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Critical analysis of Alzheimer's amyloid-*beta* toxicity to mitochondria

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1. ABSTRACT

Amyloid-*beta* peptide (A*beta*) is believed to be a central player in the Alzheimer disease (AD) pathogenesis. However, its mechanisms of toxicity to the central nervous system are unknown. To explore this area, investigators have recently focused on A*beta*-induced cellular dysfunction. Extensive research has been conducted to investigate A*beta* monomers and oligomers, and these multiple facets have provided a wealth of data from specific models. A*beta* appears to be accumulated in neuronal mitochondria and mediates mitochondrial toxicity. Mitochondrial dysfunction became a hallmark of A*beta*-induced neuronal toxicity. Mitochondria are currently considered as primary targets in the pathobiology of neurodegeneration. This review provides an overview of the A*beta* toxicity to isolated mitochondria, mitochondria in different tissues and cells *in vitro* and *in vivo*. Full texts and abstracts from all 530 biomedical articles listed in PubMed and published before January 2014 were analysed. The mechanisms underlying the interaction between A*beta* and mitochondrial membranes and resulting mitochondrial dysfunction are most disputed issues. Understanding and discussing this interaction is essential to evaluating A*beta* effects on various intracellular metabolic processes.

2. INTRODUCTION

Alzheimer's disease (AD) is a classic example of a condition in which learning, memory and cognitive function decline simultaneously, dramatically and permanently. This chronic illness progresses quite slowly, for many years, manifesting a variety of neurologic and psychiatric disorders. It is characterized by gradual loss of memory and working efficiency and associated with high economic and quality-of-life costs. So far there are no definitive premortem diagnostic tools and effective therapeutics available for AD.

The pathogenic mechanisms responsible for the origin and development of the AD are unknown. The research field has mostly been concentrated on the role of amyloid-*beta* peptides (A*beta*) stemming from the apparent fact that these peptides are formed in the brain of AD patients. A*beta* is the major amyloid component of amyloid deposits known as extracellular senile plaques that induce slow neuronal degeneration in the brains of AD patients (1). According to the amyloid cascade hypothesis (2), which have been most popular in last two decades, extracellular accumulation of A*beta* in the central nervous system initiates a reaction cascade leading to widespread neuronal dysfunction, complex pathology and clinical manifestation of disease (3).

More recent studies on neurons in culture have raised the possibility that neuronal dysfunction and degeneration could be caused by an intraneuronal gradual accumulation of A*beta* rather than by an extracellular process (4, 5). This "intracellular hypothesis" is based on transgenic mouse line studies that have demonstrated that A*beta* was generated within neurons (6). The supporting evidence includes the demonstration of A*beta* occurence within mitochondria of brains from AD patients (4). Using isolated rat brain and muscle mitochondria, Aleardi *et al*. (2005) observed initial mitochondrial accumulation of A$beta_{25-35}$ and A$beta_{1-42}$ following a short-time incubation with toxic aggregates of A*beta* and subsequently, a progressive impairment of both physical and functional properties of the mitochondrial inner membrane (7).

Evidence suggests that A*beta* is a key factor in the pathogenesis of AD and it has been proposed that mitochondria are involved in the biochemical pathway by which A*beta* can lead to neuronal dysfunction. Numerous investigations performed on animal models of AD, various cell cultures, and isolated mitochondria treated with A*beta* revealed defects in mitochondria. In this review, we discuss extensive details about mitochondrial toxicity of A*beta* including their adverse effects in mitochondria from human and animal cells, the effects of A*beta* on various mitochondrial processes, and molecular mechanisms underlying mitotoxicity of A*beta*. This report adds to and expands the recent review by Pagani and Eckert (2011) (8). Although work in this area spans with the beginning of the 21st century, comprehensive understanding of these molecular mechanisms remains a non-trifling task.

3. A*beta* ABUNDANCE AND SPECIES

A*beta* is the proteolytic product formed by processing of amyloid precursor protein (1, 10, 11). At least 18 different forms of A*beta* were determined in cerebrospinal fluid (CSF) samples from patients who underwent lumbar puncture to exclude infectious disorders of the central nervous system using immunoprecipitation (12). This semi-quantitative work has established that numerous cleavage products are created in the brain. Although A*beta* is targeted as one of the primary causes of AD, A*beta* is constitutively secreted by mammalian cells and normally occurs in plasma and CSF (1, 13). It is also a generic soluble metabolite normally detected throughout the body in blood plasma, brain tissue, urine, tissues, and non-neuronal cells (1, 14, 15).

A$beta_{1-40}$ and A$beta_{1-42}$ have been the primary focus of this field. A$beta_{1-42}$ and A$beta_{1-40}$ are expressed as internal parts of large glycoprotein, amyloid precursor protein, in all human fetal tissues examined with highest levels in brain, kidney, heart, and spleen (10), with significantly lower expression in the liver (16). They can be found in human leukocytes (17), fibroblasts (18), platelets (19, 20), CSF (21), urine (14), blood vessels (22), and blood plasma (6, 23, 24).

A$beta_{25-35}$ is a special Abeta species that requires very careful attention. It is a synthetic peptide of 11 amino acids that corresponds to a fragment of A$beta_{1-40}$ and A$beta_{1-42}$, and is an intermembrane domain of amyloid precursor protein (10). A$beta_{25-35}$ is often selected as a model for fulllength Abeta because it retains both its physical and biological properties, while its short length readily allows derivatives to be synthesized and studied (25). These properties were identified 25 years (26).

A*beta* deposition can occur in multiple sites throughout the body in AD. Growing evidence indicates that not only brain but peripheral tissues and cells are affected by AD, including skin, subcutaneous tissue and intestine (27), heart (28), CSF, plasma, urine and blood cells (erythrocytes, platelets, and leukocytes) (6, 29-32).

Numerous defects in a periphery (where, as a rule, amyloid plaques do not accumulate) in AD provide some support for the hypothesis that AD is a systemic disorder.

4. A*beta* EFFECTS IN ISOLATED MITOCHONDRIA

Most studies were performed using A$beta_{25-35}$, with about 30% of others, A$beta_{1-40}$, A$beta_{1-42}$ and A$beta_{31-35}$ (Table 1). All A*beta*s studied exerted certainly effects on many mitochondrial processes. The following defects or impairments were widely presented in the literature: decreases in Complex I, II+III and IV activities, State 3 respiration, ADP/O ratio and respiratory control index, mitochondrial ATP synthesis, ATPase activity and mitochondrial membrane potential, calcium capacity of mitochondria and Ca-induced respiration, pyruvate dehydrogenase and *alpha*-ketoglutarate dehydrogenase activities and GSH content, uncoupling of oxidative phosphorylation, increase in mitochondrial reactive oxygen species (ROS), hydrogen peroxide (H_2O_2) and

