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The role of synthetic ligand of PPARα in regulation of transcription of genes related to mitochondria biogenesis and dynamic in an animal model of Alzheimer's disease

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Abstract

Peroxisome proliferator-activated receptors α (PPARα) are members of the nuclear receptors family and a very potent transcription factor engaged in the regulation of lipid and energy metabolism. Recent data suggest that PPARα could play an important role in the pathomechanism of Alzheimer's disease (AD) and other neuropsychiatric disorders.
This study focused on the effect of a synthetic ligand of PPARα, GW7647 on the transcription of genes encoding proteins of mitochondria biogenesis and dynamics in the brain of AD mice.
The experiments were carried out using 12-month-old female FVB-Tg mice with the V717I mutation of amyloid precursor protein (APP^+) and mice without the transgene ($APP^–$). Moreover, APP^+ and $APP^–$ mice were treated for 14 days with GW7647 administered subcutaneously with a dose 5 mg/kg b.w. Brain cortex was used and qRT-PCR was performed.
Our data indicated that GW7647 upregulated the expression of genes encoding proteins of mitochondria biogenesis in ADTg mice. GW7647 enhanced the level of mRNA of Ppargc1, Nrf2 and Tfam in APP^+ as compared to APP – mice treated with GW7647. Moreover, our studies demonstrated that GW7647 had no effect on genes that regulate mitochondria fission and fusion of ADTg mice as correlated to mice without the transgene. Our results indicate that the ligand of PPARα, GW7647 may exert a promising neuroprotective effect through the regulation of transcription of genes coding proteins of mitochondria biogenesis. These data suggest that activation of PPARα at an early stage of AD could be a helpful strategy for slowing the progression of neurodegeneration.

Key words: *Alzheimer's disease, Nrf2, PPARα, mitochondria biogenesis, GW7647, Tfam, neuroprotection.*

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that causes the most severe dementia. During the last 30 years, the amyloid β (Aβ) hypothesis dominated in the research of AD. Despite many years of studies, the aetiology and pathomechanism of the sporadic form of AD are not elucidated and the therapeutic strategy is unsuccessful. It is widely accepted that sporadic, late-onset AD (LOAD) which attacks more than 90% of AD patients is a multifactorial disease in which environmental and genetic factors play an important role. For the past decade, extensive research has been dedicated to studying the genetics of AD [1,13]. The familial form of early-onset AD (EOAD) is primarily associated with mutations in genes encoding amyloid precursor protein (APP) or secretases responsible for APP metabolism. Recently genome-wide association studies (GWAS) have discovered many genetic loci connected with a risk of LOAD. Among them is the gene

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encoding peroxisome proliferator-activated receptor α (PPARα) involved in fatty acids and cholesterol metabolism [4,26]. PPARα belongs to the nuclear, non-steroid PPARs family together with receptor PPARβ/δ and receptor PPARγ, which are encoded by the corresponding genes: *NR1C1*, *NR1C2*, *NR1C3* [8,32,37]. During the last decades, much data demonstrated the role of PPARs in mood alterations, depression and in other neuropsychiatric disorders and suggested their engagement in AD pathology [9,29,37]. PPARα and other members of this receptor family dimerize with retinoid X receptor (RXR). These dimers bind to PPAR-responsive regulatory elements (PPRE) and are engaged in the regulation of transcription of genes. However, a coactivator of PPARs, PGC-1α, is necessary for the activation of RXR:PPAR but at first the transcriptional corepressor must be removed as described previously [11,20].

The role of PPARα in the physiology and pathology of central nervous system (CNS) and the association between fatty acids and other lipids metabolism and AD was recently widely demonstrated and suggested [14,31,37]. It was reported that regulation of PPARα, which is involved in lipid, glucose, energy metabolism and inflammation, improves also synaptic plasticity in the AD mouse model [3,28,29]. During the last decade, the significant role of mitochondria alterations in AD pathogenesis was postulated [5,18,22,33,34,36]. The study of Zolezzi *et al.* [40] underlined that PPARα and PPARγ agonists (ciglitazone and WY14.643) through modulation of mitochondria fission-fusion may exert a neuroprotective effect against oxidative stress and could efficiently slow the progression of AD. Previous studies have also indicated that ligands targeting PPARα, as well as PPARγ or PPARβ/δ receptors simultaneously, could potentially offer enhanced therapeutic efficacy in the treatment of type 2 diabetes with obesity and neurodegenerative/neuropsychiatric disorders [6,10,21,38]. Additionally, it has been demonstrated that PPARγ agonists and PGC-1α activators can improve cognitive deficits, alleviate oxidative stress, and reduce inflammation in animal models of Parkinson's disease [2].

