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Review

The pathophysiology of triose phosphate isomerase dysfunction in Alzheimer's disease

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Summary. Alzheimer's disease (AD), the most prevalent neurodegenerative disease worldwide, has two main hallmarks: extracellular deposits of amyloid ß-peptide (Aß) and intracellular neurofibrillary tangles composed by tau protein. Most AD cases are sporadic and are not dependent on known genetic causes; aging is the major risk factor for AD. Therefore, the oxidative stress has been proposed to initiate the uncontrolled increase in Aß production and also to mediate the Aß's deleterious effects on brain cells, especially on neurons from the cortex and hippocampus. The production of free radicals in the presence of nitric oxide (NO) yields to the peroxynitrite generation, a very reactive agent that nitrotyrosinates the proteins irreversibly. The nitrotyrosination produces a loss of protein physiological functions, contributing to accelerate AD progression. One of the most nitrotyrosinated proteins in AD is the enzyme triosephosphate isomerase (TPI) that isomerises trioses, regulating glucose consumption by both phosphate pentose and glycolytic pathways and thereby pyruvate production. Hence, any disturbance in the glucose supply could affect the proper brain function, considering that the brain has a high rate of glucose consumption. Besides this directly affecting to the energetic metabolism of the neurons, TPI modifications, such as mutation or nitrotyrosination, increase methylglyoxal production, a toxic precursor of advanced glycated end-products (AGEs) and responsible for protein glycation. Moreover, nitro-TPI aggregates interact with tau protein inducing the intraneuronal aggregation of tau. Here we review the relationship between modified TPI and AD, highlighting the relevance of this protein in AD pathology and the consequences of protein nitro-oxidative modifications.

Key words: Alzheimer's disease, Triosephosphate isomerase, Oxidative stress, Nitrotyrosination; methylglyoxal

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Introduction

Aging is characterized by a lack in redox homeostasis. Consequently, there is an increase in nitro-oxidative stress, which plays a key role in the onset and progression of neurodegenerative processes (Di Monte et al., 1992; Halliwell, 1992; Omar and Pappolla, 1993; Miranda et al., 2000; Guix et al., 2005). Nitro-oxidative stress is directly related to mitochondrial dysfunction (Schon et al., 1997), calcium deregulation (Mattson et al., 1992) and protein aggregation (Guix et al., 2009; Kummer et al., 2011), which induce neuronal death (Praticò et al., 2001; Butterfield and Boyd-Kimball, 2004; Ill-Raga et al., 2010). All these features are found in Alzheimer's disease (AD).

Alzheimer's disease

AD hallmarks

AD is the most common form of dementia in the elderly, accounting for 60–70% of all cases and affecting 10% of individuals older than 65, and nearly 50% of those older than 85 (Malenka and Malinow, 2011; Imbimbo et al., 2005). It courses with progressive deterioration of memory, behaviour and cognition because of major neuronal damages in the hippocampus and neocortex. Memory decline initially manifests as a loss of episodic memory, impeding recollection of recent events, including autobiographical activities. The progression of the disease causes a dramatic decline in

cognitive abilities (Ball et al., 1985). The specific therapies for AD address the cholinergic deficit and the overstimulation of the glutamatergic NMDA receptors, but they fail to avoid the progression of the disease.

AD can be classified into two types depending on the age of the disease onset. The early onset AD is known as Familial AD (FAD) due to the mutations in proteins such as amyloid precursor protein (APP) or presenilins (PS) (Tanzi el al., 1992; Levy-Lehad et al., 1995; Rogaev et al., 1995; Sherrington et al., 1995). FAD appears before the patients are 65 years old, being less common (less than 5% of the total AD cases) than the late onset one, but it progresses very quickly. Late onset AD is the most common AD and it has been related to some polymorphisms, especially with ApoE4 (Saunders et al., 1993; reviewed in Wasco and Tanzi., 1995).

