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EDITORIAL

MITOCHONDRIAL ALTERATIONS, OXIDATIVE STRESS AND NEUROINFLAMMATION IN ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is a multifactorial disorder characterized by the progressive deterioration of neuronal networks. The primary cause and sequence of its progression are only partially understood but abnormalities in folding and accumulation of insoluble proteins such as β-amyloid and Tau-protein are both associated with the pathogenesis of AD. Mitochondria play a crucial role in cell survival and death, and changes in mitochondrial structure and/or function are related to many human diseases. Increasing evidence suggests that compromised mitochondrial function contributes to the aging process and thus may increase the risk of AD. Dysfunctional mitochondria contribute to reactive oxygen species which can lead to extensive macromolecule oxidative damage and the progression of amyloid pathology. Oxidative stress and amyloid toxicity leave neurons chemically vulnerable. The mitochondrial toxicity induced by β-amyloid is still not clear but may include numerous mechanisms, such as the increased permeability of mitochondrial membranes, the disruption of calcium homeostasis, the alteration of oxidative phosphorylation with a consequent overproduction of reactive oxygen species. Other mechanisms have been associated with the pathophysiology of AD. Inflammatory changes are observed in AD brain overall, particularly at the amyloid deposits, which are rich in activated microglia. Once stimulated, the microglia release a wide variety of pro-inflammatory mediators including cytokines, complement components and free radicals, all of which potentially contribute to further neuronal dysfunction and eventually death. Clinically, novel approaches to visualize early neuroinflammation in the human brain are needed to improve the monitoring and control of therapeutic strategies that target inflammatory and other pathological mechanisms. Similarly, there is growing interest in developing agents that modulate mitochondrial function.

Alzheimer's disease (AD) is a neurodegenerative disorder primarily characterized by a progressive deterioration of cognitive functions with consequent reduction of memory, associated with a decrease in

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daily activities and behavioural changes. It is the most common form of dementia in mid- and late life. Patients progress from mild cognitive impairment to death within a span of 10 years. AD currently affects 20-30 million individuals worldwide. No currently available treatment has proven effective in stopping the deterioration of brain cells in AD; in addition, there is still no definitive medical diagnosis (1).

While much research continues to focus on the β-amyloid hypothesis of disease generation, as investigators gain insight into the underlying biology of AD, new theories and therapeutic targets have emerged. Mitochondria, the key cell components responsible for generating cellular energy, represent an emerging therapeutic focus. Moreover, there is significant evidence that the production of reactive oxygen species (ROS) associated with mitochondrial dysfunction is involved in the pathogenesis of several neurodegenerative diseases, including AD (2). Mitochondrial genome alteration in neurons can play an important role in the pathogenesis of these diseases; the evidence that mitochondria are an important target in neurodegenerative conditions is based, in part, on observed reductions in respiratory chain activity in AD models/tissue (2).

The pathways associated with the pathological process of neurodegeneration in AD seem to involve not only mitochondrial damage and oxidative stress, but also cytotoxic reactions, altered metal homeostasis, and neuroinflammation.

MATERIALS AND METHODS

We conducted a baseline literature search (Medline, National Library of Medicine, Elsevier Publisher) of the period 1990-2011, considering original papers, reviews and short clinical reports. The research was conducted for individual topics on AD: pathogenetic mechanisms, oxidative stress, mitochondrial dysfunction, cytokines and neuroinflammation. The aim was to obtain a complete update on these aspects of the disease. Table I depicts the principal results of the literature search.

Pathogenesis: β-amyloid peptide

Approximately 5% of AD cases are familial (1); the majority of cases are referred to as sporadic AD, meaning their origin is unknown. Several risk factors have been linked with the disease including: age, gender, family history, education, depression, hypertension, diabetes, high cholesterol, low physical and cognitive activity and medications. However, the mechanism by which any of these risk factors contributes to the pathogenesis of sporadic AD is still unclear.

