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Poly(ADP-ribose) Polymerase-1 in Amyloid Beta Toxicity and Alzheimer's Disease

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Abstract Poly(ADP-ribose) polymerase-1 (PARP-1) is a key enzyme responsible for the maintenance of genome stability, transcriptional regulation, and long-term potentiation in neurons. However, the excessive activation of PARP-1 under pathological conditions may lead to an accumulation of poly(ADP-ribose) (PAR), a novel signaling molecule that induces programmed cell death, or to NAD depletion that induces energy crisis and necrotic cell death. PARP-1 is thought to be primarily a nuclear enzyme, but some data indicate that it can also be localized to the mitochondria where it is responsible for posttranslational modification of electron transport chain complexes and alteration of mitochondria function. The enhancement of PARP-1 activity and the accumulation of PAR were demonstrated in the brain of patients with Alzheimer's disease (AD), particularly in neurons of the frontal and temporal lobes and in skin fibroblasts and lymphoblasts. Moreover, it has been reported that PARP-1 gene polymorphisms are highly associated with the development of AD. The activation of PARP-1 by oxidative stress seems to be an early and important event in the pathogenesis of AD. It is now widely accepted that the overproduction and oligomerization of amyloid β (Aβ) are responsible for the activation of a free radical cascade and oxidative stress in AD. Interestingly, the activity of PARP-1 is enhanced in AD and is also increased by Aβ peptides. The activation of PARP-1 by Aβ can lead to the PAR-mediated release of apoptosis-inducing factor from the mitochondria and its translocation to the nucleus, which leads to death of some populations of cells. A role of PARP-1 in the regulation of Aβ precursor protein metabolism processing and Aβ liberation has not been described previously. The study presented in this review indicated the relationship between PARP-1 activation, alteration of mitochondria function, and Aβ toxicity. The presented data should stimulate further studies on the role of PARP-1 in AD pathogenesis and thereby engage a new perspective regarding AD therapy.

Keywords Poly(ADP-ribose) polymerase · PARP · Amyloid beta · Aβ · Mitochondria · AD

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Introduction

The neuropathology of Alzheimer's disease (AD) is well characterized by the deposition of amyloid β (Aβ) peptides in the form of amyloid plaques and by the hyperphosphorylation and aggregation of tau protein in the form of neurofibrillary tangles [1]. The amyloid plaques also exist in physiologically aged brains and contain Aβ and many other compounds, including α-synuclein (ASN) and its neurotoxic fragment, non-amyloid β component of the Alzheimer's disease amyloid (NAC). The NAC peptide is located in the central portion of senile plaque cores and is thought to be

involved in Aβ aggregation [2]. A growing body of evidence supports the hypothesis that amyloidogenic peptides (Aβ, ASN, and NAC) in the form of a β-pleated sheet structure or an oligomer are responsible for the oxidative stress, synaptic and mitochondrial dysfunction, and cellular degeneration observed in AD [3–6]. Interestingly, many cells survive in AD; in the AD model, it is suggested that activation of aerobic glycolysis (Warburg effect) is responsible for this cell survival [7]. However, the mechanisms underlying these processes are not fully understood. One of the most important molecular events that occurs in response to oxidative/metabolic stress is modification of nuclear proteins by poly(ADP-ribosylation), which has been associated with cell fate decisions.