Both types of AD are characterized by neuronal death associated to extracellular amyloid ß-peptide (Aß) deposits and intracellular neurofibrillary tangles (NFT), composed of tau protein. Aß is a product of the cleavage of APP by the sequential action of ß-aspartyl secretase (BACE1) and γ-secretase (PS complex). Aß is able to aggregate in ß-sheet, forming primary structures called oligomers (dimers, trimers and tetramers) that can assemble to form protofibrils (PF) as intermediate structures between aggregates and mature fibrils. Oligomers are considered the most toxic Aß forms (Wang et al., 2002; Kelly and Ferreira, 2006; Shankar et al., 2007), remaining in the proximity of the neuronal membranes where they produce their harmful effects. Currently, the mature fibrils aggregation forming senile plaques and brain vascular deposits of amyloid are considered a mechanism to avoid the high oligomer neurotoxicity.

On the other hand, NFT are composed of tau aggregates, a microtubule associated protein which, detached from microtubules, aggregates to form the paired helicoidal filaments (Braak et al., 1994; Bramblett et al., 1993; Yoshida and Ihara, 1993; Morishima-Kawashima et al., 1995). Tau is hyperphosphorylated when forming NFT, which has produced a search for different kinases, such as glycogen kinase 3-beta (GSK-3ß), to be responsible for NFT formation (Moreno et al., 1996; Illenberger et al., 1998). The relevance of NFT in AD is supported by the correlationship between their presence and the dementia level, a fact that is impossible to establish with senile plaques, probably due to the major effect of oligomers, which are histochemically "invisible".

Aß and nitro-oxidative stress

There is much evidence relating AD pathology with nitro-oxidative stress. Aß aggregation into ß-sheet induces the production of free radicals due to the reduction of transition metals (Huang et al., 1999; Varadarajan et al., 1999). Misfolded Aß is capable of binding Cu (II) and Fe (III) and reduce these transitional metals to Cu(I) and Fe(II), producing hidroxyl radicals and H2O2, which causes cytotoxicity (Huang et al., 1999; Cuajungco et al., 2000; Muñoz et al., 2002) by inducing lipid peroxidation, protein oxidation, nitrotyrosination and glycation, and DNA oxidation (Miranda et al., 2000) (Fig.1).

The damage in membrane transporters and ion channels leads to an increase in intracellular calcium levels (Mattson et al., 1992; reviewed in Yu et al., 2009). It produces the synthesis of nitric oxide (NO) by the neuronal NO synthase (nNOS), since it is a Ca^{2+}-calmodulin-dependent enzyme (Guix et al., 2005). NO has an unpaired electron in the last orbital acting as a free radical (Stamler et al., 1992). Hence, NO can react with other molecules such as superoxide anion ($O_2^{\cdot-}$), forming peroxynitrite anion (ONOO-) (Beckman et al., 1990), a short lived molecule but highly reactive. Peroxynitrite nitrotyrosinates proteins, a process which consists of the addition of a nitro group (NO_2) to tyrosine residue (Ischiropoulus et al., 1992). Nitrotyrosination is highly spread in AD brains (Hensley et al., 1998).

In our lab we have demonstrated that one of the proteins most nitrotyrosinated due to Aß action is triosephosphate isomerase (TPI) (Coma et al., 2005; Guix et al., 2009), a key enzyme in the cell metabolism that controls glycolytic flow and energy production (Richard, 1993).

Triosephosphate isomerase

TPI cellular function

TPI is an enzyme that catalyses the interconversion of D-glyceraldehyde-3-phosphate (GAP) to dihydroxyacetone phosphate (DHAP) from both the glycolytic and phosphate pentose pathways, the latter being the most active glucose metabolic pathway in neurons (Bolaños et al., 2010) in order to increase antioxidant protection by producing GSH.

The rate of the catalysis is diffusion-limited, and the equilibrium favours the formation of DHAP by 1:20 (Olah et al., 2002). TPI is essential for the efficient energy production of glycolysis; therefore it is critical for the functional activity of the cells (Fig. 2). Interestingly TPI has been proposed to be affected in aging, altering energy metabolism (Hipkiss, 2011).

GAP is diverted to pyruvate producing four adenosine triphosphate (ATP) molecules. In brain cells DHAP is not a dead-end product and it can be directed to lipid synthesis (Kusaka et al., 2007). In fact, the glycolytic pathway is interconnected with the lipid metabolism, the pentose phosphate pathway, and the gluconeogenesis pathway via GAP and/or DHAP. The metabolic flow through these pathways will be affected in the case of deficiencies in TPI activity (Richard, 2008; Orosz et al., 2009).

