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Mitochondrial matters of the brain: amyloid formation and Alzheimer's disease introduction

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Abstract In recent years mitochondria, as the most abundant organelles in animal and human cells, have come to the forefront of biomedical research as they are now recognized not only as the major producers of ATP needed to drive cellular functions critical for life, but they are also the instruments of cell death. Not surprisingly, therefore, mitochondria are now known to be involved in many different diseases ranging from those that affect millions worldwide to those that affect only a few, i.e., rare diseases. These diseases include in addition to cardio-myopathies and cancer also diseases that affect many other organs/tissues including the brain/nervous system, the latter diseases now commonly referred to as "neurodegenerative diseases". Specifically, the subject of this mini-review series focuses on the role of mitochondria in Alzheimer's disease, a major age related neurodegenerative disease that results in loss or decline of memory and other cognitive abilities. This devastating disease affects millions of Americans, and globally multi-millions with very grim predictions for the future. Although the molecular and gene-related details that underlie Alzheimer's disease remain to be clearly elucidated, mitochondria appear to be very intimately involved. The purpose of this mini-review series is to summarize how various investigators working on this subject envision the role(s) of mitochondria in Alzheimer's disease. The development of future therapies for this disease is likely to rely heavily on the new knowledge gained.

Keywords Alzheimer's disease · Neurodegenerative diseases · Aging · Mitochondria

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Introduction

It is now known that there are many different types of neurodegenerative diseases. In fact, Wikipedia lists over 40 at this time. Among the most widely known is Alzheimer's disease named after Alosis Alzheimer, frequently credited for its discovery based on his study of a female patient named Auguste D. She had been admitted in 1901 at the age of 51 to the State Asylum in Frankfurt, Germany suffering from cognitive and language deficits, and several other mental related problems. Upon her death in 1906, Alzheimer examined her brain, and presented a talk on his findings in the year 1907 (Reviewed in Berrios 1990).

It would not be until 41 years later in 1948 that Albert Lehninger, then at the University of Chicago, and his graduate student Eugene Kennedy, would report the isolation of mitochondria and confirm that these intracellular organelles are the site of cellular energy production in the form of adenosine triphosphate, i.e., ATP (Lehninger and Kennedy 1948). Although at that time, the thought of relating this new discovery to neurodegenerative diseases was likely only a passing fantasy in Lehninger's mind, he would 22 years later support a study in his laboratory led by a young neuroscientist to isolate mitochondria from both bovine brain and the rabbit cerebral cortex (Hamberger et al. 1970). The lead author on the paper Dr. Anders C. Hamberger, a Post Doctoral Fellow at that time, would later engage in a highly accomplished still ongoing career in the neurosciences at the University of Goteborg, Sweden (Briefly reviewed in Lehmann and Van Gelder 2003).

Equally important, from the date of Kennedy and Lehninger's pioneering study it would be almost another 40 years, i.e., in the 1980s/1990s, that mitochondria would be appreciated as organelles not only involved in producing ATP to energize cellular reactions but also as instruments involved in cell death (reviewed in Newmeyer and

Ferguson-Miller 2003). Unlike Lehninger and Kennedy, three of earliest scientists (Sydney Brenner, H. Robert Horvitz, and John E. Sulston) involved in discoveries related to programmed cell death, would have the good fortune of sharing the Nobel Prize in Physiology and Medicine (Nobelprize.org). Most importantly, the collective knowledge obtained by all and many others has now made it possible for investigators experienced in mitochondrial research to move forward. Working with animal models, or with physicians with expertise in neurodegenerative diseases, they are now making significant progress, not only in better understanding Alzheimer's disease but many other neurodegenerative diseases.

