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Altered mitochondria, energy metabolism, voltage-dependent anion channel, and lipid rafts converge to exhaust neurons in Alzheimer's disease

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Abstract β-amyloid (Aβ) deposition, in the form of plaques and amyloid angiopathy, and hyper-phosphorylated tau deposition forming neurofibrillary tangles, dystrophic neurites around β-amyloid plaques and neuropil threads, are neuropathological hallmarks of Alzheimer's disease (AD) that accumulate in the brain with disease progression. These changes are accompanied by progressive loss of synapses and nerve cell death. Progressive cognitive impairment and dementia are the main neurological deficits. In addition, there is cumulative evidence demonstrating other metabolic disturbances that impair cell function and hamper neuron viability. The main components of the mitochondria are altered: complex IV of the respiratory chain is reduced; complex V which metabolizes ADP to form ATP is oxidatively damaged and functionally altered; and voltage-dependent anion channel VDAC, a major component of the outer mitochondrial membrane that regulates ion fluxes, is damaged as a result of oxidative stress. Mitochondria are a major source of reactive oxygen species that promote oxidative damage to DNA, RNA, proteins and lipids. Protein targets of oxidative damage are, among others, several enzymatic components of the glycolysis, lipid metabolism and cycle of the citric acid that fuel oxidative phosphorylation, mitochondrial respiration and energy production. The lipid composition of lipid rafts, key membrane specializations that facilitate the transfer of substrates, and protein-protein and lipid-protein interactions, is altered as a result of the abnormally low levels of n-3 long chain polyunsaturated fatty acids (mainly docosahexaenoic acid) that increase viscosity and augment energy consumption. Abnormal lipid raft composition may also modify the activity of key enzymes that modulate the cleavage of the amyloid precursor protein to form toxic Aβ. This is further complicated by the disruption of the complex VDAC with estrogen receptor α at the caveolae which participates, under physiological conditions, in the protection against β-amyloid. Together, all these alterations converge in reduced energy production and increased energy demands in altered cells. Cell exhaustion is suggested as being a determining element to interpret impaired neuron function, reduced molecular turnover, and enhanced cell death.

Keywords Alzheimer's disease · Mitochondria · Oxidative damage · Lipid rafts · Caveolae

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Alzheimer disease (AD)

AD is a neurodegenerative disease clinically characterized by cognitive decline and changes in behaviour and personality, eventually leading to severe dementia. The main pathologic hallmarks are the accumulation of the peptide β-amyloid (Aβ, mainly $A\beta_{1-42}$ and $A\beta_{1-40}$) in the form of extra-cellular senile plaques and amyloid angiopathy, and the presence of intracellular neurofibrillary tangles composed of the aggregation of paired helicoidal filaments of hyper-phosphorylated tau (Duyckaerts and Dickson 2003; Lowe et al. 2008). Hyper-phosphorylated tau is also found in neuropil threads and in dystrophic neurites surrounding senile plaques (Duyckaerts and Dickson 2003; Lowe et al.

2008). The distribution of tau lesions extends with time from the entorhinal and perirhinal cortex to the hippocampus, amygdala, Meynert nucleus, the whole neocortex and the brain stem, as well (Braak et al. 1999). Aggravating deposition of β-amyloid in the cerebral cortex and other brain regions also occurs with disease progression (Thal et al. 2002). There is a relation between the main pathological changes and neurological deficits. Early stages (stages I–III) are asymptomatic, and middle stages (IV and V) may manifest as mild cognitive impairment, whereas advanced stages (V and VI) are currently manifested as dementia. In addition to these cardinal features, other anomalies occur in AD including activation of astrocytes and microglia, loss of synapsis, and neuronal death (Duyckaerts and Dickson 2003; Lowe et al. 2008).

Recent studies have shown that energy production, handling of energy metabolism and membrane fluxes are actually failing in AD neurons, therefore hampering neuronal function and jeopardizing cell viability. Considering these aspects, β-amyloid and hyper-phosphorylated tau are only part of the complex alterations in AD, whereas neuronal dysfunction is probably linked to unrelated altered metabolic pathways. Crucial factors connected with the pathogenesis of AD which are relevant in the present context are mitochondrial function, oxidative stress and oxidative damage of selected proteins, as well as lipid rafts and caveolae.