Table 1. Effects A*beta* on isolated mitochondria

Amyloid	Effect	Object	References
A$beta_{25-35}$	Decrease in Complex I activity	Rat brain mitochondria	(33)
A$beta_{25-35}$	Decrease in Complexes II+III activity	Rat brain mitochondria	(33)
A$beta_{25-35}$	Decrease in cytochrome oxidase activity	Rat brain mitochondria	(34, 35)
A$beta_{25-35}$	Decrease in State 3 respiration	Rat brain mitochondria	(36)
A$beta_{25-35}$	Decrease in respiratory control index	Rat brain mitochondria	(37)
A$beta_{25-35}$	Uncoupling of respiration	Rat brain mitochondria	(36)
A$beta_{25-35}$	Decrease in calcium capacity of mitochondria	Rat brain mitochondria	(38)
A$beta_{25-35}$	Decrease in Ca-induced respiration	Rat brain mitochondria	(36)
A$beta_{25-35}$	Decrease in mitochondrial ATP synthesis	Rat brain mitochondria	(33)
A$beta_{25-35}$	Release of mitochondrial cytochrome c into cytosol	Rat brain mitochondria	(33, 35, 39, 40)
A$beta_{25-35}$	Decrease in mitochondrial membrane potential	Rat brain mitochondria	(35, 38)
A$beta_{25-35}$	Increase in mitochondrial ROS generation	Rat brain mitochondria	(33)
A$beta_{25-35}$	Induction of the mitochondrial permeability transition	Rat brain mitochondria	(35, 40)
A$beta_{25-35}$	Reduction in ATPase activity	Rat brain mitochondria	(35)
A$beta_{25-35}$	Decrease in pyruvate dehydrogenase activity	Rat brain mitochondria	(35, 41)
A$beta_{25-35}$	Decrease in *alpha*-ketoglutarate dehydrogenase activity	Rat brain mitochondria	(35, 41)
A$beta_{25-35}$	Reduction in GSH content	Rat brain mitochondria	(35)
A$beta_{25-35}$	Increase in malondialdehyde content	Rat brain mitochondria	(35)
A$beta_{25-35}$	Increased membrane polarity	Rat brain mitochondria	(39)
A$beta_{1-40}$	Stimulation of H_2O_2 generation	Rat brain mitochondria	(42)
A$beta_{1-42}$	Release of mitochondrial cytochrome c	Mouse brain mitochondria	(43)
A$beta_{1-42}$	Decrease in respiratory control index (glutamate+malate)	Rat forebrain mitochondria	(44)
A$beta_{31-35}$	Decrease in mitochondrial membrane potential	Nonsynaptic brain mitochondria	(45)
A$beta_{31-35}$	Decrease in state 3 mitochondrial respiration (glutamate+malate)	Nonsynaptic brain mitochondria	(45)
A$beta_{31-35}$	Release of mitochondrial cytochrome c into cytosol	Nonsynaptic brain mitochondria	(45)
A$beta_{25-35}$ A$beta_{1-40}$	Decrease in the ADP/O ratio	Rat brain mitochondria	(37)
A$beta_{25-35}$ A$beta_{1-40}$	Decrease in ATP/ADP ratio	Rat brain mitochondria	(37)
A$beta_{25-35}$ A$beta_{1-40}$	Decrease in mitochondrial membrane potential	Brain mitochondria from 24 month-old rats	(36)
A$beta_{25-35}$ A$beta_{1-40}$	Stimulation of H_2O_2 generation	Rat neocortex mitochondria	(46, 47)
A$beta_{25-35}$ A$beta_{1-42}$	Decrease in Complex I activity	Rat brain mitochondria	(7)
A$beta_{25-35}$ A$beta_{1-42}$	Decrease in Complex IV activity	Rat brain mitochondria	(7)

(Contd...)

Table 1. Contd...

Amyloid	Effect	Object	References
A$beta_{25-35}$ A$beta_{1-42}$	Decrease in Complex III activity	Rat brain mitochondria	(7)
A$beta_{25-35}$ A$beta_{1-42}$	Release of mitochondrial cytochrome c into cytosol	Rat brain mitochondria	(41)
A$beta_{25-35}$ A$beta_{1-42}$	Decreases in state 3 and state 4 respiration	Rat brain mitochondria	(7, 41)
A$beta_{25-35}$ A$beta_{1-42}$	Stimulation of H_2O_2 production	Rat brain mitochondria	(7)
A$beta_{25-35}$ A$beta_{1-42}$	Release of mitochondrial cytochrome c into cytosol	Rat brain mitochondria	(7)
A$beta_{25-35}$ A$beta_{1-42}$	Decrease in Complex III activity	Rat muscle mitochondria	(7)
A$beta_{25-35}$ A$beta_{1-42}$	Decrease in Complex I activity	Rat muscle mitochondria	(7)
A$beta_{25-35}$ A$beta_{1-42}$	Decrease in Complex IV activity	Rat muscle mitochondria	(7)
A$beta_{25-35}$ A$beta_{1-42}$	Stimulation of mitochondrial H_2O_2 production	Rat muscle mitochondria	(7)
A$beta_{25-35}$ A$beta_{1-42}$	Decrease in ATP/O ratio	Rat muscle mitochondria	(7)
A$beta_{25-35}$ A$beta_{1-42}$	Decrease in ATP synthesis	Rat muscle mitochondria	(7)
A$beta_{25-35}$ A$beta_{1-42}$	Decrease in state 3 and state 4 respiration	Rat muscle mitochondria	(7)
A$beta_{25-35}$ A$beta_{1-42}$	Release of mitochondrial cytochrome c into cytosol	Rat muscle mitochondria	(7)
A$beta_{25-35}$	Decrease in State 3 respiration	Rat liver mitochondria	(36)
A$beta_{25-35}$	Reduction in cytochrome oxidase activity	Rat liver mitochondria	(48)
A$beta_{25-35}$	Decrease in Ca-induced respiration	Rat liver mitochondria	(36)
A$beta_{25-35}$	Uncoupling of respiration	Rat liver mitochondria	(36)
A$beta_{25-35}$	Induction of the mitochondrial permeability transition	Rat liver mitochondria	(40, 48, 49)
A$beta_{25-35}$	Release of mitochondrial cytochrome c into cytosol	Rat liver mitochondria	(40)
A$beta_{25-35}$ A$beta_{1-40}$	Decrease in mitochondrial membrane potential	Rat liver mitochondria	(36)
A$beta_{25-35}$	No effect on Complex I activity	Rat liver mitochondria	(48)
A$beta_{25-35}$	No effect on Complex II activity	Rat liver mitochondria	(48)
A$beta_{25-35}$	No effects on Complexes I and II-III activities	Rat brain mitochondria	(34)
A$beta_{25-35}$	No effects on Complexes I and II+III activities	Rat brain mitochondria	(41)
A$beta_{25-35}$	No effects on Complexes I и IV, citrate synthase, pyruvate and *alpha*-ketoglutarate dehydrogenase activities	Rat brain mitochondria	(33)

(Contd...)

Table 1. Contd...

Amyloid	Effect	Object	References
A*beta*$_{31-35}$	No effect on state 3 mitochondrial respiration (succinate)	Nonsynaptic brain mitochondria	(45)
A*beta*$_{25-35}$	No effects on citrate synthase activities	Rat brain mitochondria	(34)
A*beta*$_{25-35}$	No effects on release of mitochondrial cytochrome c	Rat brain mitochondria	(36)
A*beta*$_{25-35}$ A*beta*$_{1-40}$	No effect on mitochondrial membrane potential	Brain mitochondria from 1.5. month-old and 12 month-old rats	(37)
A*beta*$_{1-42}$		Rat brain mitochondria	(50)
A*beta*$_{1-42}$	No effect on mitochondrial hexokinase activity	Mitochondria isolated from cultured cortical neurons	(51)

malondialdehyde production, opening of the mitochondrial permeability transition pore (PTP), and release of mitochondrial cytochrome c. These unambiguously adverse effects were typical in all mitochondrial preparations studied, including rat brain, forebrain, neocortex mitochondria, rat nonsynaptic brain, muscle, liver mitochondria, and mouse brain mitochondria.

