PPARα as Potential Therapeutic Target for Neurodegenerative Diseases

Letizia Giampietro* and Rosa Amoroso

Department of Pharmacy, university G.d’Annunzio, Italy

Submission: September 22, 2017; Published: October 16, 2017

*Corresponding author: Letizia Giampietro, Department of Pharmacy, University of Chieti, via dei Chieti, Italy, Tel: +39-0871-3554696; Fax: +39-0871-3554911; Email: lgiampietro@unich.it

Abstract

Peroxisome proliferator activated receptor α (PPARα) is ligand-activated transcriptional factor receptor belonging to nuclear receptors family. It plays a key role in lipid metabolism and glucose homeostasis and it is important in the prevention and treatment of metabolic diseases. PPARα has also a protective effects against brain cell death attributed to its anti-inflammatory and antioxidant properties. In the present work, we discuss the PPAR involvement in neurodegenerative pathologies and its potential for therapeutic target for these diseases.

Keywords: Alzheimers disease; Parkinsons disease; Neuroprotection

Abbreviations: PPARs: Peroxisome Proliferator Activated Receptors; RXR: Retinoid X-Receptor; SARs: Structure Activity Relationships; PEA: Palmitoyl Ethanol Amide; LPS: Lipo Poly Saccharide

Mini Review

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptors super family and are ligand-activated transcription factors. They are involved in the regulation of metabolic pathologies such as cardiovascular disease, obesity, lipid disorder, hypertension and diabetes [1]. PPARs exist as three subtypes commonly designated as PPARα, PPARγ, and PPARβ/δ. All PPAR isoforms, once within the nucleus, heterodimerize with retinoid X-receptor (RXR) and bind to specific DNA-response elements in the promoter of target genes. When a ligand binds to PPARs, there is a conformational change in the receptor that causes the removal of co-repressors and the recruitment of co-activators; this causes chromatin remodeling which allows the initiation of DNA transcription [2].

PPARα, PPARγ, and PPARβ/δ are expressed in different tissues and with distinct binding ligands, co-activators or co-repressors. PPARα, mainly expressed in tissues involved in lipid oxidation such as kidney, liver, skeletal and cardiac muscle, plays an important role in fatty acid oxidation and lipoprotein metabolism; PPARγ is expressed predominantly in adipose tissue and vascular smooth muscles; PPAR β/δ is expressed broadly and particularly in tissues associate with fatty acid metabolism, but also in the small intestine, liver, colon and keratinocytes [3]. A lot of studies showed that PPARs are expressed also in brain and in particular in neurons and glia [4]; for this reason, the potential use of PPAR agonists as neuroprotective agents in neurodegenerative disorders has been suggested. Neurodegenerative diseases are incurable pathologies with a progressive degeneration of neurons associated with motor and cognitive damage. These conditions are characterized by oxidative stress, mitochondrial and transcriptional dysregulation and apoptosis [5]. Because oxidative stress and neuro inflammation are involved in cell death, these dysfunctions are the key factors for the development of the most common neurodegenerative disorders such as Parkinson’s disease, Alzheimer’s disease and amyotrophic lateral sclerosis.

Therefore, novel therapeutic approaches are useful to obtain a reduction of the symptoms and slow progression of the pathology. In this contest, the role of PPARα is emerging as a promising pharmacological target for the treatment of neurodegenerative diseases. Fibrates are PPARα agonists widely studied especially for the treatment of hyperlipidemias (Figure 1). Some of these, such as gemfibrozil, ciprofibrate, WY-14643 or fenofibrate, activate selectively only PPARα, others do not have an isoform selectivity. For example, GFT505 is a dual PPARα/δ agonist and bezafibrate, that activates all three isoforms, is a PAN-agonist [6].
In the last years, the development of new fibrates that activate PPAR has been an important objective to better understand structure activity relationships (SARs) for obtaining new drugs with a better pharmacological profile [7,8]. In this context, the neuroprotective effects of PPARα agonists have been studied; some researchers attributed this effect largely to the PPARα antioxidant and anti-inflammatory properties but also to the positive effects in lipid metabolism and glucose homeostasis [9].