Mitochondria

The production of ATP in eukaryotes is carried out in mitochondria fueled by products derived from fatty acids and glucose. The first step of glycolysis takes place in the cytosol leading to the production of a few molecules of ATP and pyruvate. The pyruvate is then transported to mitochondria and catalyzed to acetyl CoA by pyruvate dehydrogenase. Similarly, fatty acids are transformed into acyl CoA which is transferred to the mitochondria and ultimately metabolized to acetyl CoA. The oxidation of acetyl CoA through the citric acid cycle (Krebs cycle) generates CO_2 and reduced coenzymes like NADH, succinate and $FADH_2$. The oxidative phosphorylation and electron transport is carried out by the respiratory chain in the mitochondria composed of five adapted complexes, NADH ubiquinone reductase, succinate ubiquinone oxidoreductase, ubiquinol cytochrome c reductase, cytochrome c oxidase and ATP synthase, that lead to the production of ATP.

Mitochondrial function and mitochondrial turnover are altered in AD. Early electron microscopic studies showed accumulation of abnormal mitochondria in dystrophic neurites of senile plaques in AD (Kidd 1964; Luse and Smith 1964; Terry et al. 1964; Hirai et al. 2001). Recent ultrastructural analyses have also shown the presence of normal-shaped and degenerating mitochondria in dystrophic neurites surrounding β-amyloid plaques in aged rhesus monkeys (Fiala et al. 2007). Similar changes occur in dystrophic neurites in AD-related transgenic mice (Fig. 1). Decreased cytochrome c oxidase expression and activity occurs in brains in AD when compared with controls (Kish et al. 1992; Mutisya et al. 1994; Maurer et al. 2000; Blass 2000; Perez-Gracia et al. 2008). Combined immunohistochemical methods have shown that abnormal mitochondria in dystrophic neurites are impoverished in cytochrome c oxidase (Perez-Gracia et al. 2008). Mitochondrial damage and reduced cytochrome oxidase c expression and activity in dystrophic neurites suggest that β-amyloid may play a causative role in the process.

Indeed, several studies have demonstrated a direct deleterious effect of Aβ on mitochondrial structure and function. *In vitro* assays, using isolated rat mitochondria, have shown that Aβ inhibits cytochrome c oxidase, α-ketoglutarate dehydrogenase and pyruvate dehydrogenase activities (Casley et al. 2002). Moreover, dimeric synthetic $A\beta_{1-42}$, in the presence of Cu^{2+}, inhibits cytochrome c oxidase in human mitochondria (Crouch et al. 2005). Finally, addition of Aβ to mouse brain mitochochondria induces cytochrome c release and mitochondrial swelling (Kim et al. 2002). Furthermore, Aβ accumulates in mitochondria in AD neurons and affects the balance of fission/fusion and mitochondrial transport (Manczak et al. 2006; Devi et al. 2006; Wang et al. 2007; Vargas et al. 2008).

However, these observations do not exclude the possibility of a primary damage of mitochondria in AD, as abnormal expression of mitochondrial proteins and abnormal mitochondrial protein function have been observed before the appearance of β-amyloid plaques in AD-like transgenic mice (Gillardon et al. 2007).

As discussed below, Aβ may directly cause cell damage, but it may also increase the generation of reactive oxygen species (ROS) and ROS-mediated damage via mitochondrial dysfunction (Castellani et al. 2002; Zhu et al. 2006; Lin and Beal 2006).

Cells are prepared to get rid of altered organelles, and this is mainly conducted by autophagy. Early reports demonstrated accumulation of lysosomes in dystrophic neurites of senile plaques (Cataldo et al. 1995; Nixon et al. 2000). Recent studies have shown that mitochondria are one of the substrates of autophagy in dystrophic neurites, as lipoic acid, one component of mitochondria, localizes in autophagic vacuoles (Moreira et al. 2007b), and LAMP-1, a common marker of lysosomes, is highly expressed in dystrophic neurites of senile plaques and co-localizes with mitochondrial porin (Perez-Gracia et al. 2008). It is however intriguing why mitochondrial debris is retained

at the dystrophic neurites. One possibility could be an increased rate of altered mitochondrial genesis; another explanation involves impaired clearance of aberrant mitochondrial debris.

Oxidative damage of mitochondrial proteins

In most aerobic cell types the mitochondrial respiratory chain is one of the main sources of generation of ROS under physiological conditions (Pamplona and Barja 2007; Moreira et al. 2007a; Starkov 2008; Gibson et al. 2008). In addition to mitochondria, peroxisomes, endoplasmatic reticulum, microsomes, nucleus and plasma membrane oxidases are potential sources of ROS.

