Review Article
http://dx.doi.org/10.5115/acb.2016.49.1.1
pISSN 2093-3665 eISSN 2093-3673
Anatomy & Cell Biology acb

The association between PGC-1α and Alzheimer's disease

Gary Sweeney[1], Juhyun Song[2]
[1]Department of Biology, York University, Toronto, ON, Canada, [2]Department of Anatomy, Yonsei University College of Medicine, Seoul, Korea

Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder and its reported pathophysiological features in the brain include the deposition of amyloid beta peptide, chronic inflammation, and cognitive impairment. The incidence of AD is increasing worldwide and researchers have studied various aspects of AD pathophysiology in order to improve our understanding of the disease. Thus far, the onset mechanisms and means of preventing AD are completely unknown. Peroxisome proliferator-activated receptor-γ coactivator (PGC-1α) is a protein related to various cellular mechanisms that lead to the alteration of downstream gene regulation. It has been reported that PGC-1α could protect cells against oxidative stress and reduce mitochondrial dysfunction. Moreover, it has been demonstrated to have a regulatory role in inflammatory signaling and insulin sensitivity related to cognitive function. Here, we present further evidence of the involvement of PGC-1α in AD pathogenesis. Clarifying the relationship between PGC-1α and AD pathology might highlight PGC-1α as a possible target for therapeutic intervention in AD.

Key words: Peroxisome proliferator-activated receptor-γ coactivator (PGC-1α), Alzheimer's disease, Oxidative stress, Cognitive dysfunction, Insulin resistance

Received November 27, 2015; Accepted November 27, 2015

Introduction

The incidence of Alzheimer's disease (AD) is expected to increase dramatically as the world population [1-3]. The peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1 (PGC-1) family of coactivators comprises proteins that mediate responses to environmental stress [4, 5]. Several studies have reported that the level of PGC-1α evidently decreases in the brains of AD patients [6, 7]. In the AD brain, oxidative stress has been regarded as the core problem, leading to other AD pathologies [8, 9]. PGC-1α controls the expression of genes related to the generation of reactive oxygen species (ROS) and prevents oxidative stress by reducing the production of ROS [10]. In AD, impaired mitochondrial biogenesis in neuronal cells causes synapse dysfunction [11] and cellular damage [12] and contributes to cognitive decline [13, 14]. Additionally, insulin resistance of the AD brain aggravates the rapid progress of AD pathophysiology [15, 16]. Much research has demonstrated that PGC-1α improves mitochondrial function [17] and insulin sensitivity [18, 19]. In this review, we summarize recent research on the association between PGC-1α and AD and provide new insights about PGC-1α's role in the mechanism of AD pathology.

Corresponding author:
Juhyun Song
Department of Anatomy, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-1659, Fax: +82-2-365-0700, E-mail: alj1008@nate.com

PGC-1α

PGC-1α is highly responsive to numerous forms of environmental stress, including temperature and nutritional status [4, 5]. PGC-1α also regulates mitochondrial biogenesis in

response to diverse environmental stimuli [20]. PGC-1α forms heteromeric complexes with a variety of transcription factors including nuclear respiratory factor (NRF)-1, NRF-2, PPARα, PPARδ, PPARγ, and estrogen-related receptor α [21]. These PGC-1α transcriptional activator complexes could displace repressor proteins, such as histone deacetylase and its small heterodimer partner and thereby induce gene activation [22]. PGC-1α is commonly expressed in tissues with a high energy demand, including brown adipose tissue, skeletal muscle, and the brain [23, 24]. In the brain, impairment of the activity of PGC-1α triggers the degeneration of neurons by inducing mitochondrial dysfunction [17, 25]. PGC-1α-knockout mice display behavioral abnormalities such as frequent limb clasping [26]. Moreover, interaction between PGC-1α and signal pathways, such as that involving Cre-binding protein [27], cGMP-dependent pathways [28], and p38–mitogen activated protein kinase pathways [29] plays a critical role in the response to oxidative stress in AD [30]. PGC-1α plays a central role by influencing the genes that regulate detoxification of ROS [31]. According to clinical research, PGC-1α may be key to maintaining brain function in AD, since its levels decreased in AD patients in comparison to that in normal subjects [6, 7]. Based on this evidence, focusing on PGC-1α's role may lead to a better understanding of the mechanisms of AD pathology.