The deficiency of this enzyme is characterized by haemolytic anaemia. Interestingly, it is the only

glycolytic enzyme defect that is associated with neurodegeneration (Olah et al., 2005). The deficiencies in TPI activity do not just affect cells by the reduction in ATP and pyruvate supply, but also by the formation of methylglyoxal (MG) (Ahmed et al., 2003). This is a toxic triose formed at a very low rate as a side-product of TPI, but its production increases when TPI is damaged (Guix et al., 2009; Fig. 3). MG modifies proteins by the glycation of different aminoacids.

TPI structure

TPI is a stable homodimer of two 27 kDa subunits. Although every single monomer has the residues for the catalytic activity, the dimerisation apparently rigidifies each of the two separate active sites, providing full catalytic power and being active just in its dimeric form (Mainfroid et al., 1996; Wierenga et al., 2010). TPI dimer is the most common quaternary structure, but in thermophylic organisms TPI is known to occur as tetramers (Maes et al., 1999). At present, there are at least 118 crystal structures of TPIs in the PDB (RCSB Protein Data Bank). Structural studies have shown that the active site is at the dimer interface, with all catalytic residues (Asn11, Lys13, His95 and Gly167) for a particular active site coming from the same subunit. Several water molecules are an integral part of the dimer interface, and six of them are highly conserved (Thakur et al., 2009). TPI has four tyrosines. The first two, Y47 and Y67, stay at the interface of the dimer in opposite orientations, while the remaining two, Y164 and Y208, interact directly and locate very close to the catalytic site (Guix et al., 2009; Fig. 4).

The spatial structure of TPI is a $(\beta/\alpha)_8$ barrel fold, also known as a "TIM-barrel". This fold consists of a regular eightfold repeating pattern of ß-strands and α-helices. The ß-strands form the inner set of eight parallel ß-strands, covered on the outside by the subsequent α-helices (Nagano et al., 2002). The α-helices and ß-sheets are linked by loop regions. Three loops of the N-terminal half of the molecule are involved in the intersubunit interactions, another three participate in the active site. Specifically, loop-1 has the residues Asn11 and Lys13; loop-4 has His95 and loop-6 has Gly167 (Orosz et al., 2009; Wierenga et al., 2010).

Loop-6 is very flexible and plays an important role in substrate binding and catalysis. In the unliganded conformation, loop-6 interacts with loop-5, whereas in the closed/liganded conformation it interacts with loop-7 (Wierenga et al., 2010). Any variation in loop-6 could affect the eficiency of the enzyme. A TPI variant, in which four residues of that loop have been removed, increases the synthesis of the toxic MG (Pompliano et al., 1990). Similar results were obtained by our group

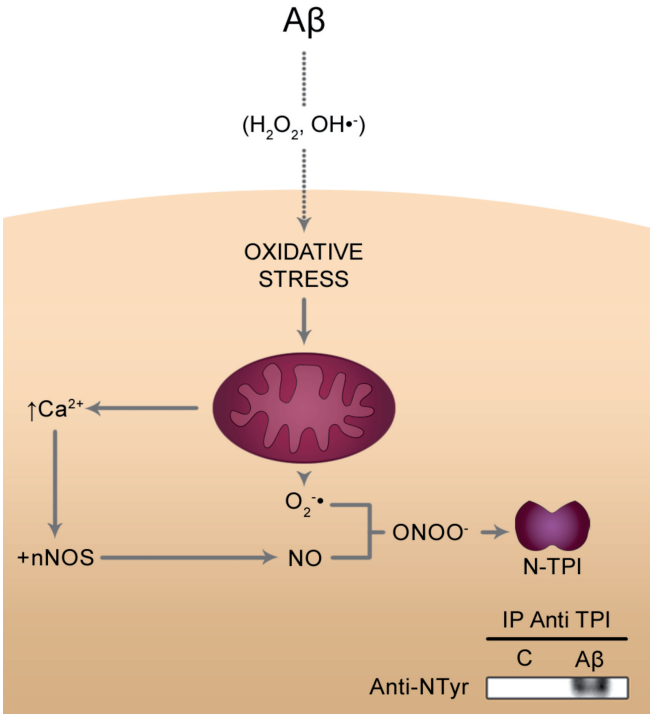

Fig. 1. Aß induces TPI nitrotyrosination. Aß fibrils and oligomers produce free radicals, which damage mitochondria. Consequently, intracellular calcium levels raise and activate the enzyme nNOS. Therefore, NO and superoxide anion react to form peroxynitrite that nitrotyrosinates TPI. In the inset it is shown a western blot of human neuroblastoma cells treated with Aß fibrils and untreated control cells (C). TPI was immunoprecipitated and the western blot was revealed with an antibody anti-nitrotyrosine.