Our previous study has shown significant changes in the transcription of genes related to mitochondria and anti-oxidative defence in an experimental model of AD [7,37]. Furthermore, last data of Qu *et al.* [27] indicate a neuroprotective effect of a PPARα ligand, GW7647 in an ADTg mouse model. These data suggest that activation of PPARα ameliorated iron homeostasis alteration in the brain of APP/PS1 mice and suppressed inflammation processes and lipid oxidation by activation of transcription of glutathione peroxidase 4 [27].

In our study, we investigated the impact of GW7647, a synthetic ligand of PPARα, on the mRNA expression of genes encoding proteins involved in mitochondria biogenesis and dynamics. The study was conducted in the brain cortex of 12-month-old ADTg mice (APP^+) and we compared the results to age-matched control mice without the transgene (APP^-).

Material and methods

Animal model of Alzheimer's disease

In our study, the female FVB-Tg (Thy1; APP LD2/B6) 12-month-old mice were used. These mice overexpressed human AβPP with the "London" V717I mutation under the control of a fragment of Thy1 promoter with specificity towards brain and spinal cord neurons, described as AD Tg or APP^+. Mice without the transgene (APP^-) were used as controls. The mice in this study were extensively characterized to encompass a wide range of electrophysiological, behavioural, and biochemical features associated with AD [19,35]. The behavioural abnormalities begin at 8 weeks of age [19]. Then these mice reservedly developed agitation and cognitive impairment. These all described modifications occurred simultaneously with alterations of neurotransmitters reactivity (3-4 months of age) and then electrophysiological alterations (between 5 and 7 months) [19]. Mice used in our experiments were bred under specific pathogen-free (SPF) conditions in controlled temperature and humidity conditions and a 12-h light/dark cycle in the Animal House of the Mossakowski Medical Research Institute PAS, Warsaw, Poland. Female mice, 12 months old, were administered subcutaneously with a dose of 5 mg/kg body weight with the PPARα agonist GW7647, a cell permeable compound (2-(4-(2-(1-Cyclohexanebutyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid). The GW7647 was dissolved in DMSO (3%). APP^- and APP^- + GW7647 mice treated with DMSO were used as appropriate controls. The treatment with GW7647 was conducted for a duration of 14 days, after which the mice were euthanized by decapitation. Soon after mice were decapitated, cerebral cortices were quickly isolated on ice and frozen in liquid nitrogen. The protocol was approved by the Warsaw Local Ethics Committee for Animal Experimentation and performed in accordance with the guidelines of the Polish National Ethics Committee and EU Directive 2010/63/EU. All applicable international, national and/or institutional guidelines for the care and use of animals were followed. Stringent measures were taken to minimize any potential suffering and to limit the number of animals utilized in the experiments. The research was conducted in compliance with protocols adhering to good laboratory practice and quality assurance standards.

Nrf1 (Mm00447996_m1)	Mfn1(Mm00612599_m1)
Nrf2 (Mm00477784_m1)	Mfn2 (Mm00500120_m1)
Tfam (Mm00447485_m1)	Opa1(Mm01349707 g1)
Ppara (Mm00440939_m1)	Fis1 (Mm00481580_m1)
Ppargc1a (Mm01208835_m1)	Dnm1 (Mm01342903_m1)
Gapdh (Mm99999915_g1)	Actb (Mm4352341E)

Analysis of gene expression

RNA was isolated using the TRI reagent (Sigma-Aldrich/Merck) as described in the manufacturer's protocols and purified by using DNase I according to the manufacturer's protocols (Sigma-Aldrich/Merck). The concentration and purity of obtained RNA were determined spectrophotometrically (A260/A280). Reverse transcription was performed by using the High-capacity cDNA Reverse Transcription Kit according to the manufacturer's instructions (Applied Biosystems). The level of mRNA for studied genes was analysed by using TaqMan Gene Expression Assays (Applied Biosystems) as described also by us previously [7].

Quantitative polymerase chain reaction (PCR) was performed on an Applied Biosystems 7500 Real-Time PCR System using TaqMan Gene Expression Master Mix according to the manufacturer's instructions. The results were normalized against Gapdh and β-actin – Actb and demonstrated as a percentage of the corresponding control. The relative levels of mRNA were calculated using the $^{\Delta\Delta}$Ct Method.

Statistical analysis

The results were expressed as a mean value ± SEM from 3-5 animals in each group. Differences between the means were analysed using Student *t*-test. Statistical analyses were performed using Graph Pad Prism version 8.0 (Graph Pad Software, San Diego, CA, USA).