PGC-1α and Oxidative Stress in AD

Salient features of AD include molecular aberrations such as oxidative stress [8], inflammation [32]. Of these features, oxidative stress appears to be the trigger of free radical-induced cellular damage, DNA oxidation, and aberration in DNA repair [33]. In AD, the primary brain areas where neuronal damage due to oxidative stress occurs are the hippocampus and the cortex [34]. Compared to control cases, AD patients exhibit some aspects of elevated oxidative stress including the production of proteins such as cytochrome c oxidase [34], increased lipid peroxidation [35]. Therefore, the markers of oxidative damage founded in neurons in AD are the hallmark of its pathologies and an indication of degeneration in the AD brain [36]. In AD, increased levels of ROS, including hydrogen peroxide and hydroxyl radicals, impede various cellular functions by degrading proteins [37]. PGC-1α plays a central role in the regulation of ROS detoxifying enzymes, such as superoxide dismutase 1 and 2, catalase and glutathione peroxidase-1 [17]. It has been reported that PGC-1α modulates the expression of uncoupling protein 2 [38] and uncoupling protein 3, which are both direct regulators of ROS formation [39]. Additionally, PGC-1α controls the level of sirtuin1 [40] and sirtuin3 [41] which reduce the generation of ROS [10]. Some research demonstrates that elevated PGC-1α levels protect neural cells from apoptosis due to oxidative stress through the induction of antioxidant genes [17]. One study showed that increased PGC-1α activity could ameliorate neuronal loss and improve neurological symptoms [42]. Taken together, the elevated activity of PGC-1α could protect neuronal cells from damage by reducing the oxidative stress in AD and subsequently alleviate several pathophysiological features of this disorder.

PGC-1α, Mitochondrial Dysfunction, and Cognitive Dysfunction in AD

In AD, neurodegeneration and synaptic degradation are caused by impaired mitochondrial biogenesis [12]. Mitochondria play a crucial role in the process of neuronal apoptosis in the AD brain [43] and are the pivotal organelle for the generation of ROS [44]. Mitochondrial dysfunction has been considered as one of the central cytopathologies of AD [45] and is known to contribute to cognitive decline through various pathways. In AD neurons, mitochondria are sites of amyloid beta accumulation, and these amyloid beta accumulations in mitochondria finally result in the death of the cell [46]. Impaired mitochondrial function leads to a severe loss in energy metabolism and ATP generation [47], and also to a deficiency in the scavenging of free radicals which triggers excessive oxidative damage in the AD brain [48, 49]. An association between mitochondrial dysfunction and memory dysfunction has been demonstrated in several human and animal studies [50, 51]. In AD, mitochondrial dysfunction, including an increase in oxidative stress [52] and defective mitochondrial biogenesis [53] occurs in neurodegeneration [54]. In the aged brain, PGC-1α regulates the expression of sirtuin 3, which is a factor related to the aging process [53]. It has been observed that in the brains of patients with neurodegenerative diseases, low levels of PGC-1α lead to mitochondrial dysfunction and oxidative stress [55, 56]. PGC-1α regulates mitochondrial density in neurons [57] and PGC-1α–knockout mice showed an increased sensitivity to the degeneration of dopaminergic and glutamatergic neurons in the brain [17]. Moreover, another study demonstrated that the reduction of mitochondrial gene expression in PGC-1α–

knockout mice finally leads to neuronal dysfunction [26]. PGC-1α stimulates expression of GA-binding protein α, a known regulator of cognitive function, in a cell culture study [58]. Given that PGC-1α plays a crucial role in neuronal function [59] and regulates mitochondrial function, PGC-1α could ameliorate mitochondrial dysfunction and improve cognitive function in AD.

PGC-1α, Insulin Resistance, and Cognitive Dysfunction in AD

Insulin modulates neurotransmitter release [60], neuronal cell survival [61], and synaptic plasticity [62] and it improves cognition and memory function in the brain[63, 64]. Insulin resistance in the brain is defined as decreased uptake of insulin into the brain, leading to the dysregulation of amyloid beta level and inflammation [65]. In AD, insulin resistance in the brain is an important issue since it contributes to the progress of the disease [66]. Recent research demonstrated that patients with AD have defective insulin signaling [67] in the brain, as well as reduced insulin receptor sensitivity [68]. The *PGC-1a* gene is expressed at high levels in obese animals [69] and diabetic mice [70] compared to that in normal animals. PGC-1α is a transcriptional coactivator involved in the mitochondrial biogenic response that counteracts insulin resistance [71]. In a study conducted with PGC-1α–knockout mice, the mice exhibited insulin sensitivity by comparison with normal controls in spite of a high fat diet [26]. Moreover, PGC-1α improves glucose tolerance, insulin sensitivity and gluconeogenesis [18]. Considering that PGC-1α alleviates insulin resistance [72], it could reduce cognitive impairment related to insulin resistance in the AD brain.

Conclusion

In this review, we summarized recent evidence indicating that PGC-1α can contribute to the improvement of AD pathophysiology. Here, we highlight four points: (1) PGC-1α could protect against oxidative stress in AD and thereby prevent neuronal cell damage, (2) PGC-1α could improve mitochondrial dysfunction in AD, (3) PGC-1α could reduce insulin resistance in AD, and (4) finally, PGC-1α could ameliorate cognitive impairment caused by AD. Thus, this review raises the possibility that PGC-1α could be used as a therapeutic agent in the treatment of AD.

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