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Role of Mitochondria in Alzheimer´s Disease

Genaro Genaro Gabriel Ortiz[1,2] et al. *
[1]*Lab. Estrés Oxidativo-Mitocondria & Enfermedad. Centro de Investigación Biomédica de Occidente (CIBO). Instituto mexicano del seguro Social (IMSS). Guadalajara, Jalisco,*
[2]*División de Ciencias de la Salud-Escuela de Medicina, Tecnológico de Monterrey, Campus Guadalajara. Zapopan, Jalisco,*
México

1. Introduction

Alzheimer's disease is the most common neurodegenerative disorder worldwide characterized by considerable atrophy and an enlargement and coarsening of the sulci, β-amyloid formation in neuritic plaques and brain vessels (amyloid angiopathy), neurofibrillary tangles, and neuronal loss, particularly in the limbic and association cortices. In addition, deficits in cholinergic transmission and associated loss of cholinergic cell bodies, granulovacuolar degeneration and rod-shaped eosinophilic inclusions (Hirano bodies) are common in Alzheimer's disease patients. Clinical symptoms are characterized by progressive worsening of memory, and cognitive impairment accompanied by one of the following symptoms: aphasia, apraxia, agnosia and disorders in the executive function (Selkoe, 2004).

The pathophysiological mechanisms that underlie the neurodegenerative characteristic of Alzheimer's disease are yet to be completely understood, although many factors in disease pathogenesis have been identified, and several theories are emerged. In the last years, mitochondrial dysfunction has been considered as a potential factor implicated at some stage of the pathogenic process (Anandatheerthavarada et al., 2003; Sullivan & Brown, 2005;

*Fermín Pacheco-Moisés[3], José de Jesús García-Trejo[4], Roció E. González-Castañeda[5], Miguel A. Macías-Islas[6], José A. Cruz-Ramos[1], Irma E. Velázquez-Brizuela[1], Elva D. Árias Merino[7] and Alfredo Célis de la Rosa[7]
[1]*Lab. Estrés Oxidativo-Mitocondria & Enfermedad. Centro de Investigación Biomédica de Occidente (CIBO). Instituto mexicano del seguro Social (IMSS). Guadalajara, Jalisco, Mexico*
[2]*División de Ciencias de la Salud-Escuela de Medicina, Tecnológico de Monterrey, Campus Guadalajara. Zapopan, Jalisco, México. Mexico*
[3]*Departamento de Química. Centro Universitario de Ciencias Exactas e Ingenierías. Universidad de Guadalajara. Guadalajara, Jalisco, Mexico*
[4]*Departamento de Biología. Facultad de Química. Universidad Nacional Autónoma de México, Mexico*
[5]*Departamento de Neurociencias. Centro Universitario de Ciencias de la Salud. Universidad de Guadalajara. Guadalajara, Jalisco, Mexico*
[6]*Departamento de Neurología. Unidad Médica de Alta Especialidad. Hospital de Especialidades-Centro Médico Nacional de Occidente. IMSS. Guadalajara, Jalisco, Mexico*
[7]*Departamento de Salud Pública. Centro Universitario de Ciencias de la Salud. Universidad de Guadalajara. Guadalajara, Jalisco, Mexico*

Atamna & Frey, 2007: Wang et al., 2008). As essential role players in cellular metabolism, mitochondria are pertinent to cell survival and thus any deviation from their operation is undoubtedly serious. Almost all aspects of mitochondrial function are altered in Alzheimer neurons; particularly it has been reported defects in oxidative phosphorylation (Chandrasekaran et al., 1996; Manczak et al., 2004; Schagger & Ohm, 1995) and both inherited and somatic mitochondrial DNA mutations in certain AD cases (Coskun et al., 2004; Qiu et al., 2001). In addition, changes in the redox status and membrane fluidity have been largely documented in brain and platelets (Mecocci et al., 1996; Zubenko et al., 1999; Mosconi et al., 2008; Ortiz et al., 2008; Su et al., 2008). The extent to which these changes in mitochondrial function represent primary or secondary components of the pathophysiological process are essential in order to understand the basic pathways that lead to the progress of disease. At this regard it has been shown that neurons are particularly vulnerable to any abnormalities of mitochondrial functioning, due to their large energy demand for their survival and specialized function. In this review we will describe the body of evidence supporting the role of mitochondria in the pathogenesis of Alzheimer's disease and discuss mitochondrial alterations in platelets from AD patients, particularly, mitochondrial enzymatic activities and membrane fluidity.

2. Mitochondrial function

2.1 ATP synthesis

Mitochondria are the major site of adenosine triphosphate (ATP) synthesis in most cells by the processes of oxidative phosphorylation. Mitochondria also mediate amino acid biosynthesis, fatty acid oxidation, steroid metabolism, calcium homeostasis, and reactive oxygen species production and detoxification. They synthesize amino acids, pyrimidines, lipids, heme, hormones and other metabolites. Each mitochondrion consists of four main compartments, including the outer membrane, the inner membrane, the inter-membranous space, and the matrix. The outer membrane encloses the entire organelle and is relatively porous, allowing the passage of small molecules. The inner mitochondrial membrane is characterized by a series of complex folds and tubules called cristae, which contain a variety of the enzymes, including those responsible for making ATP, is largely impermeant and forms the major barrier between the cytosol and the mitochondrial matrix. The space between the two membranes is referred to as the intermembrane space. The five complexes of the respiratory chain, complex I (NADH ubiquinone oxidoreductase), complex II (succinate ubiquinone oxidoreductase), complex III (ubiquinone-cytochrome c reductase), complex IV (cytochrome oxidase), and complex V (ATP synthase) are embedded in the inner mitochondrial membrane. The transfer of electrons along the respiratory chain provides the energy to pump protons from the matrix into the intermembrane space, generating the electrochemical gradient required to drive ATP synthesis (Hatefi, 1986).