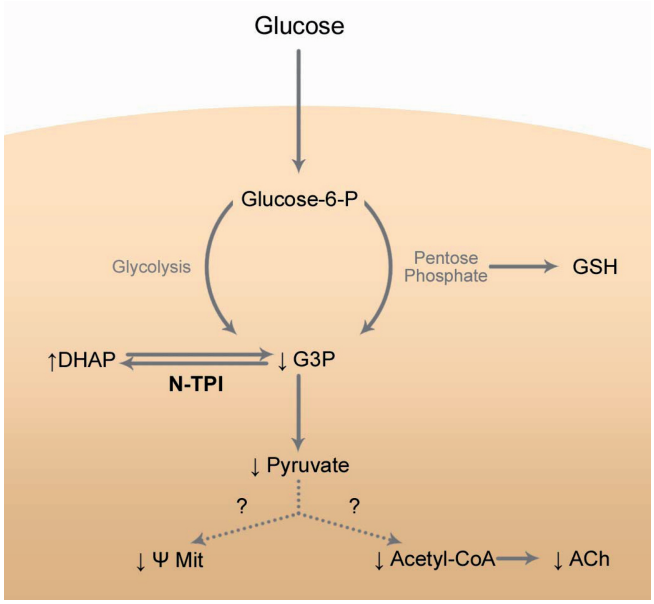

Fig. 2. TPI nitrotyrosination decreases pyruvate production. Neurons metabolize glucose mainly by the pentose phosphate cycle and at a lower rate by glycolysis. Both pathways produce G3P. When TPI is nitrotyrosinated there is a decrease in its isomerase activity and DHAP increases. Pyruvate supply is low and it will produce a fall in the mitochondrial membrane potential and acetyl-CoA, the precursor of acetylcholine (ACh), which is a neurotransmitter depleted in AD.

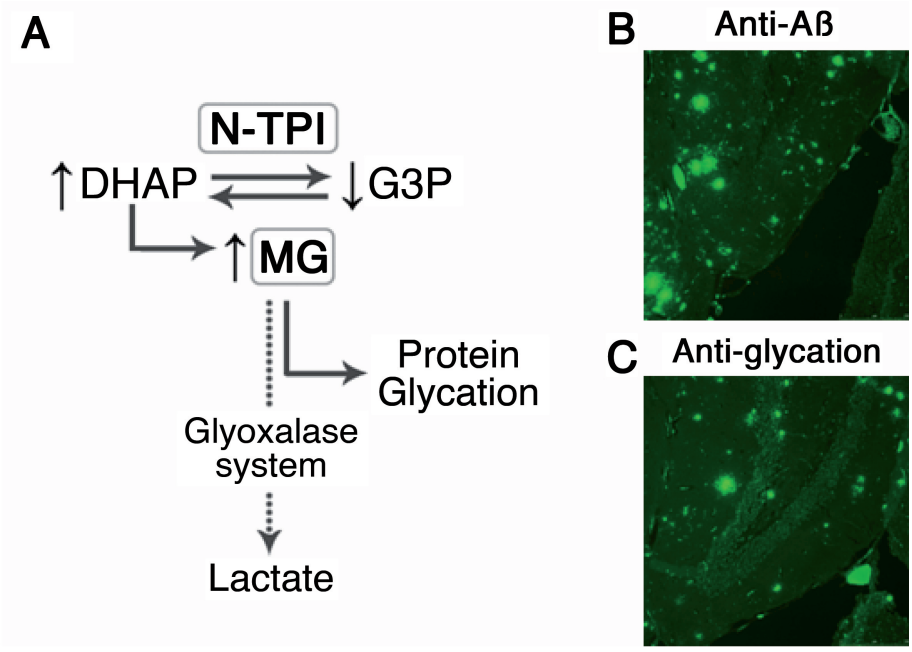

Fig. 3. Protein glycation by TPI nitrotyrosination. **A.** TPI induces MG production from DHAP. MG can be metabolized to lactate by glyoxalase system under physiological conditions. When MG production is triggered due to TPI nitrotyrosination, it glycates proteins, damaging them. **B and C.** The right panels show slides obtained from the hippocampus of a double transgenic mice overexpressing human APP and PS1. Immunofluorescence images were obtained by incubating with anti-human Aß (**B**) and anti-glycated aminoacid antibodies (**C**). High glycation is observed in the hippocampus of this AD model animal.

