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Mini Review

Nutrition-Based Modulation of Poly-ADP-Ribosylation and its Possible Role In Alzheimer's Disease

Martire S[1] and Fuso A[2,3]*

[1]Department of Biochemical Sciences, Sapienza University of Rome, Italy

[2]Department of Psychology, Sapienza University of Rome, Italy

[3]Laboratory of Lipids Biochemistry, European Center for Brain Research (CERC) / IRCCS Santa Lucia Foundation, Italy

***Corresponding author:** Fuso A, Department of Psychology, Sapienza University of Rome, Via dei Marsi 78, 00183, Roma, Italy, Tel: +39-0649766601; Fax: +39-0649766600; Email: andrea.fuso@uniroma1.it

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Abstract

Alzheimer's Disease (AD) is the most common neurodegenerative disease and the main reason of dementia in the elderly. On the pathological point of view, it is characterized by extracellular aggregates of amyloid peptides and intracellular deposits of tau protein. These deposits affect neuron viability and functions by inducing (among other pathological pathways) oxidative stress and triggering mitochondrial dysfunction. It is now evident that free radical-induced oxidative damage is strongly involved in the pathogenesis of AD. Oxidative damage occurs early in disease pathogenesis and can exacerbate its progression. Post-mortem brain of individuals affected by AD, evidenced an extensive state of oxidative stress compared to healthy controls; markers of increased oxidation include, among others, DNA damage. DNA damage can induce the activity of the enzyme poly (ADP-ribose) polymerase 1 (PARP-1) that catalyze the reaction of poly (ADP-ribosylation). This post-translational modification modulates the functions of proteins involved in many physiological processes such as gene expression, maintenance of genomic stability and cell death. Therefore, inhibiting PARP-1 activity can represent a possible new strategy to reduce the impact of the oxidative stress in AD as well as in other neurodegenerative diseases. Here we discuss the role of nutrients in modulating PARP-1 activity and its perspective potential application.

Keywords: Alzheimer' disease; Poly-ADP-ribosylation; Niacin; PARP inhibitors; Caloric restriction; Nutrition

Abbreviations

PARP: Poly (ADP-Ribose) Polymerase; AD: Alzheimer's Disease; CR: Caloric Restriction; ROS: Reactive Oxygen Species; Aβ: Amyloid-β peptide

Introduction

Neurodegenerative diseases are a growing public health concern because of the rapid increase in life expectancy in the developed world. Indeed, neurodegeneration affects a wide percentage of people and are increasing to epidemic proportions in all industrialized countries [1]. In particular, the incidence of Alzheimer's Disease (AD) and Parkinson's Disease (PD) increases with age and the etiology remains elusive. There is evidence that oxidative stress, homocysteine related vitamins, fats, and alcohol may have a role in the pathogenesis of AD. Epidemiological studies suggest that high dietary intake of antioxidants, vitamins B6, B12, and folate, unsaturated fatty acids, and fish oil are associated to decreased AD risk, although results are often contrasting [2,3].

Despite the existing evidence does not support the recommendation of specific supplements or food, it is clear that nutritional approaches able to prevent, delay, slow, or even stop the progression of the disease is a promising strategy that deserves further and more accurate study. Among the attempted nutritional approaches to the treatment of neurodegeneration, several studied tried to address the oxidative stress and the antioxidant response [2]. As a matter of fact, ROS generation is strictly associated with neurodegenerative diseases and causes damage to major macromolecules in cells, including lipids, proteins and nucleic acids [4]. DNA damage is a prime activator of the enzyme poly (ADP-ribose) polymerase 1 (PARP-1) that catalyze the reaction of poly (ADP-ribosylation), a post-translational modification of proteins involved in many physiological processes such as gene expression, maintenance of genomic stability and cell death [5-7].

PARP-1 can prompt a spectrum of strategies to induce cell death, including the ability of modifying proteins acting as a spatial and temporal modulator of a variety of cell signaling pathways such as regulation of gene expression, and transcriptional factor such as NF-kB activation and protein translocation [8].

Excessive PARP-1 activity has been implicated in the pathogenesis of several disorders such as stroke, myocardial infarction, inflammation, diabetes, and neurodegenerative disorders [9-12]. Therefore, it is not surprising that the search for PARP-1 inhibitors with specific therapeutic uses (e.g., brain ischemia, cancer) has been an active area of research. Beyond medicinal uses, naturally occurring PARP-1 inhibitors may also offer a unique preventative means at attenuating chronic inflammatory diseases through dietary supplementation. This possibility has prompted research for specific, naturally occurring inhibitors of PARP-1.