About anti-inflammatory properties of PPARα, it was showed especially in astrocytes and microglia [10,11]. In fact, several authors demonstrated that the use of PPARα agonists, such as ciprofibrate, fenofibrate, gemfibrozil and WY-14643, causes a reduction of NO production especially in mouse microglia stimulated by lipopolysaccharide (LPS). Furthermore, it has been demonstrated that the treatment with palmitolethanolamid (PEA) causes a reduction of oxidative stress in astrocytes mediated by PPARα [12]. PPARα is also expressed in brain and the anti-inflammatory role was evidenced by reduction of LPS-induced TNFα, IL-1β, IL-6 and COX-2 [13].

The anti-inflammatory effect mediated by PPARα has also been identified in reactive astrocytes. It has been shown that PPARα attenuates the inflammation in reactive astrocytes by decreasing NO and pro-inflammatory cytokines. Additional, PPARα has an important role in other glial cells such as microglia and ependymal cells in response to injury [14]. PPARα has an antioxidant effect associated with a reduction of cerebral oxidative stress depending on the increase in activity antioxidant enzymes, such as Cu/Zn superoxide dismutase and glutathione peroxidase. This activity causes a decrease in lipid peroxidation and ischemia-induced reactive oxygen species production [9].

The anti-inflammatory and antioxidant properties of PPARα explain the neuroprotective effects especially in Parkinson’s disease and Alzheimer’s disease [15]. For these reasons, PPARα could be a therapeutic target for Parkinson’s disease; in fact, it has been established that there is a neuroprotective effect in the brain of animals treated with fenofibrate by decreasing inflammation. Uppalapati et al. showed that fenofibric acid, the active metabolite of fenofibrate (Figure 2), was present in the brain of animals treated with fenofibrate, suggesting that this compound was metabolized and that crossed the blood-brain barrier in vivo [16].

It was discovered that fenofibrate prevent the dopaminergic neurons loss in the substantia nigra, and it attenuates the loss of tyrosine hydroxylase immune reactivity in the striatum [17]. Many studies have shown that PPARα could have a therapeutic
effect also in Alzheimer’s disease, even if this conclusion remains controversial. Some researchers demonstrated that PPARα has a protective effect against beta-amyloid-induced neurodegeneration [18], but others found that fenofibrate increases beta-amyloid production in vitro; perhaps this effect of fenofibrate is not connected with PPARα activation [19]. Further, PPARα activation induces vascular protection through an improvement of cerebral artery sensitivity [20].

To conclude, neurodegenerative diseases induce progressive loss of cognitive functions and current drugs only furnish temporary symptomatic alleviation without blocking disease progression. During last years, growing interest was directed towards PPARα that have the capability to positively regulate the genes expression with the aim to modulate several molecular pathways responsible of neurodegenerative diseases. In particular, different researchers have shown the positive involvement of PPARα in neurodegenerative disease.

The useful effects are principally due to PPARα anti-inflammatory and antioxidant properties but also to the capacity to restore the vascular and endothelial integrity. The potential use of PPARα agonists as neuroprotective agents against neurodegenerative disorders is an important start point to find new drugs that could cure definitively these pathologies. Though more laboratory and clinical studies are needed to understand all mechanisms involved in the neuroprotective actions of the PPARα agonists, these receptor is an effective target for neurodegenerative disorders.

