Regulation of nicotinic receptors by PPARα: therapeutic perspectives

M. Melis[1], A.L. Muntoni[2], S. Aroni[1], M. De Felice[1], M.G. De Montis[3], M. Pistis[1,2]

[1]Dept. of Biomedical Sciences, Division of Neuroscience and Clinical Pharmacology, University of Cagliari, Italy
[2]Neuroscience Institute, National Research Council of Italy, Section of Cagliari, Cagliari, Italy
[3]Dept. of Molecular and Developmental Medicine, University of Siena, 53100 Siena, Italy

Nicotine's strong addicting properties result from its ability to enhance dopamine transmission and to change synaptic plasticity. Preclinical studies have revealed that drugs targeting the peroxisome proliferator-activated-receptor-α (PPARα) show promise for the treatment of nicotine addiction. These drugs include synthetic agonists, such as the clinically available hypolipidemic fibrates, and drugs that increase the levels of fatty acid ethanolamides (FAEs), endogenous PPARα agonists. Among these lipid neuromodulators, the best studied are oleoylethanolamide (OEA) and palmitoylethanolamide (PEA), endocannabinoid-like molecules structurally similar to anandamide but devoid of activity at cannabinoid receptors. We have shown specific interaction between PPARα and nicotine, and the molecular mechanisms whereby these intracellular receptors regulate nicotinic acetylcholine receptor (nAChR) functions in neurons. Hence, FAEs modulate nAChRs and appear to counterbalance the excessive cholinergic drive, thus providing a fine modulation of dopamine pathways. Consequently, PPARα activation may be suited to attenuate disruption of dynamic balance of dopamine-acetylcholine systems, and prove beneficial in those disorders associated with dysfunction of such interplay, namely nicotine addiction, depressive states and stress. The aim of the present study was to investigate on the effects of PPARα activation in an animal model of depression derived from the learned helplessness paradigm. Rats were fed a diet containing either a PPARα synthetic agonist already marketed and clinically available (fenofibrate) or its vehicle. Electrophysiological, biochemical and behavioral results show an anti-depressant-like effect of the fenofibrate diet in this model of stress-induced depression. Our results extend the field range of FAE roles to other neural circuit functions, and broaden the already wide capability of PPARα to regulate not only nutrient metabolism and energy homeostasis, but also dopamine systems. Consequently, the mutual influence between PPARα and nAChRs might bear relevance for diverse neuropsychiatric disorders.