As many in the world are now considered to be in an "aging" population with life expectancies in some countries reaching into the 70s (~78 in the U.S.), an increased focus on research on neurodegenerative diseases directed toward the goal of preventing them altogether or, at the minimum ameliorating their symptoms when they arise, will likely become a universal priority in the future among those agencies that fund biomedical research. Specifically, as it relates to Alzheimer's disease (AD) in the U.S., the following sobering facts and figures have been noted in the most recent published report of the Alzheimer's Association (Mebame-Sims, corresponding author, 2009)

1. AD is the 6th leading cause of all deaths in the United States.
2. Between 2000 and 2006 deaths attributable to AD increased 47%.
3. An estimated 5.3 million Americans have AD.
4. The baby boom population is expected to add 10 million people.
5. In 2050, the incidence of AD is expected to approach nearly a million people per year with a total estimated prevalence of 11 to 16 million people.
6. Significant cost implications related to AD and other dementias include an estimated $148 billion annually.

Initial events in Alzheimer's disease and relationship to mitochondria

In recent years there have been two proteins in the brain that have been widely discussed as it relates to the pathology and biochemistry related to Alzheimer's disease (Luque and Jaffe 2009). One is β-amyloid and the other is tau. As emphasized throughout the recent literature on Altzheimer's disease, β-amyloid (Aβ) is derived from a larger precursor protein known as APP or "amyloid precursor protein", while tau is a protein that helps form microtubules. In the normal brain cells Aβ, the subject of minireviews comprising this volume of the Journal of Bioenergetics and Biomembranes, is not a problem as it is presumably degraded. However, in patients with Altzheimer's disease it is believed that Aβ is not degraded, or

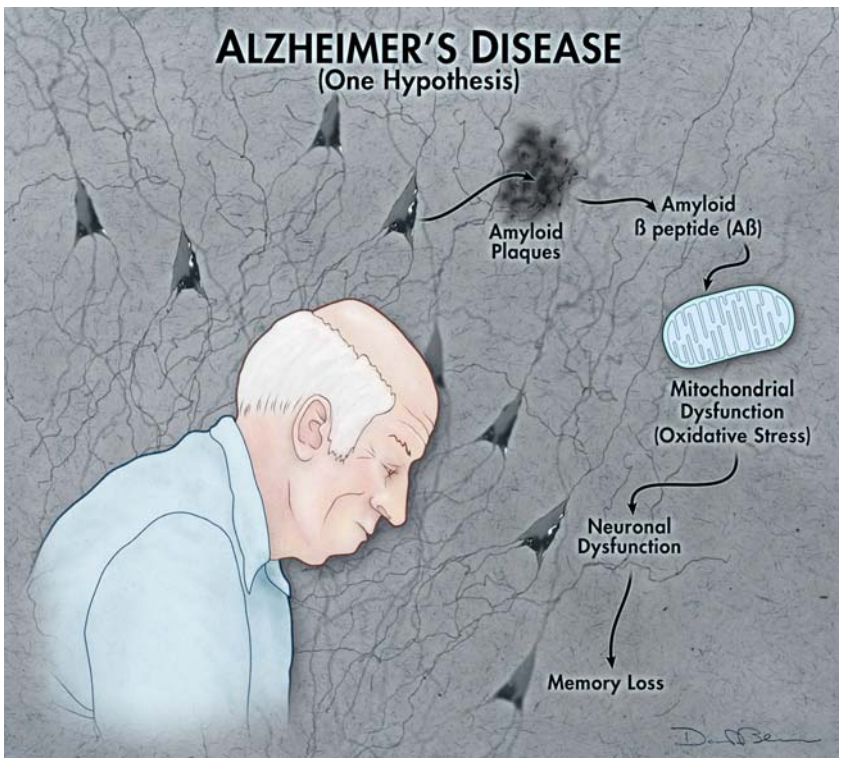

Fig. 1 Alzheimer's disease (AD) is a very serious neurodegenerative disease characterized by cognitive decline (loss of memory) that affects millions of people throughout the world. One of several hallmarks of this disease is the appearance in brain cells of deposits (amyloid plaques) comprised of the protein amyloid β (Aβ). Aβ/oligomers induce oxidative stress and are believed to promote the pathogenesis of AD, i.e., the decline/loss of memory. In this process there is much evidence that the mitochondria play a major role, the focus of this mini-review series. (David Blum, Medical Illustrator kindly generated the Figure)