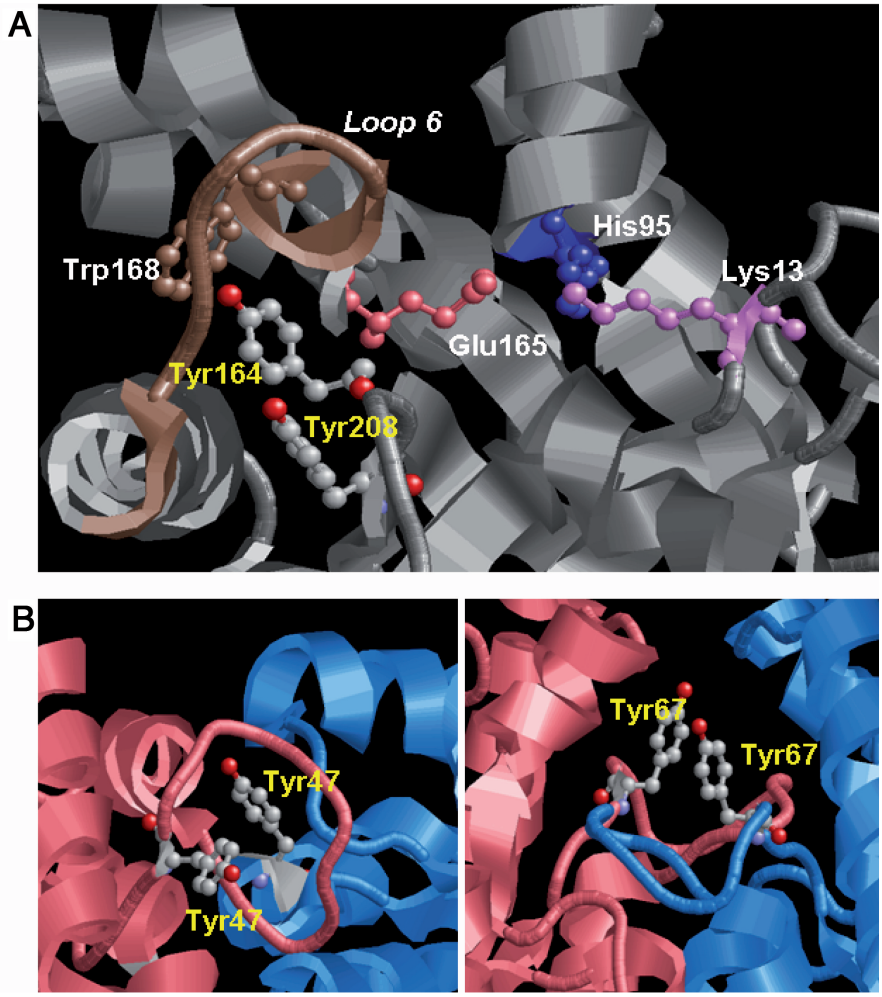

Fig. 4. Tyrosines of TPI. TPI has 4 tyrosines. **A.** Tyrosines 164 and 208, through hydrogen bonding, regulate the hinge movement of loop 6 (residues from 168-178) over the catalytic site formed by Glu165, His95 and Lys13. **B.** Tyrosine 47 (left) and tyrosine 67 (right panel) are located at the interface of the dimer, probably contributing to its stability and therefore to the activity of the enzyme. The images were obtained by the software Rasmol (www.rasmol.org) from the PDB file 2JK2 containing the structure of human TPI.

when TPI was mutated at Tyr164 and Tyr208 by Phe or by inducing the nitrotyrosination of the enzyme (Guix et al., 2009).