It is well known that the hallmarks of the disease include intracellular neurofibrillary tangles and senile or amyloid extracellular plaques. The pathogenesis is associated with two main phenomena: hyperphosphorylation of Tau-protein, resulting in its accumulation in the neurofibrillary tangles, and the formation of insoluble amyloid fibrils by β-amyloid peptide (βA), deposited early and selectively in senile plaques (1).

In healthy subjects, βA is formed from Amyloid Peptide Precursor (APP) in a reaction catalyzed by α-secretase, an enzyme which produces βA consisting of 40 amino acids. For reasons which are not entirely clear, in AD patients the enzyme involved is not α-secretase, but β-secretase, which leads to production of altered βA, consisting of 40 to 42 amino acids (3). βA is secreted from healthy neural and non-neural cells, such as skin and intestine, and circulates in both human cerebrospinal fluid and blood. Normally, βA is transported across the blood-

Table I. *Principal results of the literature search of the period 1990-2011.*

TOPICS ON AD	PAPERS FOUND			CAUSES OF EXCLUSION
	Total number	Selected number	Excluded number	
Pathogenetic mechanisms	106	56/106	35/56	Repetitive
Oxidative stress and mitochondria	295	102/295	80/102	Repetitive Not innovative
Neuroinflammation and cytokines	126	27/126	12/27	Repetitive Not innovative

brain barrier by LDL receptor-related protein 1 (LRP1). In AD brains, the clearance via LRP1 is disturbed, resulting in accumulation and aggregation of βA peptide (4).

Amyloid beta peptides are considered an important pathological marker of AD, even if neuronal death has been linked to many damaging mechanisms, but the primary cause of the neurodegeneration is still unclear and the pathogenesis of AD still remains elusive at a molecular level. Several hypotheses have been proposed in an attempt to explain the pathogenesis of AD, including theories involving oxidative stress, apoptosis (5), metal ion dysregulation, and inflammation (6). Cholinergic neurons, especially those of cortical, subcortical and hippocampal areas, are particularly affected by this pathological process. In particular, as the hippocampus is involved in learning and memory processes, the loss of neurons of this area is believed to be the main cause of memory reduction of AD patients.

There is an increasing evidence that βA interacts with mitochondria, but little is known concerning the significance of this interaction in the physiopathology of AD. The detrimental effect of βA may lead to mitochondrial dysfunction and degeneration of either neuronal and non-neuronal cells (7). How can βA reach/access mitochondria? Extracellular amyloid fibrils have been shown to bind to cellular membrane and induce expression of components that contribute to further amyloid deposition (8). The aggregation rate is significantly increased by anionic lipids, and the interaction between anionic lipids and βA induces a structural conversion from a random coil to a β-structure (9). Studies show that this conversion results in protein-protein interactions enhanced by βA binding to the cell membrane (9). These structural changes, together with increased membrane permeability led to the formulation of the "channel hypothesis". The interaction of βA with the membrane sustains the formation of small oligomeric complexes that can form multimeric channels with a central pore-like structure (10). In addition to its interaction with the plasma membrane, exogenous βA was shown to be internalized and to accumulate in neurons (1). Several pathways have been proposed to mediate this event, but the specific mechanism involved in βA uptake remains unclear. Within the cell, direct interaction between βA and mitochondria has been shown in human neuroblastoma cells (1). In AD patients, a significant decline in mitochondrial function was observed, perhaps due to the loss of integrity of mitochondrial DNA in differentiated cells, including neurons (1). Oxidative stress due to mitochondrial failure may cause increased amyloidogenic processing of the βAPP, contributing to increased βA production. In support of this mitochondrial mechanism, recent data not only localized βA in mitochondria of AD brain, but also suggested that βA is transported into mitochondria (11). The decline in mitochondrial function can reduce the efficiency of respiratory activity, resulting not only in decreased production of ATP, but also in increased generation of ROS.