not rapidly enough. Therefore, it accumulates forming insoluble plaques between nerve cells (Fig. 1). However, any Aβs that are not degraded and either remain inside the cells or dissociate from extra-cellular plaques and re-enter the cells may be deleterious. Considering that brain cells contain numerous mitochondria, by far more than any other organelle, it is not surprising that Aβs' most frequent target (site of action) is likely these organelles.

Brief overview of contributions to this minireview series

The first two articles of this mini-review series, i.e., that of Takasaki (2009) and the other by Mancuso et al. (2009) indicate that Alzheimer's disease is not initiated by events that originate within the mitochondrial genome *per se*. As Mancuso et al. (2009) state: "To date, no surely causative mtDNA mutations have been discovered in AD patients". This is consistent with subsequent articles that focus on events that take place outside the mitochondria that then impact negatively on mitochondrial function. Nevertheless, Takasaki (2009) does indicate in his article that one may be able to predict the probability of an individual becoming an Alzheimer's patient based on mitochondrial single nucleotide polymorphism (SNP) analyses leaving open the possibility of an early diagnosis, or more optimistically the probability of becoming a centenarian.

The following two articles, Colell et al. (2009) and Ferrer (2009), focus on the roles believed to be played by mitochondrial lipids in AD. The former authors propose that in AD, in addition to fostering Aβ generation, mitochondrial cholesterol determines Aβ neurotoxicity via mitochondrial glutathione (GSH), while the latter authors indicate that abnormal lipid raft composition may help modify the activity of key enzymes that modulate the cleavage of the amyloid precursor protein to form toxic Aβ.

In articles by Carvalho et al. (2009) and Sultana and Butterfield (2009) emphasis is placed on a role for mitochondrial ROS in AD. The former authors point out that hypoxia has been implicated in several neurodegenerative diseases including AD, and that the transcription factor HIF-1α (hypoxia inducible factor 1) that triggers death effectors may be involved. The latter authors have found a number of oxidatively modified brain proteins that are directly in or are associated with the mitochondrial proteome, consistent with a possible involvement of the mitochondrial targeted oxidatively modified proteins in AD progression or pathogenesis.

In the article by Alikhani et al. (2009) the authors discuss their work showing that the TOM protein located in the outer mitochondrial compartment is involved in the entry of the Aβ into this organelle, and that the protease PreP is responsible for Aβ degradation inside the mitochondria. In addition, they make the important "therapeutic point" that PreP might thereby rescue mitochondrial dysfunctions and elevated ROS production and abolish neuronal cell death.

The article by Pickrell et al. (2009) focuses on the relationship of cytochrome c oxidase deficiency in the formation of ROS and amyloid plaques as a major change often associated with AD is impairment of the electron transport chain at complex IV (cytochrome oxidase). From their work, they conclude that Aβ formation is a cause of COX deficiency as opposed to a consequence. Finally, in a somewhat related article Atama (2009) summarizes work that relates Alzheimer's disease to heme, the cofactor found in mitochondrial cytochromes that are members of the electron transport chain. Specifically, his group showed that Aβ depletes intracellular regulatory heme by forming an Aβ-heme complex, and that this can be reversed by methylene blue (MB), suggesting that MB or MB like compounds may delay the onset and progression of AD.

In summary, the articles that comprise this minireview volume of the Journal of Bioenergetics and Biomembranes should provide the interested reader with an up to date view of ongoing research in nine different laboratories as it relates to the possible causes of one of the most devastating diseases that affect human kind throughout the world. Clearly, mitochondria, the most abundant organelles in the human brain appear to be intimately involved and therefore merit continued consideration as a therapeutic target in future research on this disease. Also, the discovery of preventive agents is equally important.

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