Our previous data, as well as studies published by other researchers, indicated the significant role of the nuclear enzyme poly(ADP-ribose) polymerase-1 (PARP-1, EC 2.4.2.30) in regulating cellular survival and death. PARP-1 is the most important member of its family, which consists of 18 distinct proteins [8, 9]. In the brain, PARP-1 is responsible for more than 90 % of the poly(ADP-ribosylation) [8, 10]. In response to single- or double-strand DNA breaks (or other activators), PARP-1 catalyzes the transfer of ADP-ribose moieties from NAD to a target protein, which can be PARP itself, histones, or many other proteins, e.g., p53, topoizomerase I/II, GAPDH, and many transcription factors [11–15]. Poly(ADP-ribosylation) plays diverse roles in many fundamental molecular and cellular processes, such as the detection of DNA damage, regulation of transcription, chromatin modification, and regulation of mitotic apparatus function. Under mild oxidative stress, both DNA-binding enzymes PARP-1 and PARP-2 are involved in base excision repair. PARP-1 and PARP-2 knockout mice are early embryonic lethal (gastrulation stage). These results demonstrate that both enzymes are essential during early embryogenesis and play important roles in maintaining genomic stability [16]. Other data have demonstrated that inactivation of PARP-1 leads to an acceleration of brain aging, reduction of life span, and increased carcinogenesis [17]. Under massive oxidative stress, PARP-1 overactivation leads to necrotic and apoptotic cell death not only due to energy depletion but also through the action of the PAR polymer and apoptosis-inducing factor (AIF) [18–20]. In addition to DNA break-dependent activation, PARP-1 can also be the nuclear target of many signaling pathways and has been shown to play an important role in memory formation [21–26]. PARP-1 activity may be regulated by posttranslational modifications, such as auto-poly(ADP-ribosylation), phosphorylation, acetylation, and sumoylation [27–29]. It is important to note that some studies have provided evidence for the presence of PARP-1 in mitochondria [30–32], while in other studies, mitochondrial PARP-1 was not detected [33–35].

PARP-1 in Alzheimer's Disease

Love et al. [36] were the first to report evidence of PARP-1 activation in the brains of patients with AD. Immunostaining analysis for PARP-1 and its product, PAR, indicated much higher levels of PAR in AD brains (frontal and temporal lobes) compared to controls. Double immunolabeling for PAR and markers of neuronal, astrocytic and microglial differentiation (MAP2, GFAP, and CD68, respectively) demonstrated a significantly higher level of immunoreactivity in neurons than in glia cells. PAR was mainly accumulated in small pyramidal neurons (in cortical laminae 3 and 5), was found in a few astrocytes, and was not detected in microglia. This study, carried out on autopsy material from 20 patients and age-matched controls, directly indicated the role of PARP-1 in AD. The other study carried out by Cecchi et al. [37], which used skin fibroblasts and lymphoblasts taken from patients with familial and sporadic AD and from age-matched controls, found accumulation of PAR with no changes in the PARP-1 content. Collectively, the results of these studies indicate that oxidative stress and activation of PARP-1 are important early events in the pathogenesis of AD. Genetic analysis of association of the PARP-1 gene with the risk of AD confirmed the significance of PARP-1 in this disease. Infante et al. [38] demonstrated that interactions between *PARP1* gene polymorphism and *IL1A* gene polymorphism are associated with the risk of AD. The study by Liu et al. [39] determined that the *PARP1* gene is highly associated with the risk of AD. Furthermore, Abeti et al. [40] utilized a transgenic AD mouse model to provide evidence that Aβ plaque formation occurred concomitantly with PARP-1 activation and PAR polymer accumulation.

The Effect of Aβ Peptides on PARP-1 and Cell Death

More than a decade ago, we observed that the neurotoxic fragment (25–35) of Aβ peptide significantly enhanced (by approximately 80–100 %) the activity of PARP-1 in the hippocampus of adult rats [41]. This Aβ peptide had no effect on PARP-1 activity in the brain cortex or hippocampus from aged rats where the activity of the enzyme was altered by the aging process itself. The stimulatory effect of Aβ on PARP-1 activity was decreased by an inhibitor of constitutive isoforms of nitric oxide (NO) synthase, suggesting that Aβ induces PARP-1 activation through NO [41]. Other data indicated the involvement of NADPH oxidase(s) in Aβ peptide-evoked oxidative stress [42–44]. Our study later showed that incubation of hippocampal slices with full length Aβ(1–40) and NAC peptides led to the generation of free radicals, massive DNA damage, and PARP-1 activation [45]. As a consequence of these processes, the translocation of AIF from the mitochondria to the nucleus was induced.