In vitro studies highlight how βA neurotoxic properties may be mediated by ROS action. Cells exposed to βA show high levels of H_2O_2 from which the hydroxyl radical can be produced. These results come from the observation that addition of catalase to the cell *medium* protects against βA toxicity; although catalase is able to attenuate the toxic activity of the peptide, it can not reduce the increase in the levels of H_2O_2, suggesting that H_2O_2 is not the only mediator of βA toxicity (12).

Moreover, it was shown that the inclusion of βA in the synapses is also involved in alteration of the activity of some membrane proteins, such as Na^+/K^+-ATPase and Ca^{2+}-ATPase, which in concert with an energetic defect caused by free radical action, may lead to neuronal depolarization, glutamate release, activation of excitatory receptors by glutamate and aspartate, with consequent intracellular accumulation of Ca^{2+}, causing an increase in oxidative stress and energy demand.

Mitochondrial alterations

Mitochondria are cytoplasmic organelles essential for life and death. They perform several cellular functions including: intracellular calcium regulation, ATP production, release of proteins that activate the caspase family of proteases, alteration of reduction-oxidation potential of cells, and free radical scavenging. Mitochondrial number is indeed very high in neurons, and mitochondria are especially enriched in synapses. Due to the limited glycolytic capacity of neurons, these cells are highly dependent on mitochondrial function for energy production. However, as a Pandora's Box, mitochondria are full of potentially harmful proteins and biochemical reaction centres. They may liberate reactive oxygen species (ROS) and free radicals. Thus, mitochondria are major producers of ROS, while being targets of ROS toxicity.

Mitochondrial defects are described in a wide spectrum of human conditions, including degenerative and metabolic diseases, aging and cancer. Several studies have shown that during ageing there is a decrease in mitochondrial activity associated with an increase in mitochondrial DNA (mtDNA) damage, from what is assumed that also mitochondrial dysfunction is involved in the etiopathogenesis of AD (1). Although AD pathogenesis involves a large number of molecular and cellular events, two events that occur early in AD development are synaptic damage (13) and mitochondrial dysfunction (14). Recently, mitochondrial abnormalities in AD have been identified: changes in mitochondrial DNA; decreased

mitochondrial enzyme activities; abnormal mitochondrial gene expressions; increased mitochondrial fragmentation and decreased mitochondrial fusion (15). These events occur very early in the development and progression of AD. Mitochondrial dysfunction has been observed in AD post-mortem brains, in platelets from AD patients, in AD transgenic mice, and in cell lines that express mutant APP and/or cells treated with βA (15).

In AD, mitochondria dysfunctions are included in the neurotoxic mechanisms associated with βA. Growing evidence indicates that βA toxicity can be associated with the outer mitochondrial membrane, intermembrane space, inner mitochondrial membrane, and the matrix (16).

This mitotoxicity is still not clear but may be direct or indirect and several mechanisms have been debated. It is well known that βA crosses the cellular membrane by forming channels with a central pore-like structure (10). Within the cell, it binds to a specific carrier, known as β-amyloid binding alcohol dehydrogenase (ABAD), to reach the mitochondria (17). Transporters may carry it across the two membranes (11). In the mitochondrial matrix, βA binds to ABAD but can also bind to other mitochondrial components. It has also been suggested that βA interacts with mitochondrial proteins from the membrane permeability transition pore (MPTP), resulting in increased permeability of mitochondrial membranes (18).

A working model postulates that βA and/or βAPP interact with mitochondria by inhibiting nuclear-encoded protein import (19). Import deficits are initially insufficient to impair mitochondrial integrity, but over time, cause mitochondrial dysfunction and further import deficits. βA may inhibit protein import by direct interactions with the import machinery or by indirect mechanisms. Furthermore, a decline in protein import appears to precede increased ROS and decreased mitochondrial membrane potential, suggesting a gradual failure of mitochondria.