PARP in Alzheimer's Disease

Love et al. [13] were the first to report a correlation between PARP-1 and Alzheimer disease showing by immunostaining assay high levels of poly (ADP-ribosylated) proteins in AD human brains. So far, other groups have demonstrated PARP-1 activation in AD

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using both *in vivo* and *in vitro* models: significant PARP-1 activation was demonstrated through the evaluation of enzymatic activity and western blot in hippocampus and enthorinal cortex of transgenic mice TgCRND8 after 3 months, when early amyloid deposit occurs [14]. hAPPJ20 mice, which accumulate amyloid beta (Aβ) by the age of 6 months, crossed with PARP-$1^{-/-}$ mice, attenuated the brain dysfunctions developed, such as microglial activation, hippocampal synaptic integrity and cognitive function [15]. Moreover direct Aβ injections into hippocampus of mice showed less microglial activation induced in the area of injection by Aβ in PARP-$1^{-/-}$ mice or treated with the PARP-1 inhibitor PJ34, thus confirming a protective role of PARP-1 inhibition.

Rapid accumulation (within 1 hour) of poly(ADP-ribose) polymers (PARs) was detected in Aβ-stimulated microglia primary cultures [15] and astrocytes [16], indicating enzymatic PARP-1 activity in non-neuronal cells. In our last work [14] 7PA2 cells (CHO cell line stably transfected with a complementary DNA coding for APP751 containing the Val717Phe familial Alzheimer's disease mutation that leads to Aβ overproduction) were first assayed for PARP-1 activity and a 40% increase was observed in 7PA2 compared to control CHO cells.

The role of PARP-1 has been implicated in the pathogenesis of Alzheimer's disease through several mechanisms. First, as Berger suggested 30 years ago [17], excessive PARP-1 activity is related to massive NAD depletion that in turns leads to ATP depletion and energy failure. This hypothesis has been confirmed over the years by other authors, which demonstrated that extracellular NAD^+ restore neuronal NAD^+ levels after PARP-1 activation in astrocytes monocultures treated with NMDA [18]. The second mechanism is through the regulation of Apoptosis Inducing Factor (AIF) that once poly(ADP-ribosylated) by PARP-1 moves to the nucleus and induces DNA fragmentation and cell death, called Parthanatos [19-21]. Finally, PARP-1 is known to regulate a wide spectrum of function at genomic levels, such as chromatin stability or transcriptional activity, acting both as a cofactor and as a signaling molecule (Reviewed in [22]).

Niacin and PARP

Increasing PARP-1 activity leads to the drastic reduction of NAD^+ levels, with consequences on the ATP production and impairment of cell functions [23]. Thus, extensive PARP-1 activation has been linked to the development and progression of various chronic diseases including diabetes, cancer, viral infections and neurodegenerative diseases [24-27].

The activity of PARP-1, as well as DNA synthesis, requires NAD^+, which derives from Nicotinic acid (NA) and nicotinamide (NAM), commonly called niacin.

Nicotinamide, the amide form of NA, is changed to its mononucleotide compound with the enzyme nicotinic acid/nicotinamide adenylyl-transferase, and participates in the cellular energy metabolism that directly impacts normal physiology [28]. Nicotinamide influences oxidative stress and modulates multiple pathways tied to both cellular survival and death [29]. Nicotinamide relies upon unique cellular pathways that involve forkhead transcription factors, sirtuins, protein kinase B (Akt), Bad, caspases [30] and poly (ADP-ribose) polymerase that may offer a fine line with determining cellular longevity, cell survival, and unwanted cancer progression.

Niacin is found in variety of foods, including liver, chicken, beef meat, fish, cereal, peanuts and legumes; it can be also synthesized from tryptophan, an essential amino acid found in most forms of protein. It is well known that insufficient assumption of niacin can be responsible for several symptoms including nausea, skin and mouth lesions, anemia, headaches and tiredness. Moreover, when niacin deficiency becomes chronic, it can cause pellagra [31,32]. Niacin and nicotinamide are both precursors of Nicotinamide Adenine Dinucleotide (NAD^+) and nicotinamide adenine dinucleotide phosphate ($NADP^+$); these molecules are coenzymes for many dehydrogenases, participating in hydrogen transfer processes. NAD^+ is important in catabolism of fat, carbohydrates, proteins, and alcohol, as well as cell signaling and DNA repair, and NADP mostly in anabolism reactions such as fatty acid and cholesterol synthesis. High energy requirements (brain) or high turnover rate (gut, skin) organs are usually the most susceptible to their deficiency.