PARP-1 inhibitors protected the hippocampal cells against AIF translocation. These results suggested that some population of hippocampal cells subjected to Aβ(1–40) or NAC peptides most likely died by a mechanism dependent on PARP-1 and AIF (Fig. 1). The role of PARP-1 in AIF-dependent cell death was also observed in the ischemic brain [46, 47]. To understand the effect of endogenously liberated Aβ peptides on PARP-1, we used PC12 cells transfected with the human wild-type (wt) gene for the amyloid beta precursor protein (APPwt) or transfected with the human *APP* gene bearing the double Swedish mutation (APPsw). Cells overexpressing APP have high levels of accumulated Aβ peptides inside the cell, high concentrations of Aβ secreted by these cells, and enhanced oxidative stress [48–50]. The APPwt and APPsw cells showed 2.8- and 4.8-fold higher Aβ production, respectively, compared to the control PC12 cells. PARP-1 activity was differently modulated depending on Aβ and the oxidative stress level. PARP activity was enhanced in APPwt and significantly decreased in APPsw cells. Inhibition of PARP-1 by autoribosylation in APPsw cells has been suggested previously [51]. The studies by Strosznajder and Banasik [52] also presented a concentration-dependent effect of Aβ on PARP-1 activity. The other amyloidogenic protein involved in neurodegenerative diseases is ASN. This protein in its oligomeric and fibrilic form is involved in the pathogenesis and pathomechanism of AD and Parkinson's disease. ASN is accumulated in neurons in the form of Lewy bodies and is secreted into the extracellular space as one of the components of Aβ plaques. Our data have shown that ASN enhanced secretion of Aβ peptide and both peptides together (Aβ and ASN), may lead to irreversible changes in mitochondria function and ultimately to cell death [49].

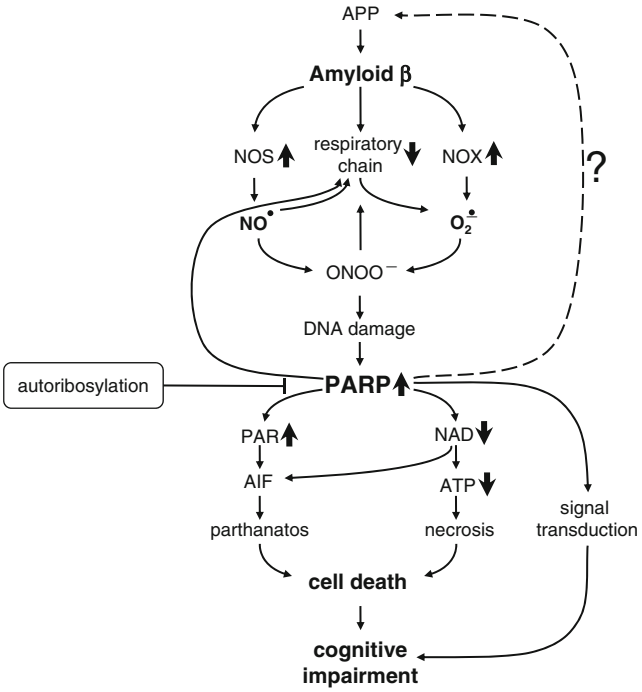

Fig. 1 The role of PARP-1 in the toxicity of amyloid β peptides. Aβ induces oxidative stress by activation of nitric oxide synthase and NADPH oxidase and by inhibition of the mitochondrial respiratory chain. The interaction of nitric oxide and superoxide radicals ($O_2^{\cdot-}$) leads to the formation of peroxynitrite ($ONOO^-$), a free radical cascade, DNA damage, and PARP-1 activation. Recent studies indicate that PARP-1 is involved in the posttranslational modification of mitochondrial proteins, including complexes within the electron transport chain. Massive DNA damage may evoke over-activation of PARP-1 and activation of PAR-mediated, apoptosis-inducing factor-dependent cell death (parthanatos). Overactivation of PARP-1 can also be responsible for the depletion of NAD/ATP and thereby necrotic cell death, leading to cognitive impairment. PARP-1 by alteration of the signal transduction pathway can also affect cognitive function. PARP-1 activity can be modulated by auto-ribosylation. No previous reports have described the role of PARP-1 in the regulation of Aβ precursor protein expression, metabolism, and processing