ATP synthase is an enzyme that works as a rotary motor to carry out ATP synthesis by using Mg^{2+}-ADP complex, inorganic phosphate and a proton electrochemical gradient across energy-transducing membranes. It is composed by two main sectors: F0, a membrane-embedded proton-translocating sector that contains up to 10 different subunits and F1, a soluble catalytic sector comprising five different subunits that is bound through two stalks to F0. The coupling between F1 and F0 is critical for efficient ATP synthesis to occur and a large body of evidence shows that F1 andF0 are structurally and functionally coupled through two stalks. The central stalk forms part of the rotor of the enzyme, and the

peripheral stalk is part of the stator that anchors the catalytic sites of F1 to the membrane. The central rotor actually gyrates relative to a stator that holds the catalytic subunits; this rotation induces the alternating binding, catalysis, and product release from three catalytic sites of F1 (Noji & Yoshida, 2001).

Because of thermodynamic and mechanical reversibility, the ATP synthase also hydrolyzes ATP under conditions of partial or total collapse of the proton gradient in all energy-transducing systems. Thus, different subunits and mechanisms have emerged in nature to control the intrinsic rotation of the enzyme to favor the ATP synthase activity over its opposite and commonly wasteful ATPase turnover. A key regulatory subunit of ATP synthase is the mitochondrial inhibitor protein (IF1). Since its first isolation in 1963 (Pullman & Monroy, 1963), this protein was shown to inhibit the hydrolytic activity of the catalytic F1 sector. This protein is therefore crucial to prevent the hydrolysis of newly synthesized ATP in conditions of low membrane potential in mitochondria. Upon membrane energization, IF1 is believed to be relocated from its inhibitory site into an unknown position within (Dreyfus et al., 1981; Sanchez-Bustamante et al., 1982) or outside the F1F0 complex (Schwerzmann & Pedersen 1981; Power et al., 1983), therefore allowing ATP synthesis to occur. In de-energized or uncoupled conditions, IF1 is productively associated with the enzyme, inhibiting the ATPase turnover of the F1I or F1F0I complexes. However, this protein allows the rotational ATP synthesis turnover during energization of mitochondrial membranes. Therefore, IF1 is an important physiological regulator of the functioning of the ATP synthase. Recently, it has been shown that IF1 also contributes to stabilize dimeric and oligomeric forms of the mitochondrial ATP synthase that promote formation of mitochondrial cristae (Minauro-Sanmiguel et al., 2005; García et al., 2006; Campanella et al., 2008), thus adding a further key role of IF1 and dimeric F1F0 in the whole mitochondrial biogenesis (reviewed in García-Trejo & Morales-Ríos, 2008).

2.2 Mitochondrial dynamics

Mitochondrial dynamics implies that mitochondria continuously undergo fission and fusion to generate smaller organelles or elongated, tubular structures, respectively. Thus, mitochondria are not static organelles, but are dynamic bodies that constantly divide and fuse within the cell as the environment demands (Chan, 2006). These processes can facilitate formation of new mitochondria, repair of defective mitochondrial DNA through mixing, and redistribution of mitochondria to sites requiring high-energy production (Frederick & Shaw, 2007; Knott et al., 2008). Both processes effectively lower the percentage of defective mitochondria in the cell and ensure stability in cellular proliferation; indeed, metabolism, energy production, calcium signaling, reactive oxidative species production, apoptosis and senescence all depend on the balance of fission and fusion. Conversely, dynamic distortion (i.e., excessive fragmentation/elongation) results in inefficiencies in cell functioning, if not cell death (Parone et al., 2008; Wang et al., 2009; Chen et al., 2005).

Mitochondrial dynamics is a tightly regulated cellular process, with dedicated molecular machinery involving GTPases. Fission is regulated by at least two proteins: a large GTPase, dynamin-like protein 1, and a small molecule, Fis1, and fusion involves three large mitochondrial transmembrane proteins localized to the outer membrane: mitofusin 1, mitofusin 2, and optic atrophy protein 1 (Chan, 2006; Knott et al., 2008).

Mitochondria structurally abnormal have been reported in Alzheimer´s disease brains, for instance significant alterations in mitochondrial cristae (Hirai et al., 2001), the accumulation of osmiophylic material and significant decreases in mitochondrial size are found

predominantly in neurons (Baloyannis, 2006). In addition, mitochondria are redistributed away of axons in the pyramidal (Wang et al., 2009). Electron-microscopic studies have showed an increase in mitochondrial fragmentation in human AD brains (Balayonnis, 2006; Wang et al., 2009). In cell-based experiments, β-amyloidproduction resulted in the appearance of fragmented and abnormally distributed mitochondria (Barsoum et al., 2006; Wang et al., 2008). The dynamic balance of fission and fusion in AD is greatly shifted toward fission, and, as a result, affected neurons contain abnormal mitochondria that are unable to meet the metabolic demands of the cell. Moreover, mitochondrial distribution in AD cells is perinuclear, with few metabolic organelles in the distal processes, where they are normally distributed in healthy cells and are needed for exocytosis, ion channel pumps, synaptic function and other activities.