The mitochondrial permeability transition and the PTP, identified as the mitochondrial megachannel play a central role in the mitochondrial function and neuronal cell death (52, 53). PTP is the protein complex containing the voltage dependent anion channel in the outer membrane, the adenine nucleotide translocase in the inner membrane, and cyclophilin D in the mitochondrial matrix (54). Cyclophilin D translocation to the inner membrane triggers opening of the PTP (55-57). Opening of PTP leads to swelling of the mitochondrial matrix, dissipation of the inner membrane potential, and generation of ROS. The consequence of opening of the pore is also outer membrane rupture and the release of apoptotic mediators, such as cytochrome c, apoptosis inducing factor (Aif-1), and Smac/DIABLO, and procaspases from the intermembrane space to cytosol (58-61).

The studies discussed above were performed mostly on mitochondria isolated from rat brain and other tissues. They evidenced a deleterious action of A*beta* on mitochondrial respiration (7, 36, 41, 44, 45), ATP synthesis (7, 33, 35), and the activity of various enzymes involved in energy production, such as enzyme Complexes I, II+III and IV of the mitochondrial respiratory chain (7, 33–35, 41, 48), pyruvate and *alpha*-ketoglutarate dehydrogenases (7, 35, 41) and ATPase (35). Also, A*beta*s induced destructive processes in mitochondria similar to those commonly observed in oxidative stress, such as increase in formation of ROS (33), H_2O_2 (7, 42, 46, 47), and malondialdehyde (35, 49), decrease in mitochondrial membrane potential (35, 36, 38, 45), induction of the mitochondrial permeability transition pore (35, 36, 38, 40, 48), the mitochondrial permeability transition (40, 48, 49), and release of mitochondrial cytochrome c into cytosol (7, 33, 35, 39, 40, 43, 45).

Similar effects were observed in brain, brain regional, liver, and muscle mitochondria, although most studies were performed on rat brain mitochondria.

In above experiments, A*beta*s exerted their effects in aggregated forms and did not so in monomeric forms. There are few reports of conflicting results as well (34, 36, 37, 50, 51) (Table 1).

Lowell *et al*. (2005) quantitatively measured changes in mitochondrial cysteine-containing proteins of primary rat cortical neuron cultures exposed to 25 μM A*beta*$_{25-35}$ for 16 h (62). They have analysed 45 non-redundant mitochondrial specific proteins and found changes in 19 proteins. The latter included Na^+/K^+ transporting ATPase *alpha*-3 chain, cofilin, dihydropyriminidase related protein-1, cyclophilin A, pyruvate kinase, voltage dependent anion-selective channel proteins 1 and 3, ATP synthase *alpha* chain, guanine nucleotide-binding proteins G *alpha* and G *beta*, lactate dehydrogenase A chain, 60S ribosomal protein L4, 14-3-3 protein *tau*, 14-3-3 protein *zeta/delta*, dihydropyriminidase related protein-5, elongation factor 2, glyceraldehyde 3-phosphate dehydrogenase, Rab GDP dissociation inhibitor *alpha*, creatine kinase B chain, and the vacuolar ATP synthase catalytic subunit A. Interestingly, these protein were increased by 20%

to 137% (62). Similar effects were measured with the use of A*beta*$_{1-40}$.

Thus, the mechanisms of mitotoxicity of externally added A*beta* include injuries of the respiratory chain, an inhibition of a number enzyme activities, a stimulation of oxidative stress in mitochondrial membranes and matrix (62). Such the picture is characteristic of mitochondria from any donor tissue studied.

5. A*beta* EFFECTS ON MITOCHONDRIA WITHIN INTACT CELLS

Table 2 shows results of documented studies regarding the effects of A*beta* on mitochondrial function in intact animal cells and cells in culture. A multitude of cell were tested, namely human platelets, mouse platelets, rat platelets, human umbilical vein endothelial cells, human brain microvascular endothelial cells, rat brain microvascular endothelial cells, brain microvascular endothelial cells from homozygous db/db (Leprdb/Leprdb) and heterozygous (Dock7m/Leprdb) mice, cortical brain cells from FTD P301L tau transgenic mice, cerebellar cells from FTD P301L tau transgenic mice, human Ntera2 teratocarcinoma cells, human neuroblastoma cells SH-SY5Y, human neuroblastoma cells SK-N-SH, human neuroblastoma cells IMR-32, human neuroblastoma cells SK-NAS, human brain microvascular cells HCMEC/D3, HeLa cells, primary rat neuronal cultures, primary rat astrocyte cultures, cultured rat cortical neurons, cultured rat hippocampal neurons, cultured rat cerebellar granule cells, cultured rat cerebral endothelial cells, rat brain endothelial cells RBE4, rat pheochromocytoma cells PC12, primary neural progenitor cell cultures from mouse cerebral cortex, murine cerebral endothelial cells, mouse hippocampal cells HT22. Virtually the same A*beta*-induced disturbations were observed in mitochondria of these cells (Table 2) as those in isolated mitochondria (Table 1), at similar concentrations of 1–50 μM A*beta*$_{25-35}$ (rarely up to 150 μM), 5–20 μM A*beta*$_{1-40}$ (up to 50 μM), and 0.5–20 μM A*beta*$_{1-42}$ (up to 50 μM).

On the cellular level, A*beta* caused decreases in mitochondrial oxygen consumption (72, 80, 81), Complex I, Complex II-III and Complex IV activities (78), ATP synthesis (78, 73), and mitochondrial membrane potential (65, 70-76, 78, 83-90). They stimulated mitochondrial H_2O_2 (76) and superoxide production (67, 70, 73, 75-77) and mitochondrial lipid peroxidation (70). A*beta* induced PTP (66, 67, 74) and release of mitochondrial cytochrome c (63–71, 73, 74) and hexokinase from mitochondria into cytosol (51, 66). A*beta*$_{25-35}$ and A*beta*$_{1-42}$ oligomers induced a massive entry of Ca^{2+} in neurons and promote mitochondrial Ca^{2+} overload in cultured cerebellar granule cells, cortical neurons and GT1 neural cells (74, 89).

In addition to results obtained on isolated mitochondria, cell-studies showed up other mitochondrial disturbations such as a decrease in total mitochondrial number (78) and mitochondrial length (93, 87), impairment of mitochondrial trafficking along the axon (87, 93, 94), oxidative damage of mitochondrial DNA (95-97), reductions in human mitochondrial transcription factor-1 mRNA (79), cytochrome oxidase-I mRNA, Compex II mRNA and Complex III mRNA (79), decrease in the adenine nucleotide translocator activity (77), suppression of mitochondrial succinate dehydrogenase (82) and aldehyde dehydrogenase 2 activities (70), increase in mitochondrial adenylate kinase release to the cytosol (50), induction of translocation of the apoptosis regulator termed second-mitochondria-derived activator of caspase (Smac) from the mitochondria to the cytosol (98), increase in phosphothreonine-voltage dependent anion channel 1 (66), increase in mitochondrial BAD levels (64), MAO-B activity and MAO-B mRNA level (99), mitochondrial Ca^{2+} overload (74). Again, A*beta*s exerted their effects in aggregated forms and did not so in monomeric forms.

Thus, the cellular mechanisms of mitotoxicity of externally added A*beta* include injuries of mitochondrial respiratory chain and the machinery for its components synthesis, an inhibition of a energy-producing enzyme activities and axonal transport of mitochondria, a stimulation of oxidative stress in mitochondrial membranes and matrix. Such the picture is characteristic of mitochondria occuring in any cell studied, neuronal and non-neuronal by nature.