βA also disrupts calcium homeostasis (20), triggering a major release of calcium from the endoplasmic reticulum. The calcium is taken up by mitochondria and mitochondrial functions are impaired. This influx may contribute to the opening of the MPTP, leading to the collapse of mitochondrial membrane potential. Furthermore, a massive increase in intracellular calcium can initiate both necrotic and apoptotic cell death.

The respiratory chain is embedded in the inner mitochondrial membrane and is disturbed by βA (1). The βA peptide seems to interact with cytochrome c oxidase, decreasing its activity (1), but the specific mechanism involved is still unclear. Govoni et al. (12) report that in AD patients a 25-30% decrease in COX activity in various brain regions was observed. However, this study did not reveal any change in the concentration of cytocrome aa3 (a component of COX), leading to the conclusion that there is a decrease in catalytic enzyme activity, rather than a reduction of concentration of the enzyme. It is pertinent to note that a reduction of COX activity was also observed in peripheral cells, such as fibroblasts of AD patients (21). In these cells, alterations in oxidative metabolism inhibit βAPP processing and amyloidogenic formations (21).

Many authors agree that, in AD, the activity of mitochondrial COX decreases, in both the brain and in fibroblasts, and also in platelets (22). Mancuso et al. (23) have recently confirmed that mitochondrial cytochrome c oxidase (COX) activity is significantly reduced in brain and platelets from AD patients compared to controls. These authors also investigated whether impaired COX activity could have functional consequences on body energy metabolism. Blood lactate concentration was monitored at rest and during incremental exercise in 22 AD patients in whom COX activity in platelets was found to be decreased compared to controls. In both resting and exercising condition, blood lactate was significantly higher in AD patients than in controls. COX activity was inversely related to lactate under resting conditions and a trend toward an inverse correlation under anaerobic threshold exercise level was observed. These results support the hypothesis of a systemic impairment of the mitochondrial function in AD and indicate that decreased COX activity could have functional consequences on metabolism.

Schmidt et al. (24) demonstrated that βA interacts also with mitochondrial ATP synthase resulting in ATP depletion. In contrast, an increase in activity of the cytochrome c reductase (complex III) has been reported in AD (25). Interestingly, complex III appears to be one of the main sites of superoxide radical production. As a result, the inhibition of mitochondrial respiration and the depletion in ATP observed in AD may be associated with the deleterious effects of ROS. Mitochondrial oxidative damage has been reported as an early event in AD progression (15). However, the causal factors are still unclear. Increased ROS levels act at multiple levels to impair mitochondrial function, inducing also mtDNA mutations (16).

Some of the alterations in mitochondrial function in AD have been attributed to mutations of mtDNA (16). Although most mitochondrial proteins are encoded by the nuclear genome, mitochondria contain many copies of their own DNA that encode 13 polypeptide complexes of the respiratory chain. The increased number of mtDNA mutations can be explained by the proximity of mtDNA to oxidative stress generated by the respiratory chain itself, the lack in mtDNA of any protective histone covering, and a deficient repair mechanism, compared to nuclear DNA. Therefore, mitochondria themselves are extremely

sensitive to oxidative stress.

