

Methods: LTP was measured in the hippocampus of PPARalpha null mice and in a mouse model of Alzheimer's disease (5xFAD) treated with the RXR agonist bexarotene or with pemafibrate, a selective PPARα activator. PPARalpha expression was acutely decreased in the hippocampus of 5xFAD mice by using an AAV-ShPpara. Glutamatergic responses were measured by calcium imaging in rat primary cortical cultures. NMDA and AMPA receptors subunits expression were assessed by RT-qPCR and western blotting.

Results: Upon RXR activation, the PPARalpha-dependent upregulation of the GluA1 subunit-containing AMPA receptors mediates LTP improvement in 5xFAD mice and AMPA-responses in cortical cells. PPARalpha deficiency severely impaired LTP and GluA1 expression in male but not in female PPARalpha null mice. PPARalpha-knockdown in the hippocampus of 5xFAD mice compromises the beneficial effects of RXR activation on synaptic plasticity only in males. PPARalpha activation with pemafibrate improves synaptic plasticity in male 5xFAD mice, but not in females.

Conclusions: PPARalpha plays a central role in hippocampal synaptic plasticity by driving the expression of GluA1 subunit of AMPARs in a gender specific manner.