A clear correlation between Niacin deficiency and tissue dishomeostasis, mediated by PARP activity has been documented in skin. As a matter of fact, keratinocytes maintained under niacin deficiency are more sensitive to photodamage, since PARP (and also sirtuins) activity is inhibited by low NAD^+, with consequent increases of DNA damage and cell death [33].

Since in an Oxford University study of older individuals with mild cognitive impairment, supplementation with other B-vitamins maintained memory performance and reduced the rate of brain atrophy [34], supplementation with niacin could be a safe approach for a possible clinical trial.

PARP inhibitors

Several drugs designed to inhibit PARP are currently in clinical development as anticancer agents due to their capacity to impair DNA repair operated by PARP-1 [35]. Anyway, since PARP-1 activation leads to NAD and ATP depletion, eventually leading to irreversible cellular energy failure, several PARP-1 inhibitors have demonstrated a role in counteracting neurodegeneration [14,36].

Besides synthetic molecules, several PARP inhibitors are endogenous or naturally occurring compounds such as nicotinamide, thymidine, or theophylline [37]. Large scale survey using *in vitro* assay system discovered many potent inhibitors [38] and in the last decades several new endogenous and naturally occurring regulators of PARP-1 have been found, which include antibiotics (e.g., tetracyclines), vitamins (e.g., vitamin D3) and others [39,40]. The mode of action for many of the endogenous and naturally occurring PARP-1 inhibitors is unclear, and discrepancies exist in the literature. Among the compounds documented as competitive inhibitors with respect to NAD^+ there are caffeine [41], formycin B [42], NADH and NADP [43], nicotinamide [44], taurine [45], theobromine, theophylline and thymidine [46]. Some of these molecules are already in use in different pathologies, but the vast majority is still studied at preclinical level.

Caloric restriction

Recent findings indicate that Caloric Restriction (CR) may have a profound effect on brain function and vulnerability to injury and

diseases, by enhancing neuroprotection, stimulating the production of new neurons, and increasing synaptic plasticity. CR or energy restriction retards age-associated increases in mitochondrial free-radical production and reduces the accumulation of cell components damaged by oxidation. CR has also been shown to slow down age-related declines in various repair capabilities, including some types of DNA repair. It would be of interest to determine if CR can decrease the half-life of poly (ADP-ribose) and modulate the activities of PARP [47]. It was demonstrated that significant age-associated increase in PARP is ameliorated in the frontal cortices of CR rats, suggesting that suggest that caloric restriction may provide neuroprotection to the aging brain by preserving DNA repair enzymes in their intact form, and/or upregulating specific antiapoptotic proteins involved in neuronal cell death [48].

Finally, recent studies have also suggested that PARP, as well as sirtuins, is a downstream target of CR, which mediate CR-induced beneficial effects including life span extension in an NAD(+)-dependent manner, due to NAD(+) increasing [49].

Conclusion

Increasing evidences indicate that epigenetic mechanisms are involved in neurodegenerative disorders onset and progression: Although DNA methylation, histone tail modification and micro-RNAs represent the main, most studied and main neurodegeneration-associated classes of epigenetic modification, poly(ADP-ribosylation) may have a relevant role in neurodegenerative diseases as a consequence of the inflammatory and oxidative processes [50]. It is not yet completely understood whether PARP activation is totally detrimental (in terms of the final pathological phenotype) or if the early and low level activation of this class of enzymes rather represent a mechanism by which the cell try to cope with the disease. However, it is clear that sustained or high level activation is associated to the neurodegenerative phenotype in AD and other diseases. Therefore, studies aimed at characterizing the effects of PARP inhibition in AD models could help to clarify the pathological processes occurring in neurodegenerating brain and to disclose the role of PARP and its possible use as a therapeutic target. It is also clear that nutrition could impact the course of normal versus diseased aging, and that nutrients can modulate the epigenome. On these bases, we suggest that studying the effects of nutrients possibly regulating PARP activity and of natural molecules introduced by diet, showing PARP inhibition effect, will be relevant in terms of comprehension AD epidemiology and treatment.

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