References

1. Grygiel GB (2014) Peroxisome proliferator-activated receptors and their ligands: nutritional and clinical implications a review. Nutr J 13: 17. 
2. Tyagi S, Gupta P, Singh SA, Kaushal C, Sharma S (2011) The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases. J Adv Pharm Technol Res 2(4): 236-240.
3. Monsalve FA, Pyarasani RD, Delgado LF, Moore-Carrasco R (2013) Peroxisome Proliferator-Activated Receptor Targets for the Treatment of Metabolic Diseases. Mediators Inflamm 2013, Article ID 549627, p. 18.
4. Warden A, Truitt J, Merriman M, Ponomareva O, Jameson K, et al. (2016) Localization of PPARα isoforms in the adult mouse and human brain. Sci Rep 6, No. 27618.
5. Tiwari SK, Chaturvedi RK (2014) Peptide therapeutics in neurodegenerative disorders. Curr Med Chem 21(23): 2610-2631.
6. Pawlak M, Lefebvre P, Staels B (2015) Molecular mechanism of PPARα action and its impact on lipid metabolism, inflammation and fibrosis in non-alcoholic fatty liver disease. J Hepatol 62(3): 720-733.
7. Giampietro L, D’Angelo A, Giancristofaro A, Ammazzalorso A, De Filippis B, et al (2012) Synthesis and structure-activity relationships of fibrate-based analogues inside PPARα. Bioorg Med Chem Lett 22(24): 7662-7666.
8. Giampietro L, Ammazzalorso A, Bruno I, Carradori S, De Filippis B, et al. (2016) Synthesis of Naphthyl, Quinolin and Anthracenyl Analogues of Clofibrate Acid as PPARα Agonists. Chem Biol Drug Des 87(3): 467-471.
9. Deplanque D, Gele P, Petraitou O, Six I, Furman C, et al. (2003) Peroxisome proliferator-activated receptor-alpha activation as a mechanism of preventive neuroprotection induced by chronic fenofibrate treatment. J Neurosci 23(15): 6264-6271.
10. Drew PD, Xu J, Storer PD, Chavis JA, Rakee MK (2006) Peroxisome proliferator-activated receptor agonist regulation of gial activation: relevance to CNS inflammatory disorders. Neurochem Int 49(2): 183-189.
11. Xu J, Storer PD, Chavis JA, Rakee MK, Drew PD (2005) Agonists for the peroxisome proliferator-activated receptor-alpha and the retinoid X receptor inhibit inflammatory responses of microglia. J Neurosci Res 81(3): 403-411.
12. Raso GM, Esposito E, Vitiello S, Lacono A, Santoro A, et al. (2011) Palmitoylethanolamide stimulation induces allopregnanolone synthesis in C6 cells and primary astrocytes: involvement of peroxisome proliferator-activated receptor-α. J Neuroendocrinol 23(7): 591-600.
13. Wang G, Namura S (2011) Effects of chronic systemic treatment with peroxisome proliferator-activated receptor-alpha activators on neuroinflammation induced by intracerebral injection of lipopolysaccharide in adult mice. Neurosci Res 70(2): 230-237.
14. Iglesias I, Morales L, Barretomol GE (2017) Metabolic and Inflammatory Adaptation of Reactive Astrocytes: Role of PPARs. Neurobiol 54(4): 2518-2538.
15. Moran EP, Ma J (2015) Therapeutic Effects of PPARα on Neuronal Death and Microvascular Impairment. PPAR Res 2015, Article ID 595426, p. 10.
16. Upalapati D, Das NR, Gangwal RP, Damle MV, Sangamwar AT, et al. (2014) Neuroprotective Potential of Peroxisome Proliferator Activated Receptor-α Agonist in Cognitive Impairment in Parkinson’s Disease: Behavioral, Biochemical, and PBPK Profile. PPAR Res 2014, Article ID 753587, p. 9.
17. Kreisler A, Gelea P, WiartC JF, Lhermitte M, Desteeb A, et al. (2007) Lipid-lowering drugs in the MPTP mouse model of Parkinson’s disease: Fenofibrate has a neuroprotective effect, whereas bezafibrate and HMG-CoA reductase inhibitors do not. Brain Res 1135: 77-84.
18. Santos MJ, Quintanilla RA, Toro A, Grandy R, Dinamarca MC, et al. NC (2005) Peroxisomal Proliferation Protects from β-Amyloid neurodegeneration. J Biol Chem 280(49): 41057-41068.
19. Kukar T, Murphy MP, Eriksen JL, Sagi SA, Weggen S, et al. (2005) Diverse compounds mimic Alzheimer disease-causing mutations by augmenting Abeta42 production. Nat Med 11(5): 545-550.
20. Inoue H, Jiang XF, Katayama T, Osada S, Umesono K, et al. (2003) Brain protection by resveratrol and fenofibrate against stroke requires peroxisome proliferator-activated receptor alpha in mice. Neurosci Lett 352(3): 203-206.

How to cite this article: Letizia Giampietro, Rosa Amoroso. PPARα as Potential Therapeutic Target for Neurodegenerative Disease. Nov Appro Drug Des Dev. 2017, 2(5) : 555599. DOI: 10.19080/NAPDD.2017.02.555599.
How to cite this article: Letizia Giampietro, Rosa Amoroso. PPARα as Potential Therapeutic Target for Neurodegenerative Disease. Nov Appro Drug Des Dev. 2017; 2(5) : 555599. DOI: 10.19080/NAPDD.2017.02.555599.