The Role of PARP-1 in Aβ-evoked Alteration of Mitochondrial Function

PARP-1 significantly influences energy metabolism in mitochondria by the use of NAD as its substrate or by epigenetic regulation of expression of mitochondrial proteins [53]. A large amount of cellular NAD is localized to mitochondria and is used by PARP, mono-ADP-ribose transferases, and sirtuins. The presence of poly(ADP-ribosylation) and PARP-1 in mitochondria was described by Lai et al. [30]. The major findings of their study demonstrated a number of targets for poly(ADP-ribosylation) including voltage-dependent anion channel-1 (VDAC-1), cytochrome c reductase, COX subunits, ATPase β subunit, Grp75, Hsp60, mitofilin, and the cytosolic enzyme GAPDH. PARP-1 affects the function of the mitochondrial respiratory electron transport chain by poly(ADP-ribosylation) of complexes III, IV, and V. Lai et al. [30] suggested that alteration of poly(ADP-ribosylation) may uncouple mitochondria and impair energy metabolism.

Recently, Aβ peptides and APP were also found in the mitochondria [54, 55]. Through inhibition of mitochondrial respiratory chain complexes, Aβ peptides enhance the production of superoxide radicals and increase the level of oxidative stress; PARP-1 becomes overactivated and thereby induces energy crisis and alteration of mitochondrial membrane potential [56, 57]. Gibson et al. [58] have previously described abnormalities of mitochondrial enzymes in AD.

It was demonstrated that activated nuclear PARP-1 consumed NAD and affected mitochondrial respiratory substrate availability [59]. The latest data by Rossi et al. [31] reported that mitochondrial PARP-1 is involved in the maintenance of mitochondrial structure and DNA integrity. Interestingly, tricarboxylic acid cycle (TAC) substrates

prevent PARP-1-mediated death of neurons and astrocytes [60]. The three enzymatic complexes of Krebs TAC (pyruvate dehydrogenase complex, isocitric dehydrogenase, and the α-ketoglutarate dehydrogenase complex) are significantly decreased in AD brain [61]. Moreover, the activity of these enzyme complexes that is reduced in AD is inhibited by Aβ peptides [62]. The most recent study by Abeti et al. [40] demonstrated that Aβ peptide-induced neuronal death is mediated by PARP-1 in response to oxidative stress generated by astrocytic NADPH oxidase.

Exposure of a coculture of hippocampal neuronal and astrocytes to Aβ peptides evoked the loss of mitochondrial membrane potential, transient membrane depolarization, and reversible opening of the mitochondrial permeability transition pores in astrocytes. The Aβ peptides activated glial NADPH oxidase and oxidative stress and decreased oxygen consumption. Oxidative stress led to stimulation of PARP-1 and to accumulation of PAR in astrocytes. Inhibition of PARP-1 or NADPH oxidase protected cells against PAR accumulation and mitochondrial depolarization. This study showed that prolonged exposure of a coculture to Aβ peptides (25–35 and 1–42) led to a significant decrease in NAD concentration and mitochondrial membrane potential and to death of these neurons. Inhibitors of PARP-1 exerted protective effect. This data showed a relationship between Aβ toxicity, mitochondrial potential, and PARP-1 alteration [40]. However, the direct relationship between PARP-1 activation and loss of mitochondrial function in Aβ toxicity is not fully understood and requires further investigation.

