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Chapter 7

Mitochondrial Function in Alzheimer's Disease: Focus on Astrocytes

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Additional information is available at the end of the chapter

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Abstract

The brain is one of the most energy-requiring organs in the human body. Mitochondria not only generate this energy, but are centrally involved critical cellular functions including maintenance of calcium homeostasis, synthesis of biomolecules, and cell signaling. Even though neurons and astrocytes preferentially use different energy substrates and metabolic pathways, these two cell types are intricately linked in their energy metabolism. Recently it has become clear that astrocytes have a key role in the regulation and support of the neuronal mitochondrial quality control, yet several questions remain unanswered to fully understand the mechanisms of mitochondrial function, transport, turnover and degradation in astrocytes. Alzheimer's disease is the most common neurodegenerative disorder, the exact mechanisms of which remain incompletely understood. The fact that astrocytic mitochondrial dysfunction is an early event in the pathogenesis of Alzheimer's disease suggests that more research on mitochondrial function and impairment is required in the hopes of disease alleviation in the future.

Keywords: mitophagy, energy metabolism, brain, neurodegeneration, mitochondrial quality control

1. Introduction

This chapter summarizes the importance of proper mitochondrial functioning in the central nervous system, with a special focus on astrocytic mitochondria and their quality control. Mitochondrial function is next discussed in the context of Alzheimer's disease (AD), before finally casting a look at potential future therapeutic approaches to modulate these events in astrocytes.

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2. Energy metabolism in the brain

The brain is one of the most energy-requiring organs in the human body, yet it contains relatively few energy reserves. The daily energy consumption of the brain is 20 times higher than that of skeletal muscle [1]. Related to its mass, the brain utilizes a large proportion of all the oxygen and glucose available in the body. Despite the fact that the mass of the human brain corresponds only to 2% of the total body weight, the brain utilizes around 20% of the all energy received from glucose [2]. In mammals, glucose is considered to be the main energy source for the brain and especially for the neuronal cells with a high-energy demand, it is converted to adenosine triphosphate (ATP) in the cell's mitochondria [2]. In neurons, the requirement for energy is highest in the synaptic regions where the signal transmission between two neurons takes place [3].

The brain is fuelled mainly by blood-derived glucose, but during some conditions, such as starvation or physical activity, ketone and lactate from blood flow are also used for energy [4, 5]. Glucose and lactate enter the brain through specific glucose transporters (GLUTs) and monocarboxylate transporter (MCTs) for further metabolic processing. There are three main glucose metabolic pathways: aerobic and anaerobic glycolysis (generates pyruvate and lactate, respectively), pentose phosphate pathway (generates NADPH and pentose), and glycogenesis (generates glycogen) [6, 7].

Neurons are highly energy demanding in comparison to other brain cell types [8]. Even though neurons and astrocytes preferentially use different energy substrates and metabolic pathways, these two cell types are intricately linked in their energy metabolism. Astrocytes are responsible for energy production, storage and delivery in the brain, and are considered as the main energy supplier for neurons [7]. For example, astrocyte-derived lactate has been shown to play a crucial role in long-term memory formation and neuronal activity control [6, 9]. Astrocytes are critical for brain energy cooperation and in addition to carrying out metabolic pathways such as aerobic glycolysis and glycogenesis, they release lactate and regulate glutamate homeostasis [7, 8].

Astrocytes uptake glucose from capillaries through GLUT1 transporters. Through glycolysis glucose is converted to pyruvate and then to lactate, which is released into the extracellular space [10]. Astrocytes are the main cellular reservoir of lactate, which is mainly produced from glycogen [9, 11, 12]. Through the so-called astrocyte–neuron lactate shuttle, lactate enters neuronal cells from the extracellular space through MCTs to be used in the tricarboxylic acid (TCA) cycle for generation of ATP – the major player in intracellular energy transfer [10]. Despite the fact that astrocytes and neurons both consume glucose and lactate, these two types of cells have very different metabolic profiles. Under normal physiological conditions astrocytes take up more than 80% of glucose, whereas neurons utilize limited amounts of glucose [7]. Astrocytes also have a higher glycolysis rate than neurons [6]. The specific activity of 6-phosphofructo-1-kinase (PFK1), a master regulator of glycolysis, is fourfold higher in astrocytes than in neurons [13].