6. A*beta* EFFECTS ON MITOCHONDRIA *IN VIVO*

Some effects of A*beta*$_{25-35}$, A*beta*$_{1-40}$, A*beta*$_{1-42}$ and A*beta*$_{31-35}$ administered to animals are shown in Table 3.

In *in vivo* experiments, increase in oxidative stress was observed in the rat hippocampal

Table 2. Effects of A*beta* on mitochondria in intact cells *in vitro*

Amyloid	The effect	Object	Reference
A$beta_{25-35}$	Release of mitochondrial cytochrome c into cytosol	Human teratocarcinoma cells Ntera2	(63)
A$beta_{25-35}$		Cultured rat cortical neurons	(64)
A$beta_{25-35}$		Human neuroblastoma cells SH-SY5Y	(65)
A$beta_{25-35}$		Rat pheochromocytoma cell line PC12	(66)
A$beta_{25-35}$		Human neuroblastoma cells SH-SY5Y	(67)
A$beta_{1-40}$		Cultured rat cortical neurons	(64, 68)
A$beta_{1-40}$		Human brain microvascular cells HCMEC/D3	(69)
A$beta_{1-40}$		Human neuroblastoma cells SH-SY5Y	(69)
A$beta_{1-40}$		Human umbilical vein endothelial cells	(70)
A$beta_{1-40}$		Rat brain endothelial cells RBE4	(71)
A$beta_{1-42}$		Primary neural progenitor cell cultures from mouse cerebral cortex	(72)
A$beta_{1-42}$		Mouse hippocampal cells HT22	(73)
A$beta_{25-35}$ A$beta_{1-42}$		Cerebellar granule cells	(74)
A$beta_{25-35}$ A$beta_{-42}$		Cortical neurons	(74)
A$beta_{25-35}$ A$beta_{1-42}$		GT1 neural cells	(74)
A$beta_{25-35}$	Increase in mitochondrial superoxide production	Human neuroblastoma cells SH-SY5Y	(67)
A$beta_{25-35}$		Cultured rat hippocampal neurons	(75)
A$beta_{1-40}$		Human umbilical vein endothelial cells	(70)
A$beta_{1-40}$		Human brain microvascular endothelial cells	(70)
A$beta_{1-40}$		Rat brain microvascular endothelial cells	(76)
A$beta_{1-40}$		Brain microvascular endothelial cells from homozygous db/db (Leprdb/Leprdb) mice	(76)
A$beta_{1-40}$		Brain microvascular endothelial cells from heterozygous (Dock7m/Leprdb) mice	(76)
A$beta_{1-42}$		Cultured rat cerebellar granule cells	(77)
A$beta_{1-42}$		Mouse hippocampal cells HT22	(73)
A$beta_{1-42}$		Cultured rat hippocampal neurons	(75)
A$beta_{1-42}$	Induction of an early increase in mitochondrial superoxide flash incidence	Primary neural progenitor cell cultures from mouse cerebral cortex	(72)
A$beta_{1-40}$	Increase in mitochondrial H2O2 production	Rat brain microvascular endothelial cells	(76)
A$beta_{1-40}$		Brain microvascular endothelial cells from homozygous db/db (Leprdb/Leprdb) mice	(76)
A$beta_{1-40}$		Brain microvascular endothelial cells from heterozygous (Dock7m/Leprdb) mice	(76)

(Contd...)

Table 2. Contd...

Amyloid	The effect	Object	Reference
A*beta*$_{1-42}$	Decrease in the adenine nucleotide translocator activity	Cultured rat cerebellar granule cells	(77)
A*beta*$_{25-35}$	Reduction in cytochrome oxidase activity	Primary rat neuronal cultures	(78)
A*beta*$_{25-35}$	Reduction in cytochrome oxidase-I mRNA	Human neuroblastoma cells SK-N-SH	(79)
A*beta*$_{25-35}$	Reduction in Complex I activity	Primary rat neuronal cultures	(78)
A*beta*$_{1-42}$	Mitochondrial glutamate/malate oxidation	Human neuroblastoma cells IMR-32	(80)
A*beta*$_{1-42}$	Decrease in mitochondrial oxygen consumption	Primary neural progenitor cell cultures from mouse cerebral cortex	(72)
A*beta*$_{25-35}$	Reduction in Complex II+III activity	Primary rat neuronal cultures	(78)
A*beta*$_{25-35}$	Reduction in Compex II mRNA	Human neuroblastoma cells SK-N-SH	(79)
A*beta*$_{25-35}$	Reduction in Complex III mRNA	Human neuroblastoma cells SK-N-SH	(79)
A*beta*$_{1-42}$	Reductions in state 3 respiration, the respiratory control ratio, and uncoupled respiration	Cortical brain cells from FTD P301L tau transgenic mice	(81)
A*beta*$_{25-35}$ A*beta*$_{1-40}$	Suppression of mitochondrial succinate dehydrogenase activity	HeLa cells	(82)
A*beta*$_{1-42}$	NO reductions in state 3 respiration, the respiratory control ratio, and uncoupled respiration	Cerebellar cells from FTD P301L tau transgenic mice	(81)
A*beta*$_{25-35}$	Reduction in citrate synthase activity	Primary rat neuronal cultures	(78)
A*beta*$_{25-35}$	Decrease in mitochondrial membrane potential	Primary rat neuronal cultures	(78)
A*beta*$_{25-35}$		Cultured rat hippocampal neurons	(75)
A*beta*$_{25-35}$		Cultured rat cortical neurons	(83, 84)
A*beta*$_{25-35}$		Human neuroblastoma cells SH-SY5Y	(65)
A*beta*$_{25-35}$		Rat pheochromocytoma cell line PC12	(85)
A*beta*$_{25-35}$ A*beta*$_{1-40}$		Cultured rat cerebral endothelial cells	(86)
A*beta*$_{1-40}$		Human umbilical vein endothelial cells	(70)
A*beta*$_{1-40}$		Human brain microvascular endothelial cells	(70)
A*beta*$_{1-40}$		Cultured rat cortical neurons	(87)
A*beta*$_{1-40}$		Rat brain endothelial cells RBE4	(71)
A*beta*$_{1-40}$		Rat brain microvascular endothelial cells	(76)
A*beta*$_{1-40}$		Brain microvascular endothelial cells from homozygous db/db (Leprdb/Leprdb) mice	(76)
A*beta*$_{1-40}$		Brain microvascular endothelial cells from heterozygous (Dock7m/Leprdb) mice	(76)
A*beta*$_{1-42}$		Primary neural progenitor cell cultures from mouse cerebral cortex	(72)
A*beta*$_{1-42}$		Hippocampal cell line HT22 of mice	(73)
A*beta*$_{1-42}$		Cultured rat hippocampal neurons	(75)
A*beta*$_{1-42}$		Cultured rat cortical neurons	(88, 89)

(Contd...)

Table 2. Contd...