The Role of PARP in Aβ-evoked Responses of Microglia Cells and in Inflammation

Aβ peptides that may play an important role in AD pathomechanisms not only influence neurons but also modify the metabolic processes of astrocytes, microglia, and endothelial cells of the brain's blood vessels. Aβ peptides trigger microglia activation that may induce neuronal death and impair cognitive function in AD through the release of several toxic compounds [63]. However, activated microglia can clear Aβ fibrils and plaques by phagocytosis and can release certain neurotrophins. Recently, Kauppinen et al. [64] proposed that PARP-1 was involved in Aβ-induced microglia activation through the regulation of NF-κB. These studies, using microglia culture, showed that PARP-1 activity through its regulation of NF-κB was important in NO, TNF-α, protease release, and morphological transformation of these cells. Both PARP-1 gene deficiency and inhibition of PARP-1 prevented Aβ-evoked toxicity, increased release of neurotrophic factors, such as TGF-β and VEGF, and preserved the ability of microglia for phagocytosis of Aβ peptides. Several previously published results also indicate the link between PARP-1 and NF-κB in microglia activation processes [65–69]. It has also been demonstrated that the interaction of PARP-1 with other transcription factors, such as AP-1, SP-1, YY-1, Oct-1, and NFAT, may modulate glia and T cells responses to different type of stress [70, 71]. Kauppinen et al. [64], using $hAPP_{J20}$ mice crossed with PARP-$1^{-/-}$ mice, demonstrated that PARP-1 depletion protected the brain against Aβ-evoked microglia activation, hippocampal synaptic integrity alteration, and cognitive impairment. Moreover, the studies with Aβ(1–42) peptides, which were injected into the brains of wt and PARP-$1^{-/-}$ mice, confirmed the role of PARP-1 in microglia activation. PARP-1 inhibition significantly reduced Aβ-evoked microglia activation. Conversely, these in vivo and in vitro studies also showed that the lack of PARP-1 expression and activity did not affect viability and proliferation of Aβ-stimulated microglia. PARP-1 had no effect on the migration of microglia or on blood-born macrophages during Aβ stimulation. The molecular alteration evoked by Aβ peptides impaired cognitive function. Cakala et al. [72] demonstrated that systemic inflammatory response (SIR) evoked by lipopolysaccharide (LPS) significantly modulated Aβ toxicity in the brain and had significant effects on cognitive function and locomotor activity. We have observed that SIR-induced expression of several pro-oxidative and pro-inflammatory genes in the hippocampus, which led to the stimulation of lipid peroxidation, enhancement of PARP-1 activity, and an accumulation of PAR. Consequently, PARP-1 activation was responsible for decreasing NAD concentration and AIF translocation from mitochondria to nuclei [73, 74]. An inhibitor of PARP-1 protected the brain against pro-oxidative processes, AIF translocation, and cell death [73]. The study by Jacewicz et al. [25] indicated that the PARP-1 inhibitor also protected against SIR-induced impairment of cognitive function and significantly improved spatial memory and locomotor activity in LPS-treated mice. Systemic inflammation may exacerbate Aβ toxicity and several symptoms of neurodegenerative diseases. However, inflammation may also have ameliorating effects on the course of neurodegeneration processes. Recent studies have shown that PARP-1 may act as a main molecular switch responsible for the regulation of inflammatory signal transduction in the CNS.

Concluding Remarks

Poly(ADP-ribosylation) of proteins plays a crucial role in a wide variety of biological processes. In this short review, we focus on the role of PARP-1 in Aβ peptide toxicity and in AD. The available data present evidence that PARP-1 may be an important player in AD pathology. Recent studies indicate the involvement of PARP-1 in mitochondrial

function and in cognition. Amyloid β, through activation of NO synthases and NADPH oxidases, can lead to a free radical cascade. These events cause DNA damage in the nucleus and thereby induce overactivation of PARP-1, which leads to NAD depletion, energy crisis, cell death, and cognitive impairment. PARP-1, as a nuclear target for signal transduction, is involved in memory formation; however, its direct role in AD dementia is unknown. The majority of studies have confirmed the original hypothesis that nuclear PARP-1 is responsible for mitochondria dysfunction. Moreover, the most recent data, using more sophisticated methods, have demonstrated PARP-1's presence in the mitochondria and its role in the posttranslational modification of respiratory electron transport complexes. The relationship between Aβ, PARP-1 and mitochondria dysfunction needs further investigation. It seems that these studies should have a significant impact on understanding AD pathology and on the development of more efficient therapies.

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Conflict of interest The authors declare that they have no conflict of interest.

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