TPI deficiencies

TPI is coded by one gene located at chromosome 12p13 in the human genome. Its amino acid sequence is highly conserved among all known TPI proteins (Schneider, 2000). There are TPI deficiencies due to autosomal recessive multisystem genetic disorder, characterized by decreased enzyme activity, which is accompanied by an increase of DHAP. This deficiency is manifested clinically, like many glycolytic

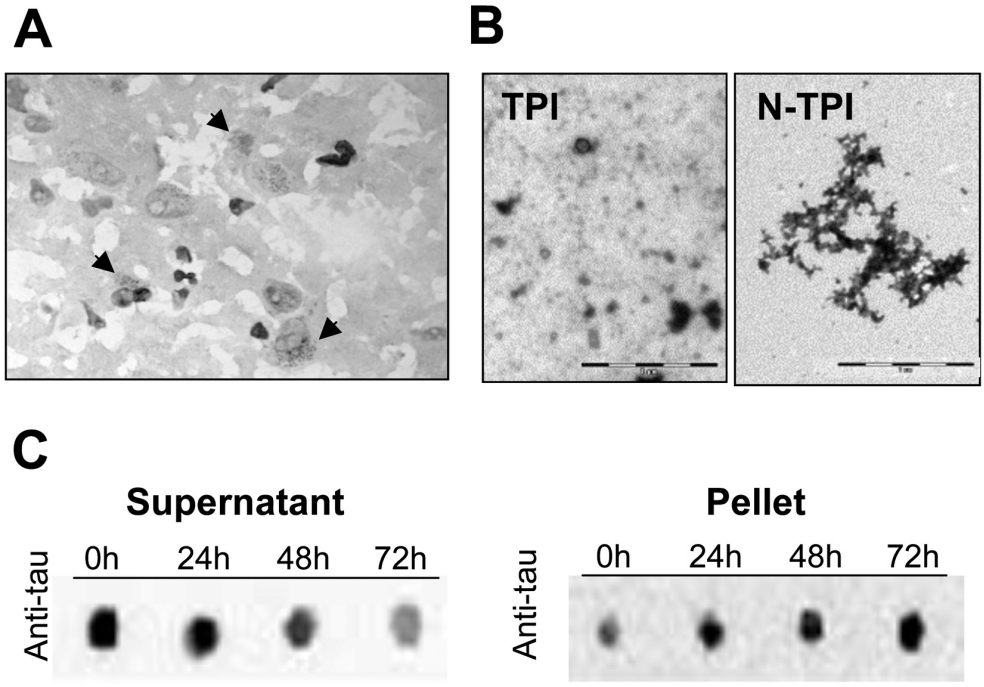

Fig. 5. TPI nitrotyrosination induces its aggregation. **A.** Immunohistochemical analysis of a cortex sample from an AD patient showing aggregated TPI inside the neurons. The image was obtained using an anti-TPI antibody and peroxidase staining. **B.** Nitro-TPI aggregates as shown in transmission electron microscopy images obtained with untreated TPI (right) and TPI treated (left) with 50 mM peroxynitrite donor (SIN-1) *in vitro*. **C.** Nitro-TPI induces tau aggregation as shown in the dot blots performed with samples incubated from 0 up to 72 hours at 1:1 (w/w) ratio. Samples were centrifuged and pellets were washed and sonicated. A representative dot blot is shown after incubation with an anti-tau monoclonal antibody. In the supernatants (right) there is a decrease of free tau when incubated with nitro-TPI from 24 up to 72 h. It corresponds with the results obtained in the pellets (left), where there is an increase in high molecular tau aggregates from 24 up to 72 h.