2.3 Energetic impairment in AD brains

Normal synapse function requires concerted activity of a multitude of metabolic pathways, including the generation of gene products involved in membrane complex formation and maintenance; mitochondrial RNA, protein, and neurotransmitter synthesis and delivery; and most importantly, the maintenance of ion gradients across the plasma membranes, as they are critical for the generation of action potentials. These actions can only be performed efficiently when sufficient energetic substrates are supplied. Glucose metabolism in the brain provides about 95% of the energy required under normal circumstances, with fatty acids only making a minor contribution. This intense demand for energy is continual, even brief periods of oxygen or glucose deprivation result in neuronal death. However, in spite of this high energy requirement, the brain is rather uncompromising in its ability to utilize substrates for energy production (Costantini et al., 2008).

Early evidence for altered glucose metabolism in AD brain comes from *in vivo* fluorodeoxyglucose positron emission tomography measurements of the cerebral metabolic rate for glucose (de Leon et al., 1983). This change in glucose utilization is linked to cognitive performance (Constantini et al., 2008). Reductions up to 45% in cerebral glucose utilization in AD patients have been reported (Ishii K et al., 1997). Other studies have reported low brain's glucose consumption rate in hippocampal and entorhinal cortical regions (Swerdlow, 2007). The posterior cingulate cortex and the neighboring precuneus are metabolically affected in the earliest clinical and preclinical stages of AD and the primary visual cortex is relatively spared (Minoshima et al., 1997; Reiman et al., 1996). That reduction in glucose metabolism is the result of both decreased glucose transport (because of a decrease in the number of synapses) and a decrease in the number of neurons. Therefore, the decreased cerebral metabolism is a true loss of neurons and synapses rather than simply the decreased glucose metabolism expected from a smaller volume of tissue seen in patients with atrophy [Bokde, 2001; Ibanez et al., 1998)]. In addition, in alzheimer´s disease there is a generalized shift from glycolytic energy production toward use of an alternative fuel, ketone bodies. Patients with incipient alzheimer´s disease exhibit a utilization ratio of 2:1 glucose to ketone bodies, whereas comparably aged controls exhibit a ratio of 29:1, whereas young controls exclusively use glucose with a ratio of 100:0 (Hoyer, 1991). On the other hand, *in vitro* analyses of AD autopsy brain show reductions in glycolysis (Swerdlow & Kish, 2002). These findings have been consistently reproduced by a multitude of studies and this pattern of hypometabolism is therefore now widely accepted as a reliable *in vivo* hallmark of Alzheimer's disease, and accurately distinguishes AD from normal aging.

The defects in glucose utilization suggest possible abnormalities in mitochondrial function. In support of this view, a range of reports have shown altered mitochondrial properties in Alzheimer's disease, in particular, the energy extracting mechanisms of the mitochondria. For instance, the temporal and parietal cortical zones consistently exhibits abnormally high oxygen utilization in comparison to the amounts of glucose utilized, and reduced phosphocreatine levels, indicating impairment of the oxidative phosphorylation process in the mitochondria (Benson et al., 1981; Phelps et al., 1982; Friedland et al., 1983 Pettegrew et al, 1994). In addition, AD brain biopsies demonstrated mitochondrial uncoupling, a non-specific abnormality indicative of an impairment in conversion of ADP to ATP (Sims et al., 1987). Interestingly the abnormalities in cerebral metabolism precede the onset of neurological dysfunction as well as gross neuropathology of AD.

In vitro analyses of AD autopsy brain studies have shown that the most consistent defect in mitochondria in AD are the reductions in maximal activities of several key enzymes responsible for oxidative metabolism, including α-ketoglutarate dehydrogenase complex, isocitrate dehydrogenase, and pyruvate dehydrogenase complex, two enzymes involved in the rate-limiting step of tricarboxylic acid cycle (Parker et al., 1994; Gibson et al., 1998; Nagy et al., 1999; Swerdlow & Kish, 2002). In addition, studies have shown reduced cytochrome oxidase activity, the terminal enzyme in the electron transfer chain that is responsible for reducing molecular oxygen (Parker et al., 1994; Gibson et al., 1998; Maurer et al., 2000; Bosetti et al., 2002; Swerdlow & Kish, 2002).

Reductions in maximal activity of cytochrome c oxidase have been reported in several areas of the brain. For instance, it has been found that AD cases had lower cytochrome c oxidase activity than controls in the posterior cingulate cortex. That reduction was significantly greater than that in primary motor cortex (Valla et al., 2001). However, it is unclear to what extent maximal activity reduction reflects reduced COX enzyme expression or a structural change in the enzyme. Numerous studies have linked abnormal mitochondrial protein function to the altered neuronal expression of nuclear and mitochondrial genes encoding subunits of the mitochondrial electron transfer chain. Liang and collaborators (2008) showed that compared to controls, AD cases had the largest proportion (70 percent) of underexpressed genes comprising the nuclear genes encoding for subunits of the mitochondrial electron transfer chain complexes and translocases of the inner and outer mitochondrial membranes in the posterior cingulated cortex, a brain region which positron emission tomography studies found to be metabolically affected in the earliest stages of AD. The visual cortex, on the other hand, a brain region relatively spared in AD, contained significantly less underexpressed genes than the posterior cingulate cortices.

