EVENT ABSTRACT

Improvement of synaptic plasticity by pharmacological activation of RXR nuclear receptors is PPARα dependent.

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Retinoid X receptors (RXRs) are receptors belonging to the nuclear receptor superfamily of ligand-dependent transcription factors, containing different members including the Peroxisome Proliferator-Activated Receptors (PPARs). These receptors regulate the transcription of target genes through their binding with sequence-specific elements located in gene promoters. Activation of PPARs, which form obligatory heterodimers with RXRs, stimulates the transcription of specific target genes encoding proteins involved in numerous biological processes such as reproduction, development, adipogenesis, energy balance, lipid and glucose biosynthesis and inflammation. Interestingly, a potential involvement of RXRs in neuronal activity was recently proposed since activation of RXRs with specific ligands improves behavior and cognition in various mouse models of neurodegenerative diseases. However, the mechanisms involved are not fully understood. We have analyzed how bexarotene-mediated activation of RXRs nuclear receptors could modulate synaptic plasticity, an activity-dependent change in synaptic strength in the hippocampus considered as a prominent mechanism underlying learning and memory formation in the mammalian brain. By measuring long-term potentiation (LTP) at hippocampal CA3-CA1 synapses, we observed that activation of RXRs improved hippocampal synaptic plasticity in a transgenic mouse model with cognitive deficits by specifically increasing the expression of the GluA1 subunit of the AMPA receptors. This upregulation of GluA1 expression together with improvement of hippocampal synaptic plasticity induced by activation of RXRs were completely abolished in the absence of PPARalpha. These results indicate that improvement of synaptic functions induced by activation of RXRs is PPARalpha dependent.

Keywords: Nuclear receptors (LXR, PPAR, RXR), synaptic plasticity, LTP (Long Term Potentiation), glutamate receptors, Hippocampus

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