Amyloid	The effect	Object	Reference
A$beta_{1-42}$		Mouse platelets	(90)
A$beta_{1-42}$		Rat platelets	(91)
A$beta_{1-42}$		Human platelets	(92)
A$beta_{25-35}$ A$beta_{1-42}$		Cerebellar granule cells	(74)
A$beta_{25-35}$ A$beta_{1-42}$		Cultured rat cortical neurons	(74)
A$beta_{25-35}$ A$beta_{1-42}$		GT1 neural cells	(74)
A$beta_{25-35}$	Decrease in mitochondrial ATP synthesis	Primary rat astrocyte cultures	(78)
A$beta_{25-35}$		Primary rat neuronal cultures	(78)
A$beta_{1-42}$		Mouse hippocampal cells HT22	(73)
A$beta_{1-42}$	Decrease in the adenine nucleotide translocator activity	Cultured rat cerebellar granule cells	(77)
A$beta_{25-35}$	Decrease in mitochondrial GSH level	Primary rat astrocyte cultures	(78)
A$beta_{25-35}$		Primary rat neuronal cultures	(78)
A$beta_{25-35}$	Reduction in human mitochondrial transcription factor-1 mRNA	Human neuroblastoma cells SK-N-SH	(79)
A$beta_{25-35}$	Decrease in total mitochondrial number	Primary rat neuronal cultures	(78)
A$beta_{1-40}$	Impairment of mitochondrial trafficking	Cultured rat cortical neurons	(87)
A$beta_{1-42}$		Cultured rat hippocampal neurons	(93)
A$beta_{25-35}$		Cultured rat hippocampal neurons	(94)
A$beta_{1-42}$	Decrease in mitochondrial length	Cultured rat hippocampal neurons	(93)
A$beta_{1-40}$		Cultured rat cortical neurons	(87)
A$beta_{1-42}$	Release of hexokinase I from mitochondria	Cultured rat cortical neurons	(51)
A$beta_{25-35}$		PC12 rat pheochromocytoma cell line	(66)
A$beta_{1-42}$	Increase in mitochondrial adenylate kinase release	Human neuroblastoma cells SK-NAS	(50)
A$beta_{25-35}$	Oxidative damage of mtDNA	Murine cerebral endothelial cell line	(95)
A$beta_{1-42}$		Human neuroblastoma cells SK-N-SH	(96)
A$beta_{25-35}$		Rat pheochromocytoma cell line PC12	(97)
A$beta_{25-35}$	Induction of translocation of the apoptosis regulator, second-mitochondria-derived activator of caspase (Smac), from the mitochondria to the cytosol	Cultured rat cerebral endothelial cells	(98)
A$beta_{1-40}$	Decrease in mitochondrial aldehyde dehydrogenase 2 activity	Human umbilical vein endothelial cells	(70)
A$beta_{1-40}$		Human brain microvascular endothelial cells	(70)
A$beta_{1-40}$	Increase in mitochondrial 4-hydroxy-2-noneal	Human umbilical vein endothelial cells	(70)
A$beta_{25-35}$	Induction of mitochondrial permeability transition	Rat pheochromocytoma cell line PC12	(66)
A$beta_{25-35}$		Human neuroblastoma cells SH-SY5Y	(67)

(Contd...)

Table 2. Contd...

Amyloid	The effect	Object	Reference
A*beta*$_{25-35}$ A*beta*$_{1-42}$		Cerebellar granule cells	(74)
A*beta*$_{25-35}$ A*beta*$_{1-42}$		Cortical neurons	(74)
A*beta*$_{25-35}$ A*beta*$_{1-42}$		GT1 neural cells	(74)
A*beta*$_{25-35}$	Increase in phosphothreonine-voltage dependent anion channel 1	PC12 rat pheochromocytoma cell line	(66)
A*beta*$_{25-35}$	Increase in MAO-B activity	Primary rat astrocyte cultures	(99)
A*beta*$_{25-35}$	Increase in MAO-B mRNA level	Primary rat astrocyte cultures	(99)
A*beta*$_{1-40}$	Increase in mitochondrial BAD levels	Cultured rat cortical neurons	(64)
A*beta*$_{25-35}$ A*beta*$_{1-42}$	Mitochondrial Ca^{2+}overload	Cerebellar granule cells	(74)
		Cortical neurons	(74)
		GT1 neural cells	(74)
A*beta*$_{1-42}$	Mitochondrial Ca^{2+}overload	Cultured rat cortical neurons	(89)
A*beta*$_{1-42}$	No effect on mitochondrial cytochrome *c* release	Human neuroblastoma cells SK-NAS	(50)
A*beta*$_{1-42}$	No reductions in state 3 respiration, the respiratory control ratio, and uncoupled respiration	Cerebellar cells from FTD P301L tau transgenic mice	(81)

Table 3. Effects of A*beta* on mitochondria *in vivo*

Amyloid injection	The effect	Object	Reference
A*beta*$_{25–35}$ Intracerebroventricularly, 3-3.7 ng/h/rat for 14 days	Increase in mitochondrial caspase 3 activity	Cortical mitochondria	(100, 101)
	Increase in mitochondrial caspase 3 activity	Cerebellar mitochondria	(100, 101)
	Increase in mitochondrial caspase 3 activity	Hippocampal mitochondria	(100, 101)
	Increase in mitochondrial caspase 9 activity	Cortical mitochondria	(100, 101)
	Increase in mitochondrial caspase 9 activity	Cerebellar mitochondria	(100, 101)
	Increase in mitochondrial caspase 9 activity	Hippocampal mitochondria	(100, 101)
	Increase in mitochondrial calpain-1 activity	Hippocampal mitochondria	(100, 101)
	Increase in mitochondrial calpain-2 activity	Hippocampal mitochondria	(100, 101)
	Increase in mitochondrial calpain-1 activity	Cortical mitochondria	(100, 101)
	Increase in mitochondrial calpain-2 activity	Cortical mitochondria	(100, 101)
	Increase in mitochondrial Cathepsin B activity	Hippocampal mitochondria	(100, 101)
	Increase in mitochondrial Cathepsin D activity	Hippocampal mitochondria	(100, 101)
	Stimulation of mitochondrial H_2O_2 generation	Cortical mitochondria	(46, 47, 102)
A*beta*$_{-40}$ intracerebroventricularly, 3-3.7 ng/h/rat for 5 days	Mitochondrial Mn-SOD activation	Cortical mitochondria	(46, 47, 102)
A*beta*$_{1-42}$ into the lateral cerebral ventricle, 20 μg/rat for 14 days	Decrease in mitochondrial Mn-SOD activity	Brain mitochondria	(103)

(Contd...)

Table 3. Contd...