Interestingly, Reddy and Beal (2008) found mitochondrial genes in the NADH ubiquinone oxidoreductase of oxidative phosphorylation system to be downregulated in both early and definite AD brains, whereas complexes ubiquinone-cytochrome c reductase and cytochrome c oxidase showed increased mitochondrial RNA expressions. Several other studies have also reported this phenomenon (Hirai et al., 2001; Strazielle et al., 2003; Manczak et al., 2004; Reddy et al., 2004), which could be interpreted as a compensatory mechanism for the decreased cytochrome c oxidase function and the consequent increase in demand on energy production. As spectral analysis of the enzyme has indicated that cytochrome c oxidase is kinetically altered in AD and lacks one of its two substrate binding sites (Parker & Parks, 1995), altogether the data would imply that cytochrome c oxidase activity is reduced not because the quantity is decreased as a result of down-regulated gene expression, but

because in AD, the enzyme is structurally different from that in controls. However, other studies have shown that cytochrome oxidase activity is reduced as a result of decreased mitochondrial RNA expression. Several studies demonstrated decreased mitochondrial RNA expression in NADH ubiquinone oxidoreductase and cytochrome c oxidase (Chandrasekaran et al., 1994, 1996, 1997) and decreased mRNA expression of nuclear-encoded mitochondrial genes in complexes cytochrome c oxidase and ATP synthase in brains of AD patients (Chandrasekaran et al., 1994, 1997; Simonian & Hyman, 1994). Clearly, at this point, it cannot be said whether reduced mitochondrial RNA expression, altered enzyme kinetics or both, contribute to reduced cytochrome c oxidase function in AD. Some studies suggest that mitochondrial DNA and mitochondrial number increase in AD, which would indicate altered cytochrome c oxidase kinetics, while others suggest that mitochondrial DNA and mitochondrial number decline, proposing reduced cytochrome c oxidase expression (De la Monte et al., 2000; Hirai et al., 2001; Baloyannis, 2006). Other studies have reported lowered biosynthesis of beta subunit of the ATP synthase, in the hippocampus and the ubiquinone-cytochrome c reductase core protein 1, respectively (Kim et al., 2000). How these changes in mitochondrial enzymes would translate into loss of specific neuronal populations, including cholinergic neurons in the forebrain, hippocampus, and neocortex is unclear. One possibility is that as yet unknown factors cause an imbalance that favours the generation of reactive oxygen species.

2.4 Mitochondria and oxidative stress

Oxidative stress is a relative increase in the ratio of free radicals to antioxidants. This may originate from an overproduction of reactive oxygen species or from a reduction in antioxidant capacity. Indeed, the activities of the antioxidant enzymes superoxide dismutase and catalase are significantly decreased in the frontal and temporal cortex of AD patients (Marcus et al., 1998). Not only that, antioxidant enzyme activity was shown to be spatially correlated with markers of lipid peroxidation (i.e. oxidative damage) and the brain areas particularly affected by neuronal loss in AD (Takeda et al., 2000). However, increased antioxidant activity in AD brains in response to increased free radical generation has also been reported (Lovell et al., 1995; Lu et al., 2004; Moreira et al., 2009). Thus, one explanation for the studies showing a lack of correlation between impaired mitochondrial function and oxidative stress is that in some AD cases, antioxidant defenses are able to counteract oxidative stress damage, whilst in others they cannot. However, this would automatically mean that in the AD cases with no oxidative stress, other impaired mechanisms must be causing AD.

Some studies show that brain tissue is especially vulnerable to oxidative attack due to its relatively low antioxidant capacity, high consumption of oxygen, high content of polyunsaturated fatty acids, and high content of redox-active transition metals such as iron (Butterfield et al., 2007). Iron can contribute to free radical damage by catalyzing the formation of the hydroxyl radical, inducing secondary initiation of lipid peroxidation and by promoting the oxidation of proteins. The increase in brain iron associated with several neurodegenerative diseases may lead to an increased production of free radicals via the Fenton reaction. Depending on the substrate attacked by the reactive oxygen species, oxidative damage will manifest as protein oxidation, DNA oxidation, or lipid peroxidation products.

Mitochondria are the primary source of cellular oxidants, taking into account that about 2–5% of molecular oxygen is not completely reduced to water at the electron transport chain and, therefore, a prime target of cumulative oxidative damage. Damage to mitochondrial proteins and mitocondrial DNA would be expected to decrease mitochondrial bioenergetics and efficiency (The underlying mechanism of abnormal mitochondrial reactive oxygen species production is the altered redox potential of mitochondrial respiratory chain carriers (due to hyperpolarization of mitochondrial membrane) and an increase in ubisemiquinone anion half-life time, resulting in slower electron transport, producing intermediates that stay reduced longer, thus increasing the chance that the electrons can escape to molecular oxygen, originating the reactive oxygen species (Sullivan & Brown 2005). Ultimately, ATP depletion will lead to necrotic cell death. Other forms of mitochondrial injury may lead to the release of pro-apoptotic factors, particularly of mitochondrial cytochrome c and the initiation of the cascade to apoptotic cell death.

2.5 Studies on platelets

The hypothesis that Alzheimer disease pathology is not brain-limited has led researchers to look for peripheral cells that may harbour changes related to this disease. On one such cell, the platelet, have the following similarities with neurons: 1) contain the amyloid precursor protein and secrete β-amyloid peptide (Di Luca et al., 2000; Sanchez-Gonzalez et al., 2006) 2) express neurotransmitters and some neuron-related proteins, such as NMDA receptors (Dreux & Launay, 1985). Interestingly, several of the enzymatic defects observed in AD brain are also found in noncerebral tissues. In addition, biochemical markers are likely to be important in the study of Alzheimer disease for several reasons. A clinical diagnosis of Alzheimer disease is inaccurate even among experienced investigators in about 10% to 15% of cases, and biomarkers might improve the accuracy of diagnosis. Importantly for the development of putative disease-modifying drugs for Alzheimer disease, biomarkers might also serve as indirect measures of disease severity. Usually biomarkers are assessed in different compartments including cerebrospinal fluid, skin fibroblasts, lymphocytes, blood and urine.