Oxidative stress

Oxidative stress appears to play an important role in the pathogenesis of AD, according to mechanisms not fully understood. Oxidative damage of macromolecules, including lipid peroxidation, protein carbonyl content formation and DNA oxidation was observed in AD patients (26). Also, controversial data exist regarding the alteration of enzymatic antioxidant systems in patients suffering from AD. Studies on post-mortem brain tissue from AD patients showed a significant increase in the typical markers of the oxidative damage (12). A more recent study (27) showed that in patients with late-onset AD serum malondialdehyde (MDA) levels were significantly higher than in control group and high MDA levels were proposed to be an essential factor in the pathogenesis and neuronal damage of AD patients. In contrast, no significant difference in serum glutathione levels (GSH) between AD patients and the control group was observed. The glutathione system is well known to be the most abundant intracellular non-protein thiol acting in important biological processes such as the metabolism of endogenous and exogenous compounds, cell proliferation and regulation of gene expression. An important function of GSH is to detoxify various oxidants by directly scavenging free radicals and GSH acts as a coenzyme in glutathione-peroxidase-catalyzed reactions. It has been well documented that increasing intracellular GSH concentration reduces, whereas decreasing its content enhances sensitivity of cells to oxidative toxicity. Neurons are highly sensitive to oxidative damage, insofar as they have, compared to other cells, relatively lower levels of antioxidants, as well as higher concentrations of iron, which mediates the production of reactive oxygen species (ROS) through the Fenton reaction. GSH is especially important for the central nervous system, not only because it is important in antioxidant defence, but also because it plays a critical role in maintaining blood-brain-barrier integrity and in synthesis of neurotransmitters such as GABA and glutamate (28). Therefore, an alteration in GSH metabolism may cause serious effects on neurons, and a defect in its biosynthesis seems to be associated with neurological problems (28). Liu et al. (29) compared the GSH content in the blood from AD patients with that from age- and gender-matched controls to elucidate potential involvement of alterations in GSH metabolism in AD. The data indicated that GSH content was decreased in the red blood cells from male AD patients, compared with age- and gender-matched controls. However, there was no significant difference in GSH content between female patients and female controls. In contrast with Aybek et al. (27), these results suggest that GSH metabolism may be altered in AD patients and that it is regulated differently in male and female AD patients. The decrease in GSH content in the red blood cells of male patients was associated with decreased activities of two enzymes catalysing *de novo* GSH synthesis, with no change in the levels of glutathione disulfide (GSSG) or glutathione reductase: this suggests that a decreased synthetic capacity may be responsible for the decline of GSH content in red blood cells from male patients. However, the mechanism underlying such gender differences in terms of GSH metabolism in AD is not currently clear. Several epidemiologic studies have shown that testosterone concentrations in plasma and brain are decreased in AD patients compared with controls (30); no significant difference in testosterone or estradiol levels between female AD patients and female control was observed (30). Interestingly, it has been reported that castration decreased GSH, whereas testosterone replacement restored GSH concentration to control levels in experimental animals (31). These data suggest that decreased testosterone might underlie the decline in the GSH content in red blood cells from male AD patients. Further research has to be carried out to clarify this issue.

Bermejo et al. (32) analysed protein carbonyl levels and erythrocyte glutathione system in the plasma of 34 subjects with Mild Cognitive Impairment (MCI), 45 subjects with AD and 28 age-matched control subjects. The results showed an increase in protein modification, a significant decrease in GSH levels and GSH/GSSG ratio in AD and MCI patients, compared to age-matched control subjects. The study shows that some peripheral markers of oxidative stress appear in MCI, with a similar pattern to that observed in AD patients, which suggests that oxidative stress might represent a signal of AD pathology.

An important goal shared by several other studies on AD is the assessment of the variation of other markers of oxidative stress. Relevant antioxidant enzymes include: catalase, glutathione peroxidase, glutathione reductase and superoxide dismutase.

A recent study (33) assessed the degree of oxidative stress in the blood from AD patients: in particular, MDA, SOD, catalase, glutathione peroxidase and glutathione reductase have been evaluated. The most patient-control differences were found in markers dependent on SOD enzyme activity and MDA levels.

Cytokine production and neuroinflammation

Microglia, astrocytes and neurons in the AD brain express and release, in addition to ROS, various neuroinflammatory mediators including complement activators and inhibitors, chemokines, cytokines and inflammatory enzyme systems (34), all of which potentially contribute to further neuronal dysfunction and eventually death. These may create and fuel a vicious

circle in the pathological progression of AD. Recent evidence suggests that inflammation, together with the generation of neurotoxic βA peptides and their deposition along with neurofibrillary tangle formation, may be a third key pathological hallmark which, once initiated in response to neurodegeneration or dysfunction, may actively contribute to disease progression and chronic AD (34).