Amyloid injection	The effect	Object	Reference
A*beta*$_{1-40}$ intracerebroventricularly, 3–3.7 ng/h/rat for 5 days	Mitochondrial MAO-B activation	Cortical mitochondria	(46, 47, 102)
	Mitochondrial catalase inactivation	Cortical mitochondria	(47, 102)
	Mitochondrial glutathione peroxidase inactivation	Cortical mitochondria	(46, 102)
A*beta*$_{25-35}$ into hippocampus, 20 *μ*g/rat, assay 8 days later	Decrease in mitochondrial glutathione peroxidase activity	Brain mitochondria	(104)
A*beta*$_{1-40}$ intracerebroventricularly, 3–3.7 ng/h/rat for 5 days	Decrease in mitochondrial GSH level	Cortical mitochondria	(47, 102)
A*beta*$_{1-42}$ into the lateral cerebral ventricle, 20 *μ*g/rat for 14 days	Decrease in mitochondrial GSH and GSH/GSSG levels	Brain mitochondria	(103)
A*beta*$_{25-35}$ intracerebroventricularly, 3–3.7 ng/h/rat for 14 days	Release of mitochondrial cytochrome c into cytosol	Cortical mitochondria	(105)
A*beta*$_{1-42}$ into the lateral cerebral ventricle, 20 *μ*g/rat for 14 days	Decrease in mitochondrial membrane potential	Brain mitochondria	(103)
A*beta*$_{25-35}$ into hippocampal area CA1, bilaterally, 1–10 *μ*g/rat for 7–21 days		Isolated rat hippocampal neurons	(106)
A*beta*$_{1-42}$ into the lateral cerebral ventricle, 20 *μ*g/rat for 14 days	Decrease in mitochondrial GSH and GSH/GSSG levels	Brain mitochondria	(103)
A*beta*$_{1-42}$ into the lateral cerebral ventricle, 20 *μ*g/rat for 14 days	Increase in mitochondrial GSSG level	Brain mitochondria	(103)
A*beta*$_{1-42}$ into the lateral cerebral ventricle, 20 *μ*g/rat for 14 days	No effect on mitochondrial glutathione peroxidase activity	Brain mitochondria	(103)
A*beta*$_{25-35}$ into hippocampal area CA1, bilaterally, 1–10 *μ*g/rat for 7–21 days	Increases in the expression levels of voltage-dependent anion channel gene	Isolated rat hippocampal neurons	(106)
A*beta*$_{25-35}$ into hippocampal area CA1, bilaterally, 1–10 *μ*g/rat for 7–21 days	Increases in the expression levels of adenine nucleotide translocator gene	Isolated rat hippocampal neurons	(106)
A*beta*$_{25-35}$ into hippocampal area CA1, bilaterally, 1–10 *μ*g/rat for 7–21 days	Increases in the expression levels of cyclophilin D gene	Isolated rat hippocampal neurons	(106)
A*beta*$_{1-42}$ (2 *μ*liters at a final concentration of 1mM) into hippocampus	Reduction in the respiratory control ratio	Hippocampal mitochondria	(107)
A*beta*$_{1-42}$ (2 *μ*liters at a final concentration of 1mM) into hippocampus	Reduction in ATPase activity	Hippocampal mitochondria	(107)
A*beta*$_{25-35}$ into hippocampus, 20 *μ*g/rat, assay 8 days later	Increase in mitochondrial malondialdehyde	Brain mitochondria	(104)

mitochondria isolated 8 days after a single injection of A*beta*$_{25-35}$ (20 nmols) into hippocampus, as evidenced by the increase in the mitochondrial malondialdehyde level (104).

Measurement of the influence of A*beta* on H_2O_2 production have been performed using rat brain mitochondria isolated 14 day after the start of chronic intracerebroventricular injection of A*beta*$_{25-35}$ (1.26 nmol) or A*beta*$_{1-40}$ (0.31 nmol) (46, 47, 102). To exclude underestimation of H_2O_2 generation, intramitochondrial catalase and glutathione peroxidase reactions were blocked by a catalase inhibitor sodium azide and glutathione peroxidase inhibitor potassium mercaptosuccinate (46, 47, 102). The rate of H_2O_2 generation in nonsynaptic neocortex mitochondria from A*beta*$_{25-35}$- or A*beta*$_{1-40}$-treated rats increased in a time-dependent manner during 14 days after the start of infusion. Thus, both A*beta*$_{25-35}$ and Abeta$_{1-40}$

induced the increase in the rate of H_2O_2 production by brain mitochondria *in vivo* as they did *in vitro* (42, 46, 47). It is notable that both A*beta*s exerted their effects only in aggregated forms and not in monomeric forms (46, 47, 102).

Acute A*beta*$_{1-42}$ injections (2 nmols) into rat hippocampus induced a reduction in the respiratory control ratio and ATPase activity of hippocampal mitochondria (107), similar to that in isolated rat brain mitochondria (37, 35). Chronic A*beta*$_{25-35}$ injection bilaterally into hippocampal area CA1 for 7–21 days or A*beta*$_{1-42}$ (2 nmols) into the lateral cerebral ventricle for 14 days resulted in a decrease in mitochondrial membrane potential in isolated rat hippocampal neurons (106) and brain mitochondria (103). After chronic dosage of A*beta*$_{25-35}$ intracerebroventricularly for 14 days, cerebral mitochondrial cytochrome c was released to cytosol (105). Increase in mitochondrial GSSG level, decrease in mitochondrial GSH level and GSH/GSSG ratio occurred in brain mitochondria after the chronic intracerebral injection of A*beta*$_{1-42}$ (103) or A*beta*$_{25-35}$ (47, 102).

Increase in the expression levels of voltage-dependent anion channel gene, adenine nucleotide translocator gene, and cyclophilin D gene in mitochondria isolated from rat hippocampal neurons on 7–21 days after chronic infusion of A*beta*$_{25-35}$ bilaterally into hippocampal area CA1 were not studied in *in vitro* experiments (106). Especially, chronic intracerebroventricular injection of A*beta*$_{25-35}$ or A*beta*$_{1-40}$ in rats resulted in much elevation of proteolytic enzyme activity such as caspase 3, caspase 9, calpain-1, calpain-2, cathepsin B, and cathepsin D as well as pro-oxidant monoamine oxidase-B activities in cerebellar, cortical and hippocampal mitochondria, and a suppression of antioxidant catalase and glutathione peroxidase activities in cortical mitochondria (46, 47, 102). Decrease in brain mitochondrial glutathione peroxidase activity was observed after an acute dose of A*beta*$_{25-35}$ into hippocampus (104). Brain mitochondrial Mn-superoxide dismutase activity decreased after 14 days of chronic dosage of A*beta*$_{1-42}$ into the lateral cerebral ventricle (103), although this activity in rat cortical mitochondria increased after 5 days of chronic intracerebroventricular infusion of A*beta*$_{1-40}$ (46, 47, 102).

The above findings suggest that toxicity mechanisms of A*beta* injected into the brain include physical injuries of mitochondria and induction (or redistribution) of a number mitochondrial catabolic enzymes, that can decomposite the key structures determining mitochondrial function. This is characteristic of cerebral cortical, cerebellar, hippocampal and whole brain mitochondria.

7. ADEQUACY OF THE MODELS USED

The above data indicated that all the experimental models used, isolated mitochondria, *in vitro* intact cells and *in vivo* brain tissue, appeared indistinct, in principle by A*beta* toxicity to mitochondria. This similarity seems to be of fundamental importance and co-incident to mitochondria of practically any tissue or cell. So, A*beta*s do impair energy metabolism, but A*beta*-induced impairement of energy metabolism is not specific to neurons.

The three models were investigated at virtually the same A*beta* concentrations. Thereupon, the question arises whether added concentrations (1–50 μM A*beta*$_{25-35}$, 5–20 μM A*beta*$_{1-40}$, and 0.5–20 μM A*beta*$_{1-42}$) and injected doses of A*beta* (1.25 nmol A*beta*$_{25-35}$ per rat or recalculated 250 nM in CSF, and 0.31 nmol A*beta*$_{1-40}$ per rat or 65 nM in CSF (100, 101) are adequate or not?

Postmortem levels of A*beta*$_{1-40}$ and A*beta*$_{1-42}$ were 208.6 and 783.6 ng/g tissue in the brain of control subjects and 608.2 and 6095.8 ng/g in the brain of AD patients, respectively (108). These figures correspond to 70 nM A*beta*$_{1-40}$ and 260 nM A*beta*$_{1-42}$ in controls and 200 nM A*beta*$_{1-40}$ and 2 μM A*beta*$_{1-42}$ in AD patients. The steady state A*beta*$_{1-40}$ levels in CSF were found to be 5–25 ng/ml (1–6 nM) in healthy volunteers and subjects diagnosed with AD (109). As for A*beta* levels in rodents, huge amounts of the A*beta*$_{1-40}$ plus A*beta*$_{1-42}$ sum were found in brain regional mitochondria from two mouse genotypes bearing the amyloid precursor protein mutations: 12–16, 10–17, 2–7 and 0.3–0.4 nmol/mg protein in cerebral, hippocampal, striatal and amygdal mitochondria, respectively (110), i.e. 0.3 to 17 mM concentrations. Even if printer's errors were of three orders of magnitude, then the level of intramitochondrial A*beta* (0.3 to 17 μM) appeared to be unusually high. The concentration gradient of two to three orders of magnitude drives the influx of A*beta* from neuronal cells to the CSF in both healthy and AD subjects. In order to direct the A*beta* concentration gradient from outside to inside, the external A*beta* concentration has be higher than the internal one.