In our group of work we are analyzed platelets from Alzheimer disease patients and healthy subjects. Diagnosis of AD was made by using the: 1) mini mental state evaluation 2) Diagnostic and Statistical Manual of Mental Disorders-IV criteria for dementia and 3) National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for diagnosis of probable dementia of Alzheimer type. Healthy control subjects were free of AD or any other disorder.

2.5.1 ATP synthase and cytochrome c oxidase

To obtain direct evidence that mitochondrial functioning is altered in AD patients; we made measurements of the rate of the hydrolytic activity of ATP synthase and pH gradient driven by ATP hydrolysis, using platelet submitochondrial particles. The hydrolytic activity of ATP synthase in patients with probable AD was 41.7 ± 4.3 nmol min^{-1} (mg protein)$^{-1}$, n =29, whereas in the control subjects was 29.1 ± 1.9 nmol nmol min^{-1} (mg protein)$^{-1}$, n = 29. It is important to note that, in the male population with probable AD, we found that hydrolytic activity of ATP synthase increased as cerebral deterioration progressed. That increase in the hydrolytic activity of ATP synthase was statistically significant. Therefore, we made measurements of the pH gradient driven by ATP hydrolysis determined from the

quenching of ACMA fluorescence induced upon 2 mM ATP addition. pH gradient was used as an indication of the enzyme proton channel function and of coupling between transport and catalysis. Data obtained showed a lower pH gradient in the submitochondrial particles of patients with probable AD (0.28 ± 0.08 pH units, n = 25) as compared to the controls (0.5 ± 0.1 pH units, n = 20). This suggests a functional alteration of the ATP synthase. In addition, proton gradient was completely abolished when 1 μM oligomycin was added to the submitochondrial particles. This indicates that the pH gradient was in fact due to the ATP-driven proton translocation through the membrane and that the proton transport activity of the enzyme from AD patients is as sensitive to the inhibitor as the control group (Martínez-Cano et al., 2004).

Functional impairment of mitochondrial ATP synthase can be explained by the following phenomena: If F0 and F1 sectors of the enzyme are separated by physical or kinetic decoupling; for an altered assembly of the regulatory subunits of the enzyme, in particular of the inhibitor protein IF1. Therefore, we made semi quantitative determinations of the inhibitor protein, IF1 in submitochondrial particles of platelets. Densitometric analyses of Western blot experiments indicated a 2-fold decrease of the relative content of the mitochondrial inhibitor protein (IF1) of the ATP synthase in platelets from AD samples compared to control subjects (Figure 1).

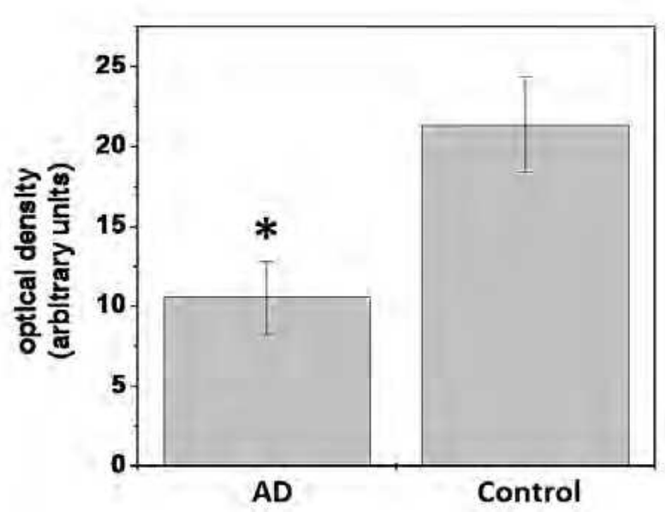

Fig. 1. Densitometric analyses of inhibitor protein IF1 in Alzheimer disease patients and control subjects. Statistical significance was assessed by Dunnett's test. *P<0.05 vs control group.

In order to assay the functional association of inhibitor protein IF1 with the ATP synthase in submitochondrial particles from Alzheimer and control group's samples, ATPase activity assays were carried out. Submitochondrial particles were incubated in conditions that induce a progressive release of IF1 to the media, i.e., pH 8.0, KCl 100 mM, and 40 °C. Additional experiments were conducted under conditions that favour the binding of the protein inhibitor of ATP synthase (sucrose medium). Figure 2 shows that the hydrolytic activity of ATP synthase of Alzheimer samples was unaffected by the medium of determination. In contrast, the activity of control samples was increased in a medium with KCl, i.e., in conditions that favours the disotiation of inhibitor protein IF1. Also note that the

hydrolytic activity of the ATP synthase of the control samples, in a medium with KCl, did not reach the values of activity of samples from patients with AD, in the same medium. Taken together, these results suggest that that increased hydrolytic activity in patients with AD is partly due to a lower content of the inhibitor protein, IF1.

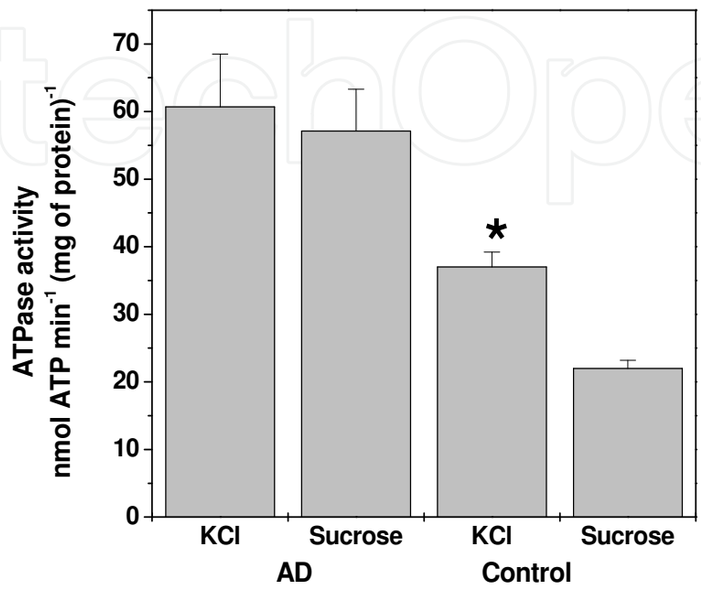

Fig. 2. Hydrolytic activity of ATP synthase in Alzheimer disease and control samples. Enzymatic activity was done at 40 °C, using a potassium chloride or sucrose medium of reaction. Data were subjected to an analysis of variance, and significant differences were assessed by Dunnett's test with $P < 0.05$ for comparison with the sucrose medium.