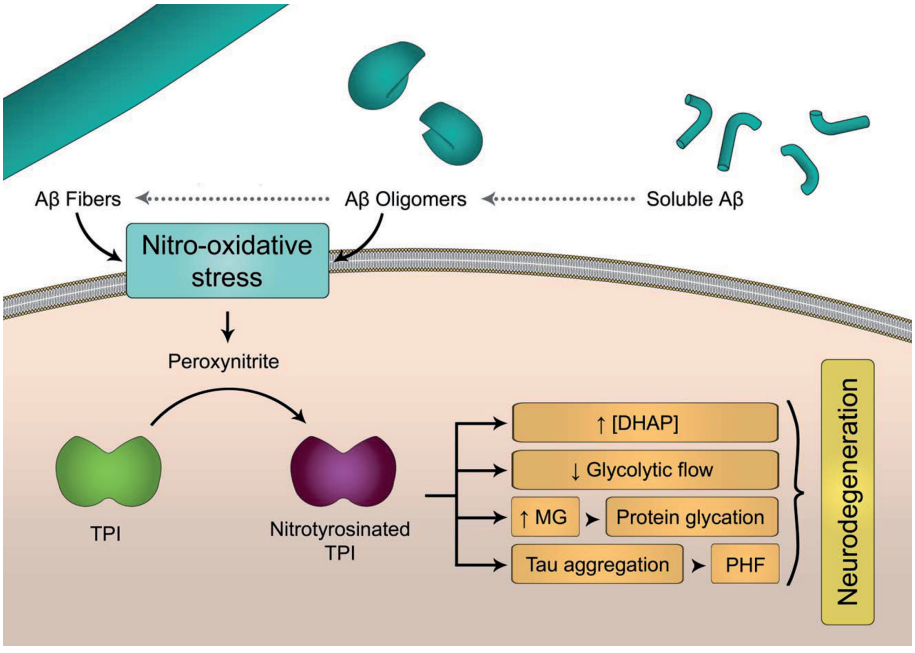

Fig. 6. Effects of TPI nitrotyrosination due to Aß toxicity. This scheme summarizes all the proposed effects of TPI nitrotyrosination in AD linking Aß with neurodegeneration.

enzymopathies, as chronic hemolytic anemia, although this disorder is unique among the glycolytic enzyme defects associated with progressive neurological dysfunction and, frequently, childhood death (Olah et al., 2005; Orosz et al., 2006, 2009). The pathogenesis of this disease is not well understood, and no effective therapy is available. However, there are experiments showing the normalization of DHAP levels in TPI-deficient cells treated with the active form of the enzyme (Orosz et al., 1999).

Patients with various inherited mutations have been identified. The most abundant missense mutation in humans occurs at codon 104 in the TPI gene (Glu104Asp mutant). This mutation is not only the most common, but also causes the most severe symptoms (Schneider, 2000; Orosz et al., 2009).

There are several theories to explain the low activity in TPI deficient cells, but most of them have in common the instability of the enzyme. Any mutation or modification in the subunit interface results in loss of activity, due to the dissociation of the active dimers into inactive monomers (Orosz et al., 1999), or aberrant dimerization (Orosz et al., 2009), and these changes could play a crucial role in the etiology of the illness. The heteroassociations with different cellular structures, such as microtubules in neurons, result in alterations in the catalytic and regulatory properties of the enzymes (Ovadi et al., 2004). Finally, another possible theory is the fact that a perturbation of the conserved network of buried water molecules that bridge the two subunits appears to be essential to maintain the stability of TPI dimers (Rodríguez-Almazán et al., 2008).

Bioinformatic analysis, based on the 3D structure of the wild-type enzyme, was used by Schneider (2000) to explain the structural and catalytic properties of the mutant enzymes observed in the patient's hemolysates. They mapped the amino acid residues, as well as the first and second degree contacts of all the residues comprising each of three functional domains of TPI substrate binding, flexible loop and dimer interface domains (Schneider, 2000).

Susan Hollán (1993) reported a very interesting case in a Hungarian family with two germ-line identical but phenotypically different heterozygote brothers who inherited two independent mutations in TPI enzyme, Phe240Leu and Glu145stop codon (Hollán et al., 1993). The activity of TPI was dramatically reduced in both brothers, resulting in 40-60-fold higher DHAP concentration in their erythrocytes as compared with normal controls (Eber et al., 1991; Valentin et al., 2000). However, only the younger sibling (affected brother) manifests neurological disorders. This fact may provide key information about the etiology of neurodegenerative symptoms associated with TPI deficiency. Some of the features that are only present on the neurological affected brother are:

i) A decrease in membrane plasmalogen and changes of membrane reactivity and fluidity, enzyme activities, signal transduction and sensitivity towards oxidative stress.

ii) Imbalance of the prooxidant/antioxidant homeostasis, highly related with neurodegeneration

iii) An increase in the expression of endothelial NOS and a decrease in POP (prolyl-oligopeptidase). High NO production is responsible for the broad protein nitrotyrosination (Coma et al., 2005) while POP plays a key role in neurotransmission and intracellular protein degradation, and its reduction contributes to the development of neurodegeneration (Ahmed et al., 2003; Orosz et al., 2006).