The concept of oxidative stress has been applied to the imbalance between the generation of reactive oxygen species, reactive nitrogen species and reactive carbonyl species, and the cellular antioxidant defence mechanisms including antioxidant enzymes superoxide dismutases SOD1 and SOD2, catalase, glutathione peroxidase, peroxiredoxin and some molecular chaperones (Halliwell and Gutteridge 2007). This may result in oxidative damage to varied molecules including DNA, RNA, lipids and proteins. The nervous system is particularly susceptible to oxidative stress due to the fact of the abundance of polyunsaturated fatty acid (PUFA) content, especially arachidonic and docosahexaenoic acids, the high oxygen consumption rate, and the relatively low levels of antioxidant pathways (Cosgrove et al. 1987; Butterfield and Kanski 2001; Barnham et al. 2004). Recent reviews have summarized protein targets of oxidative damage in human neurodegenerative diseases and related animal models (Sultana et al. 2009; Martínez et al. 2009).

For the present purposes, attention will be centred on certain mitochondrial proteins. Complex V or ATP synthase catalyzes the synthesis of ATP from ADP and inorganic phosphate with a flow of protons from the inter-membrane space to the matrix side. ATP synthase is lipoxidized and nitrated in AD (Pamplona et al. 2005; Sultana et al. 2006a; Reed et al. 2008a). Moreover, ATP synthase oxidative damage is a very early event in AD, as ATP synthase has been found oxidized and its function reduced in the entorhinal cortex in asymptomatic cases at very early stages of AD-related pathology (Terni et al. 2009). Importantly, ATP synthase oxidation and its loss of activity are not accompanied by reduced total expression levels of this protein (Terni et al. 2009).

Ubiquinol-cytochrome c reductase complex core protein I is a component of the complex III which helps to link the complex between cytochromes c and c1. This protein is more lipoxidized in frontal cerebral cortex in AD when compared with control samples (Pamplona et al. 2005).

These observations obtained in different laboratories by using different methods together with those detailed in the previous section provide evidence that at least two crucial complexes of the mitochondrial Ox-Phos system, cytochrome c oxidase and ATP synthase, are altered in AD thus producing impaired function of complexes IV and V, and reduced ATP production. Whether complex III is dysfunctional as suggested in a single report requires validation.

Energy metabolism in AD

Reduced oxygen uptake and impaired glycolysis have been recognized in AD and in pre-clinical stages of individuals with familial AD by means of neuroimaging functional studies. Although these deficiencies can be the result of cell death and neuron loss in advanced stages of the disease, the presence of similar anomalies in pre-clinical stages makes it unlikely that this possibility is the sole reason for impaired energy metabolism.

The alternative scenario considering impaired enzymatic function as a cause of altered energy metabolism is supported by the identification of several proteins related with glycolysis and Krebs cycle as targets of oxidative damage. Aldolase A, aldolase C, triose phosphate isomerase, phosphoglycerate kinase, and phosphoglycerate mutase are oxidatively damaged in advanced AD stages manifested as dementia and at middle stages manifested as mild cognitive impairment (Castegna et al. 2003; Korolainen et al. 2005; Korolainen et al. 2006; Sultana et al. 2006a; Reed et al. 2008a, b). Glyceraldehyde 3-phosphate dehydrogenase is modified by S-glutathionylation (Newman et al. 2007) and nitration (Sultana et al. 2006b) in AD.

Enolases, which modulate the reaction of 2-phosphoglycerate to phosphoenolpyruvate in the next-to-last step of glycolysis, have increased carbonylation, lipoxidation, S-glutathionylation and nitration levels in AD (Castegna et al. 2002b; Castegna et al. 2003; Pamplona et al. 2005; Sultana et al. 2006a, b; Butterfield et al. 2006; Newman et al. 2007; Reed et al. 2008a, b). The last enzyme of glycolysis is pyruvate kinase (PK) which catalyzes the step from phosphoenolpyruvate to pyruvate thus transfering phosphate to ADP to form ATP. Increased oxidation of isoform PK-M2 was reported in human brain samples of cases with mild cognitive impairment (Butterfield et al. 2006; Reed et al. 2008a).

In addition to enzymes involved in glycolysis and Krebs cycle, several proteins linked with variegated metabolic reactions have been shown to be targets of oxidative damage in AD. These include carbonyl reductase 1, carbonyl anhydrase, carbonic anhydrase II, creatine kinase, lactate dehydrogenase B glutamine synthase and glutamate dehydrogenase (Aksenov et al. 2000; Castegna et al. 2002a; Butterfield et al. 2006; Korolainen et al. 2006; Sultana et al. 2006a, b; Reed et al. 2008a, b).