Glutamate, most well known for being the main excitatory neurotransmitter in the brain, is also a key player in energy metabolism. Astrocytes take up glutamate from the synaptic cleft via glutamate transporters, and either transform it into glutamine, or utilize it in the TCA cycle [10]. Interestingly, glutamate uptake also increases glucose utilization and promotes astrocytic lactate production to provide energy sources for neurons [5, 14, 15].

3. Mitochondrial function in the brain

In the human body the fatty acids and carbohydrates acquired from the diet form a base material for a chain of oxidative reactions where the energy is stored in small energy rich molecules such as ATP. Mitochondria are called the small powerhouses of the cell, which in oxidative conditions take the major responsibility for ATP production. Based on an endosymbiosis theory, the mitochondria originate from an aerobic proteobacteria engulfed by a prokaryotic cell. Nowadays they are important organelles of the eukaryotic cell, with various tasks critical for cellular health and well-being [16].

In addition to being the key organelles for energy production, mitochondria also take care of other critical cellular functions including maintenance of calcium homeostasis, synthesis of biomolecules, and cell signaling [17]. Related to calcium homeostasis, the mitochondria function as Ca^{2+} storage reservoirs in cells. Calcium is an important signaling molecule, the release of which from the mitochondria to the cytosol is tightly controlled [18]. Depolarization of the mitochondrial membrane potential releases Ca^{2+} to the cytosol, which can induce cell apoptosis [19]. Induction of apoptosis leads to cytochrome c release, which activates pro-apoptotic caspases when released to cell cytoplasm from the inner membrane of the mitochondria.

In comparison to astrocytes, neurons express or have less active enzymes for protection against oxidative stress [20]. Because of this, neurons are dependent on the nearby astrocytes in their strategies to cope with reactive oxygen species (ROS). The ROS have in tightly controlled amounts an important function as signaling molecules in the cell. However, in situations of uncontrolled high concentrations of ROS, the cell may face a harmful cascade leading to disruption of cell structures, apoptosis and senescence. In the brain the ROS can originate from either exogenous or endogenous sources. Exogenous sources for ROS include for example ultraviolet (UV) radiation and toxins, chemicals or drugs that produce ROS as their by-products in the body [21]. Importantly, mitochondria are considered as a significant endogenous source for ROS [22, 23]. It has also been reported that exogenous ROS may also induce the release of endogenous ROS from the mitochondria [24]. In summary, mitochondrial ROS are important signaling molecules, controlling the balance of which is important to limit the harmful effects of ROS overload in the brain.

In addition to their various important roles, mitochondria have also been reported to affect cognitive function and memory in the brain. Recently it was observed that the amount and

morphology of the presynaptic mitochondria in specific brain regions affects memory and synaptic health in non-human primates [25]. The study shows that estrogen treatment, which has been considered to enhance working memory, prevents working memory impairment in aged ovariectomized monkeys. The monkeys treated with cyclic estradiol had a higher number in total and less morphologically malformed donut-shaped mitochondria in their presynaptic regions compared to controls. This observation sets as of yet unanswered questions of even wider functions of mitochondria in the mammalian brain.

4. Mitochondrial function in astrocytes

According to recent calculations, the human brain is estimated to contain glial cells and neurons in a ratio of 1:1 [26]. The major glial cells are classified as oligodendrocytes, microglia and astrocytes. The astrocytes play a central role in maintaining of CNS homeostasis, expression of neurotransmitters and neuroprotection [27]. The astrocytes co-operate closely with the neurons, being critical components of important processes such as synapse formation, maintenance of synaptic plasticity, maintenance of blood brain barrier integrity and removal of excessive neurotransmitters from the synaptic cleft [28]. The morphology of astrocytes is ideal for their various functions. Each astrocyte has its own territory in the brain, with minimal overlapping with other cells [29]. The astrocytes can communicate with neurons and reach the synaptic regions with their fine shaped processes, and reach the brain vasculature with larger protrusions (endfeet). Notably, the astrocytic endfeet is potent at regulating the cerebral blood flow [30].

Mitochondrial dynamics of astrocytes is less studied than that of neurons. Enzymes metabolizing glycogen are highly expressed in astrocytes and thus astrocytes in the human brain are usually considered more glycolytic in their energy metabolism compared to highly oxygen dependent neurons. However, besides glycolytic metabolism, there is also evidence of a strong aerobic metabolism in astrocytes [31]. Glycolysis in astrocytes is directly linked to the energy metabolism in neurons via the astrocyte–neuron lactate shuttle. There the lactate, produced in astrocytes, can be transferred to neurons as a supplement for their TCA cycle in mitochondria [32]. Therefore, neurons and astrocytes are intricately linked in their energy metabolism, and in mitochondrial function.