Results

In this study we analysed the effect of the novel synthetic ligand of PPARα receptor, GW7647 on

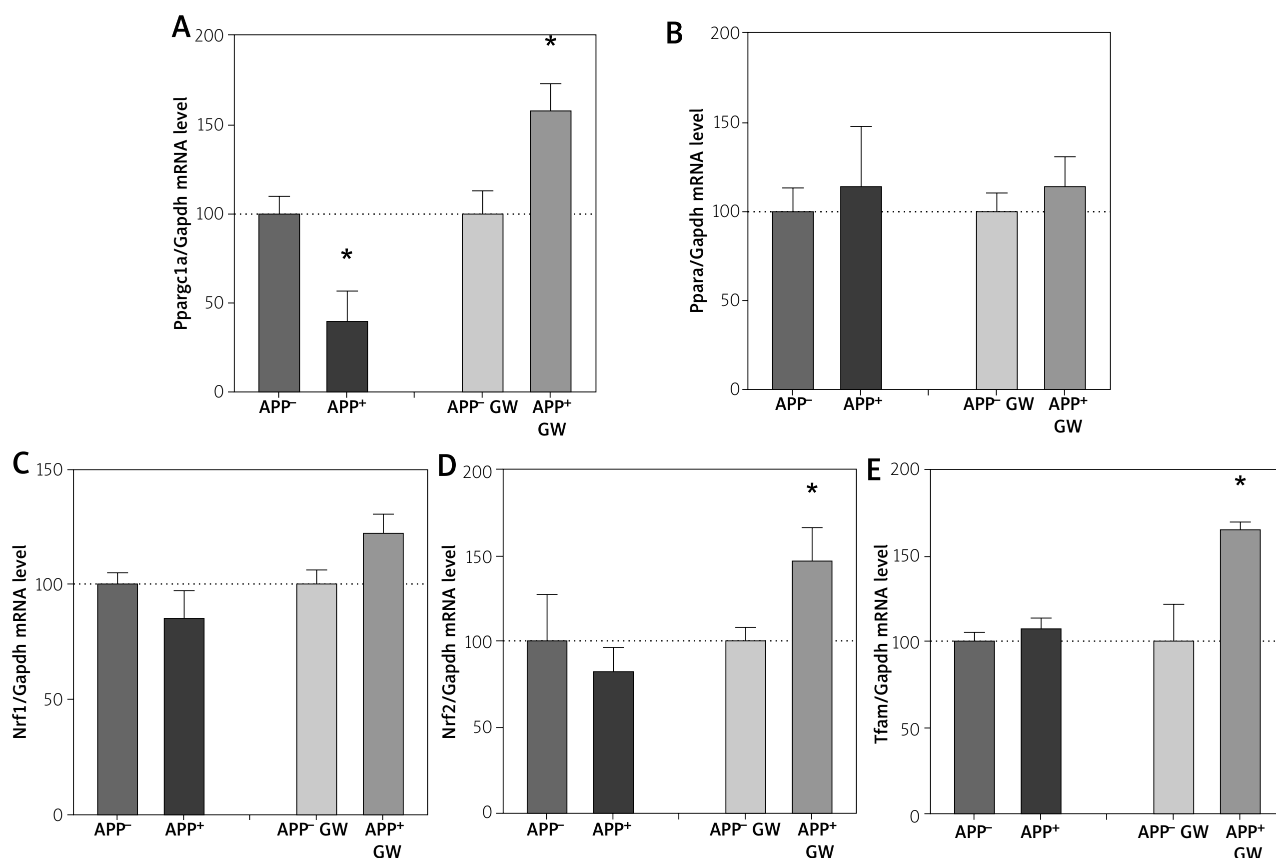

Fig. 1. The effect of GW7647, the synthetic ligand of PPARα on the mRNA level of genes engaged in mitochondria biogenesis. The mRNA levels of the following genes: **A**) Ppargc1a, **B**) Ppara, **C**) Nrf1, **D**) Nrf2, **E**) Tfam. The results were normalized to *Gapdh* gene expression and demonstrated as a percent of appropriate controls. Statistical analysis was performed using Student *t*-test, $^{*}p < 0.05$, as described in Material and methods.

the transcription of genes related to mitochondria in the brain cortex of AD Tg mice.