Thus, added concentrations and injected doses of A*beta* were adequate in the three models.

8. A*beta* PENETRATION INTO THE MITOCHONDRION

A*beta*s represent a group of proteins that polymerize into cross *beta*-sheet amyloid species. When a synthetic A*beta* is injected into an animal or added to the incubation medium of cells or mitochondria and affects any mitochondrial process or function, it means that the A*beta* enters tissue, cell and mitochondria. Other direct way appears to be absent. To be internalized into a cell and/or the mitochodrion, exogenous A*beta* would pass the hematoencephalic barrier and penetrate across the cellular and/or mitochondrial membranes.

For different reasons, the similarity of A*beta* toxicity to mitochondria in the three experimental models is unlikely to be the case. First, it contravenes the doctrine that all the cellular, outer and inner mitochondrial membranes are impermeable for low molecular mass metabolites and cations, incuding the ammonia molecule and proton, let alone for high molecular mass proteins and conjugates. Nonetheless, A*beta* proteins do affect mitochondria.

It is unknown how A*beta* crosses the blood-brain barrier to act on susceptible cells within the brain and blood vessels. Mechanisms of A*beta* transport at the level of the neuronal cell membrane are being studied (111), but remain to be fully elucidated. However, it is obvious that the plasma membrane of the neuronal or non-neuronal cell is the biggest physical impediment to A*beta* influx.

Petersen *et al.* (2008) recently discussed the access of A*beta* to mitochondria (112). The authors hypothesized that A*beta* is transported into mitochondria via the translocase of the outer membrane (TOM) machinery. TOM has been proposed by Neupert and Herrmann (2007) as a mechanism of translocation of mitochondrial preproteins from the cytosol into mitochondria (9). This hypothesis, however, has not been formally confirmed and has certain limitations and obscurities. Three surface receptor components of TOM are believed to recognize preproteins, whereas four membrane-embedded subunits form the translocation pore of about 2 nm in diameter (113). There are no data on recognizing A*beta* by these (or other) mitochondrial receptors. Alzheimer's disease neuritic and vascular A*beta*s present at the average ratio of monomers, dimers, and trimers as 55:30:15 (114). However, only oligomeric A*beta*s are toxic to cells and mitochondria. So, for example, when aggregated $A\beta_{1-42}$ and $A\beta_{25-35}$ were incubated with isolated rat brain and muscle mitochondria, it resulted in reduced respiration rate, ATP synthesis and ATP/O ratio, inhibited complexes I, III and IV activities, induced H_2O_2 production and cytochrome c release (7). Oligomeric and fibrillar, but not monomeric $A\beta_{1-42}$ caused the mitochondrial dysfunction in mouse cortical brain cells (81). Oligomeric $A\beta_{1-42}$ generated the maximal effect on mitochondrial superoxide flash incidence in neural progenitor cells, whereas these cells treated with $A\beta_{1-42}$ monomers did not show any change in mitochondrial superoxide flash incidence (72). Aggregated $A\beta_{1-40}$ stimulated H_2O_2 production by rat brain mitochondria *in vivo* and *in vitro* while disaggregated $A\beta_{1-40}$ did not so (46, 47).

Dimeric and trimeric components of A*beta* peptides have molecular masses 9.0 and 13.5 kDa, respectively. Atomic force microscopy and electron microscopy rotary shadowing revealed that the monomers polymerized into 8−10-nm filaments, whereas the dimers generated prolate ellipsoids measuring 3−4 nm in diameter (114). Schwartz and Matouschek (1999) have determined the effective internal diameter of the protein import channel in the mitochondrial outer membrane to be between 2 nm and 2.6 nm during translocation, much less than that necessary for the dimeric A*beta* passage (115).

Furthermore, PTP is potential dependent and allows molecules with a molecular weight less than 1500 to pass the inner membrane (116). The PTP, called porin, is a protein complex at contact sites between the inner and outer mitochondrial membranes. At a contact site, the voltage dependent anion channel is built-in outer membrane and continued the adenine nucleotide translocase channel that built-in the inner mitochondrial membrane (54). The open state of mitochondrial porins in pig heart, rat heart, rat liver, and yeast has effective diameters of about 1.7. nm (117). The diameter of most pores would allow the permeation of substances up to a molecular weight of 2500 (118), that is much less than a molecular weight of thrimeric, dimeric and monomeric A*beta*.

Thus, there is no pore of a large enough size in the outer mitochondrial membrane to be capable of A*beta* oligomer translocating into the intermembrane space.

The TIM23 complex, the translocase of the inner mitochondrial membrane, is the major preprotein translocase in the inner membrane of the mitochondrion (9). The pore sizes of the TIM23 channels is proposed to be lower than that of the TOM channels (119).

Other authors suggested a hypothesis that oligomeric A*beta*, in contrast to monomeric A*beta*, has the ability to permeabilize cellular membranes and lipid bilayers thereby entering mitochondria (8, 120). They claimed that these mechanisms might explain why exogenous aggregated A*beta*s affect mitochondrial function, but not disaggregated A*beta*. It seems to be the unproven and hardly possible assumption.

Exogenous A*beta* penetration into the mitochondrial matrix can be facilitated by trivial rupture of both outer and inner mitochondrial membranes, as a consequence of the inadequate preparative procedures employed. For example, isolated non-synaptic brain mitochondria having respiratory control ratio of 1.3 (41) cannot be considered as intact mitochondria. Such mitochondrial preparation appears to be similar to leaky and uncovered bucket. In other case, isolated brain mitochondria were stored at 4°C until being used (81). The respiration parameters of such preparations were as followed: State 3 respiration rate of 90 pmol/s per mg of protein with succinate as a substrate and 140 pmol/s per mg of protein with malate/glutamate as substrates (81). These figures correspond to 5.4 and 8.4 nmol/min per mg of protein, respectively, and such mitochondrial preparation cannot be considered as functional mitochondria (that usually have the State 3 respiration of 100 nmol/min per mg of protein, by order of magnitude). Mitochondria can be easily done permeable by incubation them for 20 min at 25^{o}C with or without A*beta* (7) or for 10 min at 37°C (46).

Do A*beta*s accumulate in mitochondria in an amount sufficient to elicit their hurtful effects? After 2–24 h treatment of SK-N-AS human neuroblastoma cells with A$beta_{1-42}$, one to three gold particles per single mitochondrion (including the outer membrane, inner membrane, cristae and matrix) were seen using JNA$beta_{1-42}$ antibody and electron microscopy (50). One to ten gold particles, or 108 gold particles from 20 mitochondria, on an average 5 particles per single mitochondria were counted in human cortical brain biopsy (112). Such amyloid particles count is unlikely to influence directly on the mitochondrial respiratory chain containing 17000 molecules of each cytochrome pigment and about 130000 molecules of respiratory pigments in each mitochondrion (121).