Following signal transmission between two neurons, astrocytes surrounding the synapse clear the neurotransmitter glutamate from the synaptic cleft via specific glutamate transporters expressed in their cell membrane. The glutamate taken up by astrocytes is then converted either to glutamine and released back to neurons, or used as fuel in the TCA cycle in the mitochondria in the form of α-ketoglutarate. The enzymes required for this glutamate metabolism are expressed in astrocytes at high levels [31]. The neuronal activity and following glutamate uptake by astrocytes has also been reported to affect mitochondrial movement inside the astrocytes. The astrocytes are endowed with the ability to pause or move mitochondria in cell compartments with highest activity [33, 34].

5. Mitochondrial quality control

Due to the significance of mitochondria to the well-being of cells, the mitochondrial quality is hierarchically regulated and controlled, aiming to maintain a healthy population of mitochondria. The quality control system regulates mitochondrial biogenesis, dynamics, and degradation, and through influencing mitochondrial health, has major potential to improve health and lifespan [17]. In order to maintain this population of fully functional and morphologically optimally shaped mitochondria, the mitochondria constantly take part in a cycle of fusion and fission events [35]. However, the cell also requires another strategy to degrade severely damaged or surplus mitochondria. Due to the fact that compromised mitochondria release potentially harmful substances such as cytochrome c and calcium [36], it is very important that defective mitochondria are eliminated quickly and efficiently. Efficient degradation of damaged mitochondria is particularly important for neurons because their survival and activity depends on mitochondrial homeostasis [37, 38]. In general, macroautophagy is a process through which organelles and cytosolic components are engulfed in membrane-bound vesicles and degraded upon fusion with lysosomes. It serves housekeeping function essential for homeostasis and survival of the cells. The specific process through which severely damaged or surplus mitochondria are degraded through an autophagic process is called mitophagy [39, 40]. Mitophagy is a crucial mechanism for mitochondrial quality control [41]. The fact that the majority of mature lysosomes are concentrated close to the cell soma [42] brings yet another challenge for neuronal mitophagy: axonal transport of damaged mitochondria to the soma takes time although rapid degradation is required to prevent the release of toxic substances.

Until very recently, it was presumed that each cell in the central nervous system degrades its own cell organelles. This notion was revoked by a study showing that the majority of neuronal mitochondria in axons are internalized and degraded by adjacent astrocytes with high phagocytic activity under normal physiological conditions in vivo [43]. This process of transcellular mitochondrial degradation is known as transmitophagy (TM). Using a tandem fluorophore protein reporter of acidified mitochondria, the study showed that acidified axonal mitochondria are associated with astrocytic lysosomes in the optic nerve head. After this phenomenon was found there have emerged also other studies stating that the transfer of mitochondria between neurons and astrocytes occurs the other way around as well. For example, astrocytic mitochondria transferred in extracellular particles have been shown to be functional in neurons. The transfer of mitochondria is suggested to be mediated via CD38 signaling, an important enzyme for calcium signaling in the cell [44]. However, it should be noted that the results presented by Hayakawa et al. [44] have also received commentaries about proof of the actual internalization and functionality of the astrocytic mitochondria in neurons [45].

Previous studies show that the fine astrocytic processes contacting the synaptic regions contain plenty of mitochondria [31]. In addition, the mitochondria in astrocytic fine processes are smaller in size and less elongated than those located in the major branches around the cell

soma [46]. These results awake further interest of whether TM or the transfer of mitochondria between brain cells are universal phenomena critical for the proper functioning of mitochondria in the healthy and diseased brain.

6. Astrocytes in Alzheimer's disease

AD causes an enormous socio-economic burden on societies as it impacts millions of people. It is the most common chronic neurodegenerative disorder that is associated with cognitive decline and progressive memory loss [47]. AD pathology is characterized by accumulation of misfolded amyloid beta (Aβ) proteins in extracellular amyloid plaques, deposition of modified tau proteins in intraneural neurofibrillary tangles, and sustained neuroinflammation and oxidative stress [48]. There are two types of AD: familial (FAD) and sporadic. Familial AD affects a small minority of patients and is associated with mutations in genes encoding amyloid precursor protein (APP) or the presenilins (PSEN1 and PSEN2) [49, 50]. Approximately 95% cases of AD are sporadic and are associated with age-related increase in free-radical production, oxidative stress, impaired mitochondrial energy metabolism and mitochondrial dysfunction [51]. There is a great deal of research that has contributed to our understanding of the etiological and pathological features of AD, but the cause and underlying mechanisms of this disease remains incompletely understood. Because of this, there is no effective cure for AD.

