Regulatory Role of PPARs in Neuroinflammation and Their Underlying Mechanisms for Neuroprotective Effects

E.Esposito[1], I. Paterniti[1], R. Crupi[1], M. Cordaro[1], S. Cuzzocrea[1]

[1]Dept of Biological and Environmental Sciences, University of Messina, Italy

In recent years, beneficial effects of various ligands of three peroxisome-proliferator-activated receptor (PPAR) isoforms (α, β, γ) have been reported in neurodegenerative diseases through delaying the onset and progression of diseases, reducing lesion size and improving functional recovery. PPAR activity is modulated by post-translational modifications and cofactors, towards which they show differential affinity. The three PPARs mutually interact, being integrated in a complex system, leading to the concept of a "PPAR triad". Nevertheless, the isotypes also show distinct actions on cellular physiology and partially different tissue, ligand and target gene specificities. The neuroprotective role of PPARs is suggested to be closely associated with the inflammation control and regenerative function. The anti-inflammatory properties on peripheral immune cells (macrophages and lymphocytes) as well as direct effects on neural cells including cerebral vascular endothelial cells, neurons, and glia were demonstrated. Their activities on glial cells, with a particular emphasis on microglial cells as major macrophage population of the brain parenchyma and main actors in brain inflammation, were observed. In the brain, while the functions of PPARγ and its ligands are being thoroughly investigated, the actual and potential roles of PPARα and β/δ have to be clarified. PPARα appears especially intriguing, since it is selectively expressed in certain brain areas and neuronal/glial populations, and modulates antioxidant responses, neurotransmission, neuroinflammation, neurogenesis, and glial cell proliferation/differentiation. This receptor and its endogenous ligands, including palmitoylethanolamide, are involved in physiological and pathological responses, such as memory consolidation, and modulation of pain perception. The protective role of PPARα agonists in neurodegenerative diseases and in neuropsychiatric disorders makes manipulation of this pathway highly attractive as therapeutic strategy for neuropathological conditions.