Role of PPAR-α and its pharmacological modulation in experimental models of Parkinson's disease

C. Avagliano[1], C. De Caro[1], R. Russo[1], C. Cristiano[1], G. La Rana[1], G. Mattace Raso[1], R. Meli[1], A. Calignano[1]

[1]Dept. of Pharmacy, University of Naples Federico II, Via D. Montesano 49, 80131 Naples, Italy

Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting 1% of the population over 60 years of age and its incidence increases with age[1]. PD is an irreversible and progressive neurodegenerative disorder that impairs movement control. It is characterized by motor symptoms such as rigidity, resting tremor, bradykinesia and postural abnormalities[2].

Preclinical and epidemiological data suggest that chronic neuroinflammation may be a slow and steady reason for neuronal dysfunction during the asymptomatic stage of PD[3]. Several evidences support the hypothesis that glial reactive and inflammatory processes participate in the cascade of events leading to neuronal degeneration[4].

Palmitoylethanolamide (PEA), a fatty acid ethanolamide, has shown anti-inflammatory[5], analgesic[6,7] and neuroprotective properties[8,9]. To date it is widely recognized that the long-lasting pharmacological effects of PEA are mediated by activation of peroxisome proliferator activated receptor (PPAR) α[10-12]. Recently, D'Agostino et al.[13] have shown that activation of PPARα by PEA reduces learning and memory deficits caused by central injection of amyloid β 25-35, a model of Alzheimer's disease. Moreover, Esposito et al.[14] have demonstrated that peripheral administration of PEA reduced 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced glial activation, restored tyrosine hydroxylase expression in the *substantia nigra*, effects that are blunted in PPARα knock-out mice. This model is the most widely used even if MPTP toxin provokes a nigro-striatal damage that can be extremely fast and aggressive, in contrast to the assumed human disease development. The 6-hydroxydopamine (6-OHDA)-induced PD may be a valid alternative model, since it leads to a progressive loss of nigral-striatal neurons. Only recently Alvarez-Fischer et al.[15] have characterized this model in mice. Considering the involvement of PPARα in neurodegenerative diseases, its role and pharmacological modulation in this model has been investigated.

In vitro, pre-treatment with PPARα agonists PEA (0.1-3μM) and GW7647 (0.1-1μM) in SHSY5Y cells differentiated towards a dopaminergic phenotype reduced the expression of pro-inflammatory enzymes, such as inducible nitric oxide syntase (iNOS) and ciclooxigenase-2 (COX-2), and of pro-apoptotic protein Bax induced by 6-OHDA (100 μM) stimulation. At the same time, PEA was able to increase anti-apoptotic protein Bcl-2 and PPARα expression.

In vivo, striatal injection of 6-OHDA (4μg/2μL) induced motor impairment. PEA (3-10-30 mg/kg) or GW7647 (5 mg/kg) were administrated for 14 days subcutaneously. On days 3, 7 and 14 apomorphine and rotarod tests were carried out. Results showed that on day 3 PEA ameliorated motor dysfunction only at medium and higher doses. PEA efficacy was significant on days 7 and 14 following 6-OHDA injection at all doses used. This results was also obtained using GW7647, a synthetic PPARα agonist.

Taken together, these data strongly suggest that PEA, through PPARα receptor activation, may be beneficial for the treatment of neurodegenerative diseases like PD.

[1]de Lau LM et al. (2006). *Lancet Neurol. 5(6):525-35.*
[2]Lee CS et al. (1994). *Brain. 117(Pt3):501-7.*
[3]Lee JK et al. (2009). *J Neuroimmune Pharmacol. 4(4):419-29.*
[4]Banati RB et al. *(*1998). *Mov Disord. 13(2):221-7.*
[5]Mazzari S et al.(1996). *Eur J Pharmacol. 300(3):227-36.*
[6]Calignano A et al. (1998). *Nature. 394(6690):277-81.*
[7]Calignano A et al.(2001).*Eur J Pharmacol. 419(2-3):191-8.*
[8]Koch M et al. (2011). *Neurotox Res. 19(2):330-40.*
[9]Scuderi C et al. (2011). *J Cell Mol Med. 15(12):2664-74.*
[10]Lo Verme et al. (2005). *Mol Pharmacol. 67(1):15-9.*
[11]D'Agostino G et al. (2007). *J Pharmacol Exp Ther. 322(3):1137-43.*
[12]D'Agostino G et al. (2009). *Eur J Pharmacol. 613(1-3):54-9.*
[13]D'Agostino G et al. (2012). *Neuropsychopharmacology.* 37(7):1784-92.
[14]Esposito E et al. (2012). *PLoS ONE.* 7(8):e41880.
[15]Alvarez-Fischer D et al. (2008). *Exp Neurol.* 210(1):182-93.