To study AD mechanisms and test new therapeutic approaches preclinically, a large number of animal models have been developed. For example, in the non-transgenic AD model, Aβ or tau proteins are injected into the rodent brain. In transgenic AD animals, single or multiple mutations in genes associated with AD (such as APP, PSEN1/2, tau) are introduced to model familial AD. Transgenic AD models can be divided into two different groups depending on plaque deposition – early plaque AD models such as APPswePS1dE9, 3xTG-AD, 5xFAD, and late plaque AD models such as TG2576, PDAPP-J20 [52]. In addition to rodent models, recent advances in stem cell technologies have promoted the use of human-based cell models for AD research. For example, it is now possible to model AD in vitro by using induced pluripotent stem cells (iPSCs) and cells derived from these by differentiation [53–55].

A full understanding of the importance of astrocytes in AD has become evident only recently. For a long time it has been known that astrocytes have numerous functions that act at maintaining of CNS homeostasis and the blood brain barrier, expression of neurotransmitters and neuroprotection, supplying neurons with energy and antioxidants [27, 28]. Even though Alois Alzheimer first observed pathological astrocyte modifications in the AD brain over a century ago [56], it is only now becoming clear that the dysfunction of astrocytes is an essential and even early component of many neurodegenerative diseases, including AD [27, 57].

Researchers have utilized several AD animal models for studying astrocyte alterations associated with AD. For example, in the 5xFAD mouse model, expressing five FAD mutations

in genes encoding APP and PSEN1 [58], impairment in energy metabolism and activation status in neonatal astrocytes of transgenic mice was very recently discovered [59]. In addition, an impairment in Aβ uptake and neuronal support was demonstrated in old 5xFAD astrocytes [60]. In another mouse model of AD, the 3xTG-AD mice (with three FAD mutations in genes encoding APP, PSEN1 and tau) atrophy of astrocytes was described to start early, at the age of 3 months [61, 62]. The double transgenic APPswePS1dE9 AD mouse model has revealed a decline in normal functioning of old astrocytes leading to diminution of neuronal support [63]. At the same time, astrocytic pathology associated with AD is also found in late plaque AD models. In [64] authors shown the involvement of astrocytes in the degradation of amyloid plaques and autophagic processes in PDAPP-J20 mouse model of AD. In contrast, results in the TG2576 mouse model demonstrated that reactive astrocytes become Aβ producers through expression of BACE1, which catalyzes the first step in the formation of the Aβ peptide from APP [65].

It is important to note that rodent astrocytes are different from human astrocytes. For example, human astrocytes are larger and more complex in morphology and they have faster calcium responses and more robust responses to glutamate [66]. Very recently, AD-associated astrocyte dysfunction has also been described in human iPSC-derived cell models. Using this model, atrophy of astrocytes and abnormal expression of astrocytic markers were demonstrated in iPSC-derived astrocytes from patients with familial and sporadic forms of AD [54]. We have also shown that iPSC-derived AD astrocytes are compromised in neuronal supportive function, and display increased β-amyloid production and oxidative stress, altered cytokine release, and dysregulated Ca2+ homeostasis [67]. In addition to cellular models, human post-mortem brain from AD patients also can be used for the study astrocytic pathology at the disease end stage. In recent studies, astrocytic atrophy also was found in FAD human post-mortem brain [57].

Recently it has become realized that there are two types of reactive astrocytes: A1 astrocytes, which are harmful and induced by neuroinflammation, and A2 astrocytes, which are helpful and induced by acute brain injury [68, 69]. The A2 astrocytes have a protective role and promoting neuronal survival, whereas A1 astrocytes are destructive for neurons and have neurotoxic properties [70]. In human AD, harmful A1 astrocytes constitute the majority of all astrocytes in CNS and can play a crucial role in induction and progression of AD [70].