Microglia represents the brain's innate immune system and hence the first line of defence against bacterial, viral or fungal infection. Although these functions are of major importance and beneficial under normal physiological conditions, it has become clear that microglial activation may also be evoked by endogenous proteins and can significantly contribute to neuronal damage. In AD, activation of microglia occurs in response to formation of amyloid plaques. Microglial cells have been suggested to be preferentially associated with certain amyloid plaque types, indicating that plaque development and the degree of microglial reaction are interrelated (34). However, it remains unclear whether βA plaque deposition is an absolute requirement for microglial activation, or whether this can already be evoked by soluble and toxic βA species.

Along with microglia, astrocytes and even neurons directly react and contribute to the chronic neuroinflammatory changes in AD (34). Both activated microglia and T lymphocytes can be a source of cytokine production such as interleukins (IL), and tumor necrosis factor (TNF). Among these, IL-1β and IL-18 appear to be significantly increased in patients with AD, as well as in amyloid-β-treated neurons and transgenic mice models (35). The immunoreactivity is mainly local. Others have demonstrated that IL-1β can induce the phosphorylation of Tau-protein and hence mediate formation of neurofibrillary tangles (36). TNF-α has also been linked to AD progression, but its role is less clear, since βA can induce TNF-α secretion which, in turn, induces βA production (37). TNF-α has both pro-apoptotic and anti-apoptotic effects. This pro-inflammatory cytokine accounts for most of the neurotoxic activity secreted by monocytes and microglia. On the other hand, TNF-α has been reported to have neuroprotective properties in the AD brain (34). In addition to the general role of cytokines, AD-specific interactions of certain cytokines and chemokines with βA may be pathophysiologically relevant. For example, TNF-α can regulate APP processing and βA production *in vitro*. In turn, fibrillar βA has been reported to increase neurotoxic secretory products, proinflammatory cytokines and reactive oxygen species (34). IL-1, IL-6 and TNF-α increase in a dose-dependent manner after cultured microglia are incubated with βA. Additionally, βA is able to stimulate a NFkB-dependent pathway required for cytokine production (34). The production of interleukins and other cytokines and chemokines may also lead to microglial activation, astrogliosis, and further secretion of pro-inflammatory molecules and amyloid, thus perpetuating the cascade. The concomitant release of anti-inflammatory mediators may partly antagonize the action of pro-inflammatory cytokines, ultimately contributing to the chronicity of the disease.

Additional information on how inflammatory mediators and excitotoxic factors potentiate their detrimental effects is required. Moreover, more information is needed regarding the extent to which inflammatory mediators functionally impair cognition and memory.

Mitochondrial and anti-inflammatory therapeutics

The critical role of mitochondria in the early pathogenesis of AD may make them attractive as a preferential target for treatment. In AD, mutant APP and βA enter mitochondria and/or block the transport of nuclear-encoded mitochondrial proteins to mitochondria, in turn inducing free radicals, increasing oxidative damage, and causing cell death. Through studies elucidating the role of mitochondria in disease onset and development, investigators have begun focusing on developing therapies, such as molecules that target and protect mitochondria and neurons from toxicity aging and mutant proteins.

Given the huge involvement of mitochondrial dysfunction and oxidative stress in AD, it is reasonable to treat or supplement a patient's diet with antioxidants. However, some epidemiologic studies suggest that increased intake of antioxidant vitamins (including vitamin E, vitamin C, and beta carotene) may reduce the risk of developing AD or Parkinson's disease, while other studies did not (14). Currently, available antioxidant approaches are not effective in treating neurodegenerative diseases because naturally occurring antioxidants, such as vitamins E and C, do not cross the blood-brain barrier and cannot reach the relevant sites of free radical generation. To overcome these problems and to better assess whether antioxidant approaches may be valuable therapeutic treatments, improved delivery of antioxidants to the brains of patients with neurodegenerative diseases is needed. In the last decade, considerable progress has been made in developing mitochondrially-targeted antioxidants, but their application is in its early stages, and is focused on animal models of AD, Parkinson's disease, and ALS. Transgenic mice models with some pathological aspects of AD are hence very valuable in monitoring therapeutic interventions at the mitochondrial level. Recent data suggest that natural antioxidants such as a standardized *Ginkgo biloba* extract or the green tea component epigallocatechin-3 gallate may be promising treatment strategies. It is also important to