To our knowledge the hydrolytic activity of ATP synthase in patients with AD has been controversial since it has been reported that ATP hydrolysis activity in platelets was similar in patients with AD and controls (Boseti et al., 2002). Other authors reported a slightly increased in the frontal and occipital brain of AD. These data do not correlate with a 50-60% decrease in the level of mRNA encoding the β subunit of ATP synthase in the temporal cortex of AD patients (Chandrasekaran et al., 1996) or with the reduced amount of ATP synthase in the hippocampus of AD patients (Schagger & Ohm, 1995). Although it is unknown whether the deficiency of mitochondrial enzymes is a cause or an effect of Alzheimer disease, it has been speculated that can be a normal physiological response to a reduction in energy demand in the brains of patients (Jung et al, 2000; Chandrasekaran et al., 1996). So, the functional alterations in key enzymes of mitochondrial metabolism such as ATP synthase, can lead to a decrease in energy generation and can contribute to the neurodegenerative process. Thus, a reduction in cellular ATP concentration can activate specific protein kinases that phosphorylate tau protein, leading to the formation of neurofibrillary tangles (Stanley et al., 1996), and may cause increased susceptibility of neurons to excitatory amino acids, leading to neuronal degeneration by an excitotoxic process (Roder et al., 1993). On the other hand, mitochondrial dysfunction characterized by a combined deficiency of ATP synthase and cytochrome c oxidase can lead to the generation of free radicals that can damage proteins, nucleic acids and membranes and contribute to

aggregation and plaque deposition of β-amyloid and neurofibrillary tangles formation (Beal, 1992; Troncoso et al., 1993).

By restriction analysis we identified the pathogenic mutation of the mitochondrial DNA in the gene encoding the subunit 6 of the ATP synthase. That mutations is T8993G converting the highly conserved leucine to arginine in a transmembrane helix. The mutation causes a severe impairment in the vectorial proton flow through F0 (García et al., 2000) and instability of the monomeric and dimeric forms of the ATP synthase without altering assembly or dimerization of the enzyme (Cortés-Hernández et al., 2007).

On the other hand several mutations in cytochrome c oxidase II gene have been previously described. Sequence chromatogram of mitochondrial cytochrome c oxidase II gene obtained from blood samples of our population revealed that four patients with probable Alzheimer´s disease had a point mutation A8027G (3 of them were identified as early onset, with familial history of the disease). Other four patients with early onset have the following mutations: A8003C, T8082C, C8201T and G7933A, respectively. To our knowledge none of these mutations were found in other neurodegenerative diseases.

It could argue that the mutations found in this work modified the protein conformation, since the different physichochemical characteristics of replaced aminoacids. That conformational change could alter the electrons binding site or the electrons transfer and this contributes to a diminution in enzymatic activity. The diminished cytochrome c activity could cause a decrease in ATP synthesis and diversion of electrons from their normal pathway resulting in increasing in superoxid radical production. Thus, cytochrome oxidase alterations can lead to increased reactive oxygen species generation, oxidative damage to mitochondrial membranes, and increased vulnerability to excitotoxins, and may be important in the pathogenesis of Alzheimer´s disease.

2.5.2 Membrane fluidity

It has been reported that cells of Alzheimer´s disease brains have altered phospholipid metabolism (Blusztajn et al., 1990; Ellison et al., 1987; Klunk et al., 1998; Nitsch et al., 1992) and a diminished unesterified cholesterol:phospholipid mole ratio (Mason et al., 1992), leading to altered membrane fluidity (Mecocci et al., 1996). On the other hand, submitochondrial particles are mainly constituted of inner mitochondrial membrane and are the site of oxidative phosphorylation and other enzymatic systems involved in the transport and utilization of metabolites. Therefore we assessed the membrane fluidity in platelet submitochondrial particles and erythrocyte membranes from Mexican patients with Alzheimer disease. That estimate was achieved from the excimer to monomer fluorescence intensity ratio (Ie/Im) of the fluorescent probe 1,3 dipyrenylpropane incorporated in membranes. That probe at submicromolar concentrations forms intramolecular excimers and its formation in membranes depends mainly of the medium microviscosity and temperature of determination. This method is very simple and does not require higher concentrations of other fluorescent lipophilic probes such as 1,6-diphenyl-1,3,5-hexatriene and its cationic derivative trimethylamino-,6-diphenyl-1,3,5-hexatriene. Thus, the risk of perturbation of the phospholipid phase inherent in the use of all probe molecules is minimized. Intramolecular excimer formation of this probe is related with the membrane fluidity, such the excimer formation depicts mainly the lateral motion of the probe within the membrane (Jurado et al., 1991). The higher the values of the excimer to monomer ratio, the more fluid the membrane, while the lower the ratio, the more rigid the membrane.

Therefore that ratio is directly proportional to membrane fluidity, which is reciprocal to membrane viscosity.