Our findings revealed that GW7647, a novel ligand of the PPARα receptor, had a positive impact on the mRNA levels of genes involved in mitochondrial biogenesis. However, it did not show any significant influence on the expression of genes associated with mitochondrial dynamics. Analysis of our data showed that the mRNA level of Ppargc1 is significantly lower in ADTg mice vs. APP⁻ (Fig. 1A). The synthetic ligand enhanced the mRNA level of the gene coding PGC1α (the crucial protein of mitochondrial biogenesis) in APP⁺ as compared to APP⁻ mice (Fig. 1A). However, it is demonstrated that the mRNA level of the Ppara in APP⁺ is similar as in APP⁻ brain cortex of mice treated with GW7647 (Fig. 1B). Moreover, GW7647 remained without effect on the mRNA level of Nrf1 (Fig. 1C) although it significantly activates transcription of Nrf2 (Fig. 1D) and Tfam (Fig. 1E) in the brain cortex of ADTg mice (APP⁺) comparing to APP⁻ treated with GW7647. The following experiments focused on the effect of GW7647 on the transcription of genes coding proteins involved in mitochondrial fusion and fission. In these cases, the effect of GW7647 was compared also to the corresponding control. It was found that GW7647 did not affect the expression of genes coding proteins engaged in fusion such as MFN1, MNF2 and OPA1 (Fig. 2A-C). Moreover, in the case of gene expression coding FIS1 and DRP1 the mRNA levels of these genes were similar in investigated groups (Fig. 2D, E).

Discussion

Our data indicated the beneficial effect of PPARα synthetic agonist, GW7647 in ADTg mice. Previous studies have reported that the activation of PPAR, a nuclear receptor and transcription factor and potent regulator of lipids and energy metabolism, exerts a beneficial effect on synaptic plasticity in animal models of AD [29]. Furthermore, it has been demonstrated that the regulation of PPARα by APP influences the pharmacological modulation of synaptic activity [28]. Synaptic dysfunction, synaptic degeneration and synaptosis were indicated as