Enzymatic assays carried out in parallel in a significant number of studies have shown that oxidative damage to proteins linked with energy metabolism is accompanied by the corresponding detriment of function (Aksenov et al. 2000; Sultana et al. 2006b; Butterfield et al. 2006; Newman et al. 2007; Reed et al. 2008a, b; Terni et al. 2009). Therefore, although not demonstrated for every enzyme, available data indicate that oxidative damage of enzymes linked with glycolysis and the citric acid cycle result in functional deficiencies in the extra-mitochondrial production of ATP and in the metabolism of the Krebs cycle.

Voltage-dependent anion channel (VDAC)

VDAC (isoforms VDAC-1, VDAC-2 and VDAC-3), a major component of the outer mitochondrial membrane, is a highly conserved large conductance anion channel involved in fluxes of ions and metabolites across the outer mitochondrial membrane (Baker et al. 2004; Shoshan-Barmatz et al. 2006; Shoshan-Barmatz et al. 2008; Lemasters and Holmuhamedov 2006; Tan and Colombini 2007; Colombini 2007; Rostovtseva and Bezrukov 2009). VDAC has been considered a component of the mitochondrial permeability transition pore (MPTP) although its role as the core of MPTP remains controversial (Chiara et al. 2008; Juhaszova et al. 2008; Halestrap 2009; Mannella and Kinnally 2009).

The role of mitochondrial VDAC in AD is not known but recent pieces of information give support to the concept that VDAC is cardinal in the pathogenesis of AD. Huge VDAC accumulation occurs in the dystrophic neurites of β-amyloid plaques in AD and related transgenic mice models (Fig. 1) in association with mitochondrial porin (Perez-