note that in addition to their antioxidant properties, these compounds stabilized mitochondrial functions such as the mitochondrial membrane potential, ATP levels, and mitochondrial respiratory complexes (38). Moreover, in APP transgenic mouse models, an antiamyloidogenic effect of these compounds was reported by inhibiting amyloid fibril formation either by a direct interaction with βA (39) or indirectly by reducing ROS levels (38). However, the precise actions and the mitochondrial targets of these drugs at the molecular level are unclear and need further clarification.

Other than mitochondrial dysfunctions and oxidative stress, neuroinflammatory changes may occur at early stages in the AD brain and significantly contribute to the pathogenesis of the disease. This raises the question whether therapeutic strategies can be developed which successfully target the ongoing inflammation. Epidemiological studies have suggested a beneficial effect of non-steroidal anti-inflammatory drugs (NSAIDs) in AD (40). In particular, long-term NSAID therapy seemed to delay the onset and progression of AD, reduce symptomatic severity, and significantly slow the rate of cognitive impairment (40). Studies from aged controls and post-mortem AD patients, both on reported NSAID medication, show that long-term NSAID therapy reduces the degree of plaque associated inflammation (34). Nevertheless, these beneficial effects are limited to certain NSAIDs since naproxen and celecoxib were not able to modify AD (34). The underlying mechanisms by which NSAIDs prevent AD are unclear, however several mechanisms have been proposed, and there is the distinct possibility that actions at multiple rather than single level of AD relevant pathology account for the observed beneficial effects of NSAIDs. Potential mechanisms include: 1) protection against βA aggregation through alteration of the β-sheet conformation (34); 2) effect on APP processing, although there is debate about the molecular mechanism involved (34); 3) inhibition of cyclooxygenases, the canonical targets of NSAIDs.

Clinically, novel approaches to visualize early neuroinflammation in the human brain are needed to improve the monitoring and control of therapeutic strategies that target inflammatory and other pathological mechanisms.

DISCUSSION

In this review we summarise the current knowledge on AD pathophysiology in relation to mitochondrial dysfunction, oxidative stress and neuroinflammation. Although existing data clearly highlight a role for mitochondrial dysfunction and oxidative stress in AD, the identification of specific molecular mechanisms underlying β-amyloid-induced neurodegeneration remain to be determined. Rigorous scientific research has identified multiple mechanisms of βA interaction with mitochondria at different mitochondrial compartments: the outer mitochondrial membrane, intermembrane space, inner mitochondrial membrane, and the matrix.

Current developments in therapies for AD are largely based on anti-amyloid strategies and it remains to be shown that such approaches will be disease-modifying or improve cognitive functions. One alternative strategy is to target mitochondria which are central for neuronal survival and have been shown to have impaired function in neurodegenerative disorders. To specifically target an organelle with double membranes is a challenge since the compound has to pass through the blood brain barrier, cell membrane, and mitochondrial membrane. For the last step, one can take advantage of the fact that the matrix of mitochondria is negatively charged and that positively charged molecules will accumulate inside mitochondria. Preservation of proper mitochondrial function is central for the maintenance of synaptic activity and neuronal function in general.

In view of the increasing interest in mitochondrial protection as a treatment strategy in AD, besides strategies with regard to the treatment and/or removal of both βA and Tau pathology, the findings of a substantial protection of mitochondria against βA-induced dysfunction deserve further attention.

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