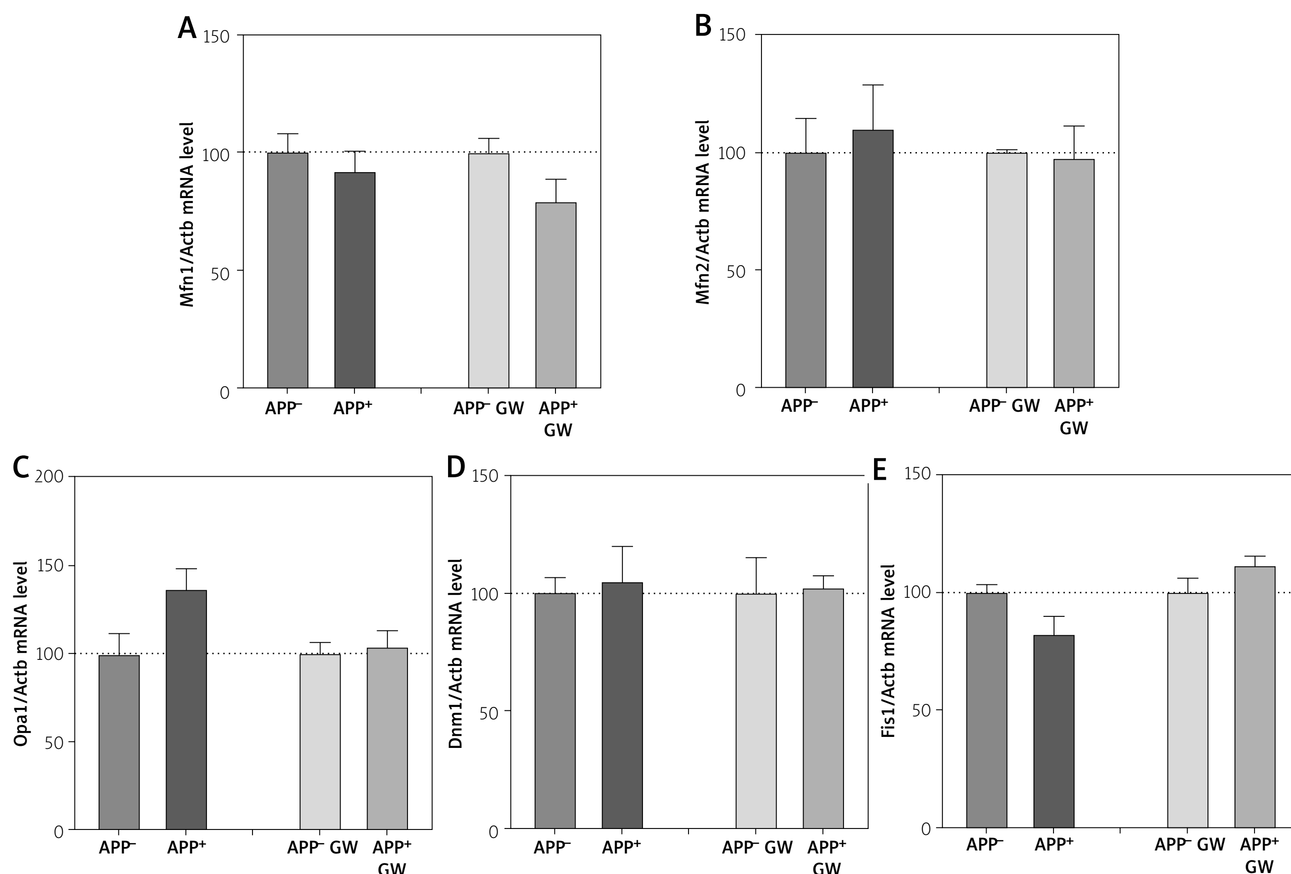

Fig. 2. The effect of GW7647, the synthetic ligand of PPARα on the mRNA level of genes engaged in mitochondria dynamic. The mRNA levels of the following genes: **A**) Mnf1, **B**) Mnf2, **C**) Opa1, **D**) Dnm1, **E**) Fis1. The results were normalized to *Actb* gene expression and demonstrated as a percent of appropriate controls. Statistical analysis was performed using Student *t*-test, as described in Material and methods.

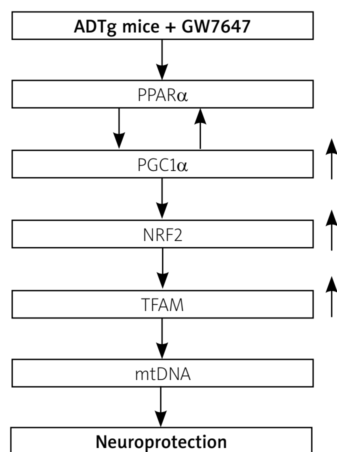

Fig. 3. Schematic representation of the effect of GW7647 on the brain cortex of AD Tg mice. Arrows ↑ indicate an increase in mRNA expression encoding proteins related to mitochondria biogenesis.

very early events of AD pathology [24,39]. These alterations, closely associated with mitochondrial function, may occur prior to the onset of typical neuropathological changes and could potentially contribute to cognitive impairment. Moreover, subsequent studies have provided further evidence that dysregulation of lipid metabolism and impaired PPARα function may have a significant impact on the progression of AD [16].

Our data revealed the favourable impact of the PPARα synthetic agonist GW7647 on mitochondrial biogenesis. GW7647 by activating the transcription of genes related to mitochondria may exert a neuroprotective effect. Our results demonstrated elevated mRNA levels of Ppargc1a, Nrf2, and Tfam genes in GW7647-treated AD Tg mice compared to control animals without the transgene (APP^{-} + GW7647). These results imply a potentially important role of the nuclear receptor PPARα in AD, as well as the promising neuroprotective effect of its novel synthetic agonist [17,30]. Through the PPARα/PGC-1α pathway, GW7647 has the potential to influence transcription processes and multiple molecular pathways. PGC-1α has been identified as a crucial regulator of several genes involved in oxidative stress, mitochondrial function, neuroinflammation, apoptosis, autophagy, and various other processes related to brain function under both physiological and pathological conditions. PGC-1α belongs to the family of transcriptional coactivators together with PGC-1β and PGC1-related coactivator (PRC). It regulates the transcription of numerous genes, including those encoding nuclear receptors such as all members of the PPARs family and estrogen-related receptors (ERR). It also modulates other transcription factors involved in mitochondrial biogenesis, such as NRF2 and TFAM. The synthetic agonist GW7647 significantly enhances the expression of Ppargc1a and then the transcription of the gene coding NRF2 and TFAM. NRF2 (nuclear factor, erythroid2-related factor 2) is one of the most important molecular regulators engaged in antioxidant defence, calcium and iron homeostasis. NRF2 plays an important role in several signalling pathways in inflammation processes, immunity, and autophagy and in mitochondria [12,23,25]. It was discovered that in mitochondria biogenesis, NRF2 interacts with TFAM in the regulation of mtDNA. Our study indicated that the expression of the gene coding TFAM is activated by GW7647 in the AD Tg brain cortex. TFAM is a mitochondrial DNA binding protein that determines mitochondrial genome maintenance (mtDNA) and which response may have an impact on mitochondria homeostasis [15]. In summary, our findings indicate that GW7647, by activating the transcription of genes involved in mitochondria biogenesis, may have a beneficial effect in an experimental model of AD (Fig. 3). Further studies are currently underway to gain a better understanding of the mechanism underlying GW7647's action in the brains of AD animal models.

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Disclosure

The authors report no conflict of interest.

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