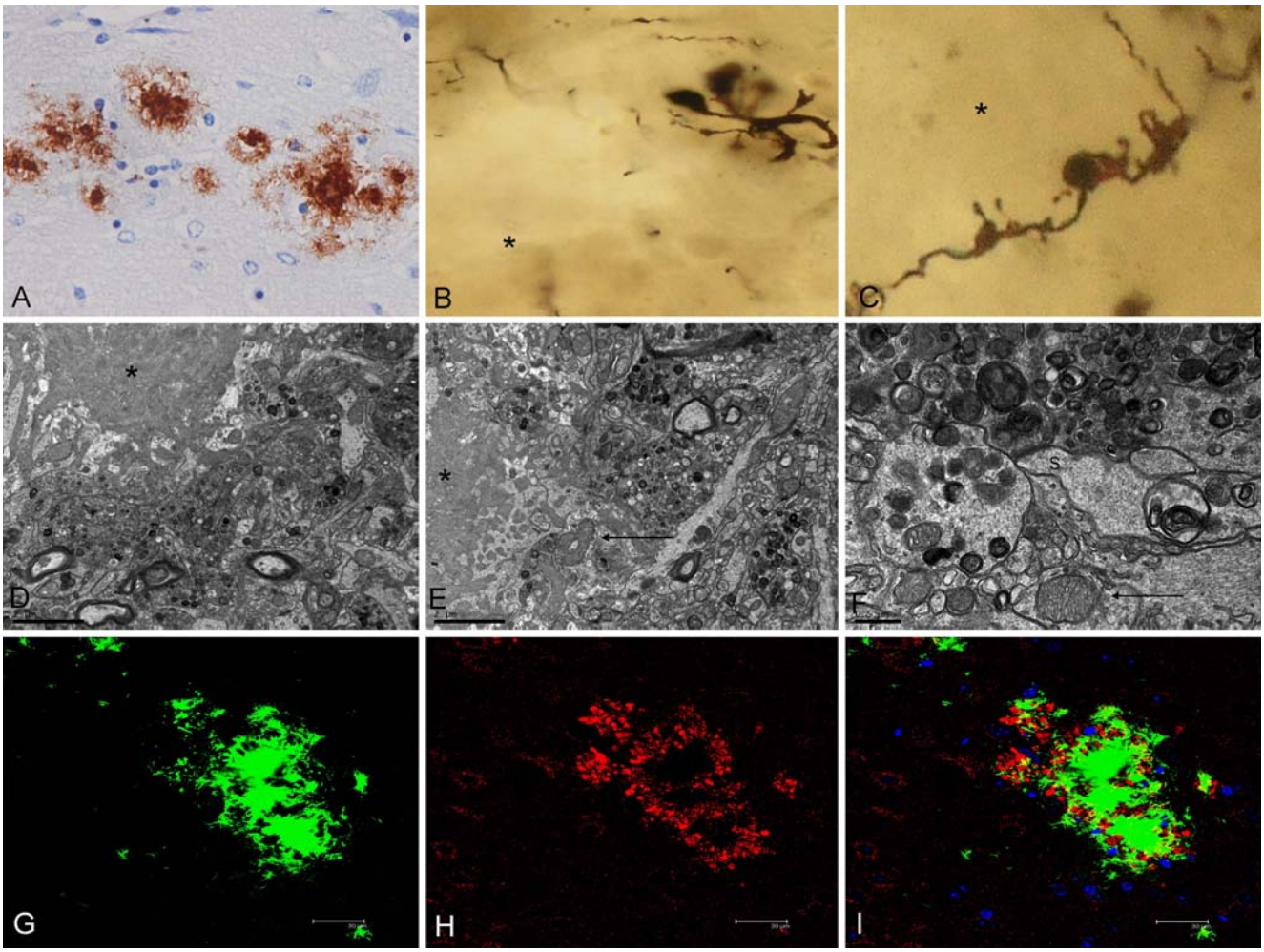

Fig. 1 Characteristics of plaques in APP/PS1 transgenic mice, 12 months old. **A** Amyloid plaques in the entorhinal cortex revealed with anti antibodies ??. **B** and **C**: Dendritic varicosities, neuritic sprouting and loss of dendritic spines in neuronal processes surrounding Aβ plaques (*asterisks*) as seen with the rapid Golgi method. **E**–**G**: Electron microscopy aspects of huge dystrophic neurites filled with abnormal mitochondria, dense bodies and vesicles surrounding Aβ deposits (*asterisk*). Enlarged mitochondria are marked with arrows; s: synapsis. **G**–**I**: double-labelling immunofluorescence and confocal microscopy for β-amyloid (*G, green*) and VDAC (*H, red*) showing abnormal VDAC accumulation surrounding β-amyloid deposits (*I, merge*)

Gracia et al. 2008). Electron microscopy of amyloid plaques correlates VDAC with massive amounts of altered mitochondria and lysosomes filled with dense debris, together with vesicles (Fig. 1). Whether VDAC accumulation is the mere result of impaired turnover and removal of damaged mitochondria or damaged mitochondria at the dystrophic neurites are the consequence of altered VDAC function is not known. Yet acrolein exposure of gerbil synaptosomes increases protein carbonylation which targets VDAC, among other proteins (Mello et al. 2007). Since acrolein is a major endogeneously produced unsaturated aldehyde of lipid peroxidation, it is feasible that VDAC is carbonylated by acrolein in AD. Yet direct evidence of oxidatively damaged VDAC comes from the observation that nitrated VDAC-1 is significantly increased in AD (Sultana et al. 2006b). Since VDAC provides the main trans-membrane transport of ions, ATP and other metabolites through the outer mitochondrial membrane, it can be suggested that altered VDAC results in disablement of bidirectional energy fluxes across the mitochondrial membrane. Figure 2.

Lipid rafts and caveolae

Lipid rafts are membrane micro-domains resistant to solubilization by non-ionic detergents at low temperatures, and characterized by their high content in sphingolipids, cholesterol and saturated fatty acids, as well as by reduced content in PUFA. Lipid rafts serve as platforms for intracellular cell signaling by promoting protein-protein and protein-lipid interactions (Brown and London 2000; Pike 2003). Several proteins such as flotilin and prion protein are localized in lipid rafts. Caveolae are microstructures of the plasma membrane that are considered to be a specific form of lipid rafts (Anderson 1998; Simons and Ikonen 1997). Amyloid precursor protein (APP) is encountered in lipid rafts (Lee et al. 1998; Hayashi et al. 2000; Ehehalt et al. 2003), together with enzymes that regulate proteolytic processing and APP cleavage such as α-secretase, BACE1 (β-secretase) and presenilin 1, PSEN1 (γ-secretase) (Ikezu et al. 1998; Riddell et al. 2001; Marlow et al. 2003; Cordy et al. 2003; Vetrivel et al. 2005; Hattori et al. 2006).