Similarly to the data reported from mitochondria in AD brains fluidity (Mecocci et al., 1996), a reduced fluidity in the platelet inner mitochondrial membrane was found. It can partially be due to increased levels of lipid peroxidation. Reduced membrane fluidity can diminish the activities of the enzymes of oxidative phosphorylation and other transport and receptor proteins, inasmuch as these enzymes are regulated by the physicochemical state of the lipid environment of the membrane. It may diminish significantly the ATP generation from the mitochondria. Interestingly, dysfunctional mitochondria and oxidative damage has been involved in Alzheimer's disease (Bonilla et al., 1999). In agreement with previous reports, membrane fluidity from erythrocyte was not altered in AD (Hajimohammadreza et al., 1990), regardless of increased lipid oxidation in erythrocyte AD patients. This suggests that, in AD, mitochondrial membranes are more sensitive to oxidative stress than erythrocytes.

In contrast to platelet inner mitochondrial membrane, it has been reported an increase in fluidity in whole membranes from platelets of AD patients (Zubenko et al., 1999). This increase results from the elaboration of an internal membrane compartment resembling endoplasmic reticulum that is functionally abnormal (Zubenko et al., 1987). At this regard, it is worth noting that the contribution of mitochondrial membranes to the whole cell membranes in platelets could be minimized since platelets contain few mitochondria (Fukami & Salganicoff, 1973).

On the other hand, Morais Cardoso et al. (2004), using DPH and TMA-DPH as fluorescent probes, found similar fluidity in mitocondrial membranes in platelets from AD patients and controls. That discrepancy with our data may be due to intrinsic differences in the populations tested, the purity of the used mitochondrial fraction and the nature of the probes used. Additionally, it's clear that the lipophilic probes are sensitive to slightly different membrane properties. For instance, DPH and TMA-DPH are rotational probes (Ameloot et al., 1984) and dipyrenylpropane is a lateral diffusion sensitive probe (Zachariasse et al., 1982). In addition, DPH partitions into the interior of the bilayer and its average location has been shown to be about 8 Å from the center of the bilayer. TMA-DPH is oriented in the membrane bilayer with its positive charge localized at the lipid-water interface. Its DPH moiety is localized at about 11 Å from the center of the bilayer and reports the interfacial region of the membrane (Kaiser & London, 1998). Whereas dipyrenylpropane is a highly hydrophobic probe which partitions into the membrane lipid bilayer (Zachariasse et al., 1982). At the moment we do not know whether the diminished membrane fluidity in AD is etiologically significant or a minor result of neurodegeneration

2.5.3 Amyloid precursor protein

Amyloid precursor proteins are transmembrane proteins of about 100 to 130 KDa, located primarily on the cell surface as well as on the endoplasmic reticulum, Golgi apparatus, and endosomes. Amyloid precursor protein may play a role in neuronal trafficking, migration and development (Van Gassen et al., 2000). Although a clear function of amyloid precursor protein has yet to be identified, it is the biochemical pathway leading to β-amyloid generation that demonstrates its link to AD pathogenesis. Amyloid precursor protein is subject to cleavage by three proteases, α, β, and γ secretases through two primary pathways. The first pathway involves cleavage of amyloid precursor protein 12 residues N-terminal to the transmembrane sequence by a group of integral membrane enzymes. Termed α-secretase cleavage, this cut creates a large, ectodomain fragment that is released from the cell

surface as well asand a smaller C-terminal fragment (83 residues) attached to the membrane. Subsequent cleavage of this membrane-retained fragment by a unique complex of proteins, referred to as γ-secretase, releases a 3-kDa peptide unable to form amyloid fibrils. The second pathway involves an alternative cleavage by β-secretase, located at the N-terminus of the to *β*-amyloid sequence. This releases a unique ectodomain fragment and a C-terminal (C99) membrane-retained fragment. Then, cleavage of C99 by γ-secretase results in formation of to *β*-amyloid. The length of the C-terminal end of to *β*-amyloid varies depending on the specificity of γ-secretase cleavage, resulting in production of Aβ1-40 or a longer, more fibrillogenic *β*-amyloid 1-42/43 (Selkoe, 1998). The longer to *β*-amyloid peptide has a major role in to *β*-amyloid deposition because plaque formation follows a distinct pattern with the 42-43 amino acid peptide detected first followed by the more common to *β*-amyloid 1-40 (Lemere et al., 1996). The balance between α-secretase and β-secretase cleavage of amyloid precursor protein is important for to *β*-amyloid production and AD pathogenesis.

Western blotting experiments of amyloid precursor protein in platelets showed two main bands with molecular weights of 106 to 110 KDa and 130 KDa, respectively. The upper, 130 KDa, band corresponded to the full-length, mature of amyloid precursor protein. The lower, 106–110 KDa, band corresponded to the of amyloid precursor protein immature isoforms. The ratio of amyloid precursor protein isoforms between the 130 Kda amyloid precursor protein and 106–110 KDa amyloid precursor protein and odds ratios were obtained to determine risk factor of this component. Amyloid precursor protein ratio on AD subjects was lower than that of control subjects: 0.36 ± 0.18 vs. 0.67 ± 0.10, respectively. A low amyloid precursor protein ratio (< 0.6) showed an odds ratio of 4.63. When onset of disease was taken into account, an amyloid precursor protein ratio on early onset Alzheimer´s disease subjects of 0.39 ± 0.19 was found vs. 0.34 ± 0.19 on late onset Alzheimer´s disease subjects ($p > 0.05$). This suggests an increased degradation of amyloid precursor protein in AD platelets.