9. CALCIUM AND A*beta* TOXICITY TO MITOCHONDRIA

Table 2 shows that A$beta_{25-35}$ and A$beta_{1-42}$ oligomers evoke mitochondrial Ca^{2+} overload in cultured cerebellar granule cells, cortical neurons and GT1 neural cells (74, 89). A concentration of 20 μM A$beta_{5-35}$ and 0.5 μM A$beta_{1-42}$ induced a mitochondrial Ca^{2+} increase by approximately 1 mM in 62–75% of these three cell cultures. It is even more important that inhibition of mitochondrial Ca^{2+} overload protects against the neurotoxicity induced by A$beta_{1-42}$ and A$beta_{25-35}$ (74). These results indicate that mitochondrial Ca^{2+} ions are mediators of A*beta* cytotoxicity.

Dysregulation of mitochondrial (as well as intracellular) Ca^{2+} homeostasis may underlie A*beta* mitotoxicity and cytotoxicity known as excitotoxicity. So, for example, incubation of cultured rat cortical neurons with A$beta_{1-42}$, apart from enhancements in mitochondrial and cytosolic Ca^{2+} contents, increases mitochondrial ROS production and reduces the mitochondrial membrane potential (74, 89). These effects were prevented or reduced by N-methyl-D-aspartate (NMDA) receptors antagonists MK801, AP5, and memantine, demonstrating that NMDA receptors mediate A$beta_{1-42}$-induced mitochondrial dysfunction (89).

The NMDA receptor is the glutamate receptor specifically binding NMDA and mediating the excitatory neurotransmission in the brain. It is composed of four subjunits forming the cation channel in the synaptic membrane of the postsynaptic neuron. This channel is permeable to Na^{+}, K^{+}, and Ca^{2+}, however, it is more selective for Ca^{2+}. Activation of the NMDA receptor results in the opening of the ion channel and specific influx of Na^{+} and Ca^{2+} ions. NMDA receptors in the hippocampus have been shown to play the key role in spatial learning and memory (122).

The NMDA receptor-mediated Ca^{2+} influx alters intracellular Ca^{2+} concentration and triggers many biological functions and pathological processes. Physiological concentrations of Mg^{2+} act to prevent influx of Ca^{2+}. Numerous studies show that NMDA receptor channel blockers are

neuroprotective in animal models of neurological disorders, such as neurodegenerative diseases, including Alzheimer disease (123). The NMDA receptor antagonists, AP5 and memantine, have neuroprotective properties (124-126). Synthetic MK801 is noncompetitive antagonist of the NMDA receptor, most popular in the treatment of animals.

Intracellularly, calcium ions are known to activate a number of Ca^{2+}-dependent proteolytic enzymes. Most notably, A*beta*-induced Ca^{2+} accumulation in neuronal cells leads to activation of calpains, non-lysosomal calcium-activated neutral proteolytic enzymes (127). Under pathological conditions, calpains can cleave completely soluble and structural proteins in neuronal cells, interrupt synaptic transmission, and impair learning and memory. A$beta_{1-42}$ oligomers produce mitochondrial dysfunction by an NMDA receptor dependent mechanism in hippocampal neurons (128).

Calpain-1 and calpain-2 activities are located in the mitochondria and lysosomes as well, and they increase many-fold after the chronic injection of rats with A$beta_{25–35}$: from 3.5 to 24 times on day 7 and from 7 to 42 times on day 14 (100, 101). The mechanism underlying this increase is presently unknown, although synaptic membrane NMDA receptors and mitochondrial Ca^{2+} influx appear to be involved. The dynamics of the enzymes suggests that the lysosomal membrane and particularly mitochondrial membranes are gradually and greatly damaged under the influence of A$beta_{25–35}$, allowing cytosolic calpains to enter the organelles. Another possibility is that calpains are constitutively expressed in the inactive lysosomal form and are activated by A*beta*, e.g., as a result of increase in free cytosolic Ca^{2+}.

Chronic administration of A$beta_{25–35}$ induces activation of mitochondrial caspase-3 and caspase-9. Activities of caspases 3 and 9 in mitochondria from three brain regions, neocortex, cerebellum, and hippocampus, increased 2- to 3-fold after 14-day course of A$beta_{25–35}$ infusion (100, 101). About 3-fold increase in mitochondrial caspase 3 and caspase 9 activities was observed in A$beta_{1-42}$- or A$beta_{25-35}$-treated human SH-SY5Y neuroblastoma cells (67), human teratocarcinoma cells Ntera2 (63), primary cortical neuron cultures (88), primary rat cortical neurons (83), murine cerebral endothelial cell line (86, 95), rat brain endothelial cell line RBE4 (71), and rat pheochromocytoma cells PC12 (129).

Elevation of mitochondrial cathepsin B and D (and of cytosolic *alpha*-galactosidase and *beta*-galactosidase) activities in the hippocampus (100, 101) suggests that a lesion of the lysosomal membrane, and efflux of lysosomal glycohydrolases and proteases into the cytoplasm and their intake by mitochondria occur by chronic administration of A$beta_{25–35}$, and that these changes are involved in neurodegeneration.

Isolated mitochondria incubated with aggregated A$beta_{25-35}$ showed swelling and membrane disruption. A$beta_{25-35}$-induced mitochondrial swelling and Ca^{2+}-dependent permeability transition could be prevented by pre-incubation with ruthenium red, cyclosporin A, or N-ethylmaleimide (48). Ruthenium red is an inhibitor of mitochondrial Ca^{2+} uptake and interacts with Ca^{2+} binding proteins such as calmodulin, while N-ethylmaleimide is an irreversible inhibitor of all cysteine peptidases, including calpains and caspases. Cyclosporin A is a blocker of the PTP. It means that the presence of A$beta_{25-35}$ is not the sufficient condition for an impairment of the mitochondrial function. A*beta* can induce oxidative stress and apoptosis only when the functional mitochondrial electron-transfer chain is present (63). In other words, current evidence suggests but does not prove an indirect effect of A*beta* on mitochondrial function. These results indicate that mitochondrial Ca^{2+} and mitochondrial calpain(s) and caspase(s) are involved in A*beta* mitotoxicity, whereas inhibition of mitochondrial Ca^{2+} overload can provide a mechanism of neuroprotection.

The nearest to the above consideration is "Ca^{2+} hypothesis" of brain aging and AD by Khachaturian (1994) (130). It postulates that abnormal Ca^{2+} homeostasis mediates or directly leads to most manifestations of A*beta*-induced neuronal damage in AD. However, "Ca^{2+} hypothesis" does not consider of and account for A*beta*-induced mitochondrial disturbances. Therefore, we propose here a modified, "mitochondrial Ca^{2+} hypothesis" of A*beta* toxicity to mitochondria, based on calcium signaling as a development of the Khachaturian's hypothesis.

10. CONCLUSION

A*beta* peptides exert their harmful effects by impairing energy metabolism in mitochondria isolated from any cell studied to day. The impact of A*beta* is seen in a multitude of mitochondrial

functions, in all isolated mitochondria, cultured cells, and whole organisms. The minimal molecular size of oligomeric A*beta* (such as A$beta_{1–40}$ or A$beta_{1–42}$) achieves 8–9 kDa or 3–4 nm that does not allow to penetrate the outer and inner mitochondrial membranes. Thus, A*beta*s can cause mitochondrial dysfunction indirectly, either only in damaged mitochondrial population or by the mechanisms of A*beta* signaling.

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Abbreviations: A*beta,*Amyloid-*beta* peptide; AD, Alzheimer disease; CSF, cerebrospinal fluid; ROS, reactive oxygen species; H_2O_2, hydrogen peroxide; PTP, mitochondrial permeability transition pore; Aif-1, apoptosis inducing factor; Smac, second-mitochondria-derived activator of caspase; NMDA, N-methyl-D-aspartate

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