Alterations in the molecular composition and cell distribution of lipid rafts may have implications in pathological events. There is increasing evidence that lipid rafts may be targets of neurodegenerative diseases such as AD (Michel and Bakovic 2007). Recent studies have demonstrated that lipid rafts from AD brains have abnormally low levels of n-3 long chain polyunsaturated fatty acids (mainly 22:6n-3, docosahexaenoic acid) and monoenes (mainly 18:1n-9, oleic acid), as well as reduced unsaturation and peroxidability indexes (Martín et al. 2009). Biochemical changes in lipid composition in lipid rafts presumably result in a considerable increase in membrane viscosity and in energy demands to maintain metabolite transfer across the membrane.

In addition to the outer mitochondrial membrane, VDAC has also been localized in the plasma membrane (pl-VDAC) (Bahamonde and Valverde 2003; Elinder et al. 2005; Thinnes 2007) and in isolated caveolae-like domains (Bàthori et al. 1999; Marín et al. 2007; Ramirez et al. 2009). Recent studies in the murine brain have shown that VDAC in caveolae forms a complex with estrogen receptor α (mERα) which participates in the protection against β-amyloid (Marín et al. 2007). This complex appears to be

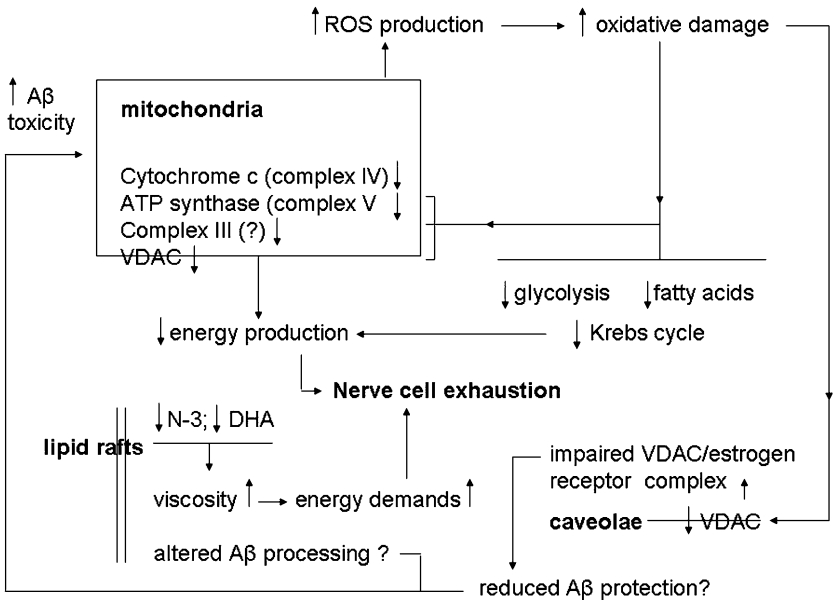

Fig. 2 Summary of the proposed altered metabolic events leading to nerve cell exhaustion

disrupted in dystrophic neurites of Aβ plaques thus facilitating β-amyloid-mediated cell damage (Ramirez et al. 2009).

It can be suggested, as a working hypothesis, that anomalies in the composition of lipid rafts together may interfere APP processing and cleavage by secretases thus facilitating the production of Aβ, whereas altered VDAC in caveolae may reduce the defences facing toxic β-amyloid peptides, which in turn increases mitochondrial damage, oxidative stress and protein damage.

Exhausted neurons

The present data imply that AD is not a disorder related to the two proteins β-amyloid and tau but, rather, is the consequence of very complex and convergent deleterious factors resulting in impaired neuronal function. Factors revisited here are not the only ones but just the part of them that affect cell respiration, and energy production and use.

Mitochondrial defects augment with age and they are even increased in AD. Practical consequences of such impairment are defects in several complexes of the respiratory chain, increased ROS production and oxidative damage of mitochondrial proteins which in turn amplify mitochondrial harm. Oxidative and nitrosative injury also affects a large number of substrates including enzymes of the glycolysis, citric acid cycle and lipid metabolism. Weakened energy metabolism may result in reduced ATP production and decreased capacity to respond to current energy demands such as those derived from physiologic responses to synaptic inputs. As a result, affected neurons are not properly equipped to cope with energy requirements. This is further complicated in the context of extra energy requirements resulting from impaired transport across altered membranes in lipid rafts. Mean energy offering and surplus of energy consumption is a serious putative cause of neuronal dysfunction and progressive decline leading to nerve cell wasting in AD.

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