Astrocyte dysfunction, so called "reactive astrogliosis," is associated with all neurodegenerative diseases including AD, and characterized with various complex molecular and functional changes in the cells [71]. Both in the human and in rodent AD brain, reactive astrocytes are characterized by hypertrophy and overexpression of intermediate filaments like glial fibrillary acidic protein (GFAP) [69, 72]. Alterations in astrocytes lead to changes in synaptic activity and neuronal survival [73]. It is interesting to note that in the CA1 subfields of the hippocampus, reactive astrocytes, proximal to Aβ plaques, have significantly higher GFAP expression than astrocytes distal to amyloid plaques [62, 71]. Moreover, these distal astrocytes display atrophy [62], which is thought to occur before plaque formation, suggesting that astrocytes may be associated with early changes occurring during the development of AD [32].

AD astrocytes are also characterized by a number of molecular alterations. Dysregulation in the release of chemical neurotransmitters including glutamate, D-serine, GABA, as well as calcium in astrocytes leads to a disturbance in the normal communication between neurons and astrocytes and eventually impairs synaptic plasticity [32, 71]. Moreover, the majority of hippocampal astrocytes (86%) in the AD brain express heme oxygenase (HO-1), while normal astrocytes almost do not express HO-1 at all (6–7%). This is indicative of oxidative stress occurring in the astrocytes during AD [74].

In the AD brain, reactive astrogliosis is associated with a reduction of normal astrocyte glycolytic activity in response to Aβ [75]. As mentioned above, astrocytic glycolysis has a central role in supplying neurons with lactate, which is crucial for long-term memory formation [6, 9, 76]. Reduction of lactate released from astrocytes has been demonstrated in arctic Aβ mice [77]. Moreover, correlation of memory impairment with reduced level of hippocampal lactate has been reported to occur in response to Aβ in rats [78].

7. Impaired mitochondrial function in Alzheimer's disease: focus on astrocytes

In the last years, research on neurodegenerative diseases has begun to change its focus from neurons to the neighboring supportive cells. For example, it is now known that astrocytes have a key role in the regulation and support of the neuronal mitochondrial quality control [79, 80]. Furthermore, recent studies in the AD field have shifted attention from the "amyloid hypothesis" to the "neuroenergetic hypothesis" [81], thereby focusing on the importance of the cellular bioenergetic interplay in disease conditions. In this part of the chapter we summarize what is thus far known about the impairment of astrocytic mitochondria in AD.

Impairments in mitochondria of brain cells lead to cerebral hypometabolism - specifically neurons are very sensitive to alterations in basal energy levels since they need a fine energetic homeostasis to employee their function (**Figure 1**). As the mitochondria are the principal source of ATP as well as of ROS, they retain a critical role at the centre of a complex web of processes leading to cellular and organismal aging and neurodegeneration [82]. Studies on mitochondrial function specifically in astrocytes have shed some light on the pathological features of AD. Already almoust 10 years ago Kaminsky and Kosenko [83] investigated the effects of Aβ peptides on mitochondrial and non-mitochondrial sources of ROS and antioxidant enzymes in rat brain in vivo: the authors demonstrated that the continuous infusion of Aβ for up to 14 days stimulated the generation of hydrogen peroxide in isolated neocortical mitochondria through an alteration of the antioxidant enzymes activity. Abramov et al. [84] demonstrated that Aβ peptides induce a loss of mitochondrial potential ($\Delta\psi m$) in astrocytes but not in neurons, with a remarkable augmentation of intracellular calcium concentrations [85]. Calcium overload is considered the main biochemical feature of Aβ excitotoxic stress and it causes free radical accumulation in neurons and the formation of the mitochondrial permeability transition pore (mPTP) [86]. The formation of the