DHAP increase and its consequences

The most important biochemical feature of TPI deficiency seems to be the dramatic increase in the cellular concentration of DHAP (20-60 fold) overall in erythrocytes. DHAP is involved in lipid metabolism, and its accumulation provokes a disturbance in the lipid balance. The levels of plasmalogen, an ether lipid, are reduced in TPI deficiency, and as a consequence, the protection against oxidative stress related to this lipid is impaired.

On the other hand DHAP is decomposed by non-enzymatical reaction to MG, a highly reactive glycating agent which is responsible for protein glycation and a precursor of advanced glycation end-products (AGEs). MG is toxic to neurons and may contribute to AD progression (Kikuchi et al., 1999; Orosz et al., 2006). Under oxidative stress conditions glyoxalases cannot efficiently detoxify MG, which may underlie the associated neurodegeneration (Ahmed et al., 2003; Fig. 3).

TPI and Alzheimer's disease

The nitration of tyrosines occurs in young and aged individuals, but it is increased in the latter. Certain levels of nitrotyrosination can be managed by the organism eliminating the damaged proteins, but when the process is accelerated it represents a pathological event that is associated with neurodegenerative diseases, in particular with AD (Smith et al., 1997). Specifically, $O_2^{\cdot-}$ superoxide anion, produced by Aß cell damage, and NO, whose production is altered in AD, react to form the highly reactive peroxynitrite anion, which generates cytotoxic species that oxidize and nitrate proteins (Castegna et al., 2003; Guix et al., 2005).

Glucose is the primary source of energy for the brain, and the interruption of glycolysis causes brain dysfunction and memory loss, favoring neuro-degeneration. In fact, inefficient glucose metabolism is characteristic in AD (Hoyer, 1996). A plausible explanation is that TPI is one of the proteins most nitrotyrosinated in AD (Coma et al., 2005; Butterfield et al., 2006b, 2007) and when nitrotyrosinated it decreases TPI isomerase activity, reducing the glycolytic flow, and increasing MG production (Guix et al., 2009). The relevance of nitrotyrosination in this effect was shown

when TPI was mutated at Tyr164 and Tyr208 by Phe, mimicking TPI nitrotyrosination, and producing similar results (Guix et al., 2009).

Since a lower amount of pyruvate would be available for neurons, mitochondrial activity can be decreased. There are no works addressing this scenario, but a lower acetyl-CoA bioavailability can be expected, and one of the consequences could be related with a decreased production of acetylcholine (ACh), contributing to the characteristic cholinergic deficit in AD (Schliebs and Arendt, 2011).

Moreover, TPI nitrotyrosination as well as TPI mutations induce the aggregation of the enzyme, forming several ß-strands (Rice et al., 1990), a process likely favored by its homology in the sequence with the Aß peptide (Contreras et al., 1999). The presence of intracellular nitro-TPI aggregates into ß-sheets was demonstrated in immunoprecipitated samples from AD cortex (Guix et al., 2009). Interestingly, TPI from subjects with heterozygote variants of mutated enzyme, bound more strongly to microtubules than TPI from normal controls. The mutation in the enzyme could lead to aberrant protein-protein interaction (Ovadi et al., 2004), affecting the trafficking machinery of the cell (Bonnet et al., 2004). In the same direction, nitrotyrosinated TPI aggregates are able to bind tau protein, a microtubule associated protein, inducing a conformational change in tau that precipitates paired helical filament formation, the other hallmark of AD (Guix et al., 2009; Fig. 5). It would link the effects of Aß oligomers and fibrils with the characteristic intraneuronal tau aggregation and neurodegeneration (Fig. 6).

Conclusions

The nitrotyrosination of the enzyme TPI by Aß aggregates seems to be critical in AD neurodegeneration. Nitro-TPI decreases G3P bioavailability that will affect all cellular functions. Moreover, it produces toxic MG, damaging proteins irreversibly. Besides this metabolic and toxic effect, nitro-TPI can induce the aggregation of tau protein, disassembling the neuronal cytoskeleton and avoiding normal intracellular trafficking and the intercommunication of the neurons.

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