Uncovering the role of the lipid receptor PPAR-alpha on higher brain functions

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Peroxisome proliferator-activated receptors (PPARs) are targets of drugs in use and in development to treat disease, and they modulate metabolic and inflammatory pathways by responding to nutritional signals through ligand activation of transcription. Although PPAR-alpha is an ubiquitously expressed receptor, its contribution on the regulation of brain functions is largely unexplored. We will show evidence that loss of function of PPAR-alpha gene in mice determines a neurodevelopmental phenotype with behavioral alterations reminiscent of the human diseases and that pharmacological and pharmacogenetic manipulation of PPAR-alpha phenocopies the behavioral profile of mutant null mice. We will also show the contribution of brain PPAR-alpha receptor in preclinical model of brain diseases and how its modulation by high affinity ligands may represent an effective strategy for treating behavioral defects associated with neurodevelopmental disorders.