On the other hand we performed *ApoE* genotyping in AD platelets and controls. Data obtained showed that there was no association between amyloid precursor protein ratios and any specific ApoE allele (Sanchez-Gonzalez et al., 2006).

In concordance to previous studies, we observed a significant decreased amyloid precursor protein ratio on AD subjects as compared to that of control subjects (Utermann, 1987; Borroni et al., 2003). This means that an increased degradation of this precursor protein is being performed in peripheral tissues. Whether or not this phenomenon reflects a similar process occurring in the brain of AD subjects is still a matter of controversy. However, the existence of this phenomenon cannot be minimized, for processing and secretion of this precursor protein has been already demonstrated and its importance as a predictor for conversion to dementia of Alzheimer type in subjects with mild cognitive impairment has recently been proved (Borroni et al., 2003).

The precise mechanism of amelioration of amyloid precursor protein concentration is not deciphered yet. Modifications in the splicing mechanism, in the stability of messenger RNA encoding for amyloid precursor protein 751/770 or in the regulation of translation processes are some hypothesis (Di Luca et al., 1996). Our study is consistent with the results of Strittmatter et al., (1993) concerning an increased ApoE ε4 allele frequency in AD patients (Strittmatter & Saunders, 1993). A 4.5-times risk of presenting AD as related to the ApoE ε3/ε4 genotype and a 9.4-times risk related to the ε4 allele was also found. This is in accordance to studies published before showing an increased risk of presenting AD as

related to either ε4 heterozygocity or homozygocity (Amouyel et al., 1993; Anwar et al., 1993; Ben-Shlomo et al., 1993; Czech et al., 1993; Lucotte et al., 1993).

The coexistence of β-amyloid with the ApoE ε4 allele in the pathogenesis of AD has long been thought (Saunders et al., 1993) Increased risk of presenting AD in ApoE ε4 allele porters as well as augmented amyloid precursor protein degradation in platelets led us to consider the probability of relating both factors to determine a combined model for risk factor evaluation. We observed a 5-times risk of presenting the disease when both ε3/ε4 genotype and a low amyloid precursor protein ratio (taken as a ratio below (0.6) were stratified, and a 4-times risk with both the ε4/ε4 genotype and a low amyloid precursor protein ratio. These data confirms the relevance of peripheral amyloid precursor protein altered isoforms as an assessment of risk factor of the disease (Rosenberg et al., 1997). The stratified analysis helped us to exclude the effect of ApoE genotypes on the low amyloid precursor protein ratio. We observed no significant OR amelioration or increase of the low amyloid precursor protein ratio, thus strengthening the importance of a low amyloid precursor protein ratio in peripheral blood as an indicator of the disease.

3. Conclusion

Up to now several hypotheses about the complex etiology of Alzheimer´s disease have been proposed. According to the amyloid hypothesis, abnormal processing, and accelerated deposition of oligomeric forms of beta-amyloid are central mechanisms underlying pathological processes in Alzheimer disease. Although the amyloid hypothesis remains the main pathogenetic model of Alzheimer's disease, its role in the majority of sporadic Alzheimer cases is unclear. Therefore, other innovative proposals have been made in recent years, particularly the association of mitochondrial functional impairment in the development of the Alzheimer's disease. Immunohistochemical, biochemical, neuroimaging, electronic microscopy and molecular studies have demonstrated the existence of signs of mitochondrial impairment in Alzheimer´s disease brain. Interestingly, these changes are evident very early in Alzheimer disease progression. Current evidence shows that oxidative stress, mitochondrial impairment and altered mitochondrial dynamics contribute to the precipitation of Alzheimer´s disease pathology and thus cognitive decline.

On the other hand, using platelets as a model of study we found the following data: 1) an increased degradation of amyloid precursor protein; 2) an increased lipid oxidation products in mitochondria; 3) a dysfunction of mitochondrial ATP syntase; 4) lower levels of inhibitor protein (IF1) of ATP synthase; 5) reduce membrane fluidity in inner mitochondrial membrane; 6) point mutations of the mitochondrially encoded ATP synthase 6 and citochrome oxidase II genes.

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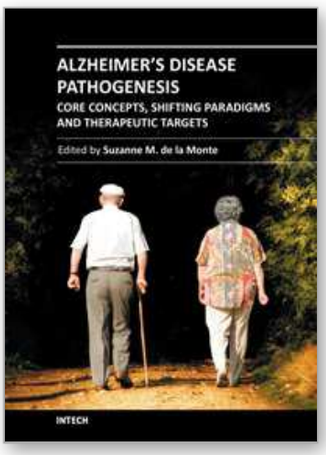

Alzheimer's Disease Pathogenesis-Core Concepts, Shifting Paradigms and Therapeutic Targets

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Alzheimer's Disease Pathogenesis: Core Concepts, Shifting Paradigms, and Therapeutic Targets, delivers the concepts embodied within its title. This exciting book presents the full array of theories about the causes of Alzheimer's, including fresh concepts that have gained ground among both professionals and the lay public. Acknowledged experts provide highly informative yet critical reviews of the factors that most likely contribute to Alzheimer's, including genetics, metabolic deficiencies, oxidative stress, and possibly environmental exposures. Evidence that Alzheimer's resembles a brain form of diabetes is discussed from different perspectives, ranging from disease mechanisms to therapeutics. This book is further energized by discussions of how neurotransmitter deficits, neuro-inflammation, and oxidative stress impair neuronal plasticity and contribute to Alzheimer's neurodegeneration. The diversity of topics presented in just the right depth will interest clinicians and researchers alike. This book inspires confidence that effective treatments could be developed based upon the expanding list of potential therapeutic targets.

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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