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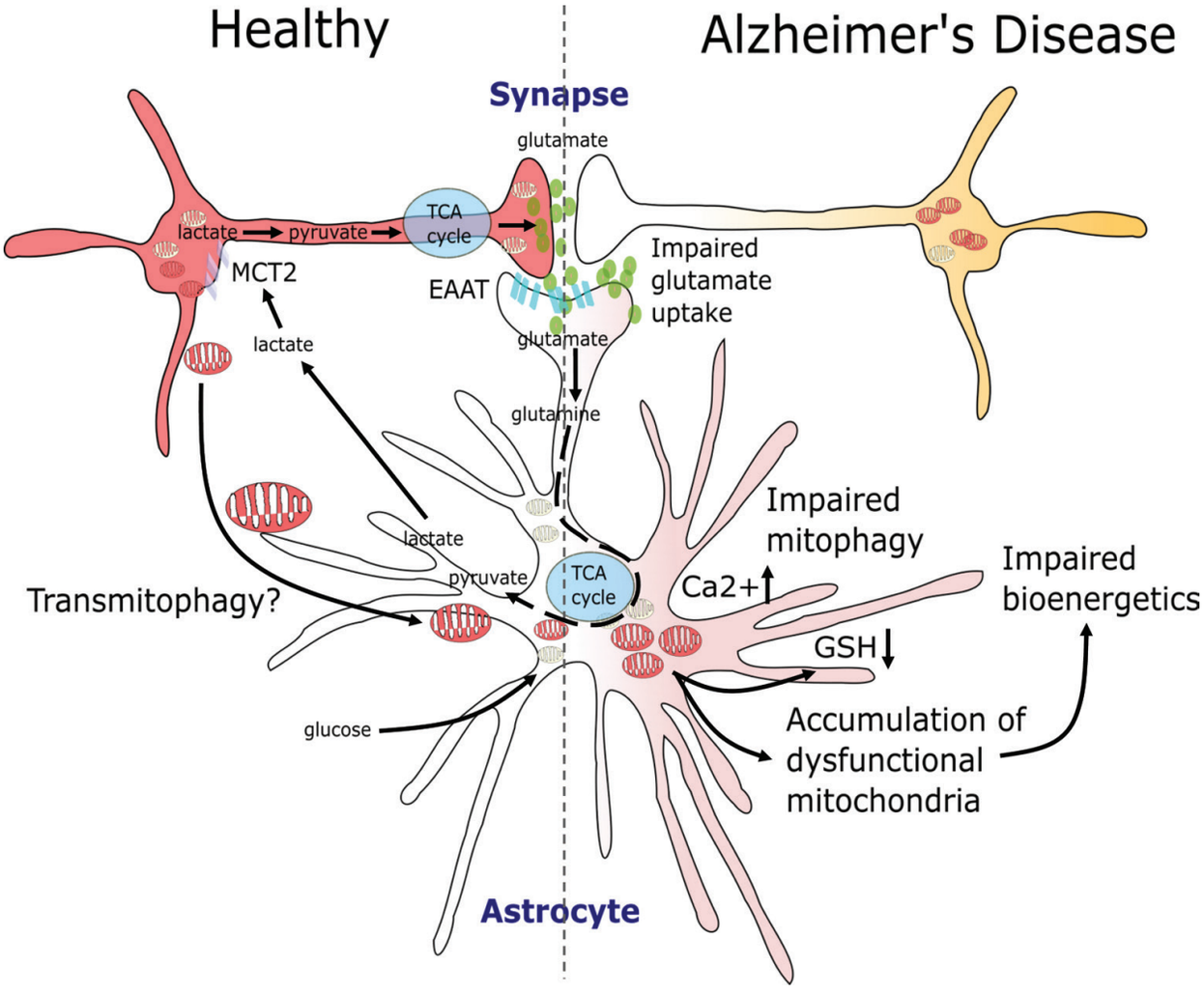

Figure 1. Alzheimer's disease pathology alters astrocytic neurosupportive functions.

mPTP leads to a phenomenon known as mitochondrial swelling, which occurs along with several mitochondrial perturbations described in "the mitochondrial cascade hypothesis in AD" [87]. Mitochondrial impairment precedes AD-associated synaptic damage, neuronal cell death and deficits in learning and memory [88]. Importantly, mitochondrial dysfunction is a key cellular feature of both sporadic and genetic AD and observed also in apolipoprotein E-4 (ApoE4) carriers [89]. This suggests that mitochondrial dysfunction is a key pathological feature of AD [90].

The central nervous system presents a high rate of production of oxidative molecules and relative low levels of antioxidant agents. It is particularly sensitive to oxidative damage because of the high consumption of oxygen, the presence of membrane polyunsaturated fatty acids susceptible to free radical attack, and the low ratio between ROS and antioxidant enzymes [91]. Astrocytes support neurons in the fight against oxidative damage by production of glutathione (GSH), the main antioxidant of the brain. Already some 25 years ago

it was reported that impairment of astrocytic antioxidant systems causes neuronal death: Sagara et al. [92] demonstrated that there is a relationship between the GSH decline in neurons exposed to Aβ1-42 neurotoxic peptide and the concomitant decrease of GSH levels and the increase of intracellular calcium influx in astrocytes. The reduction of GSH and the increase of oxidation of proteins related to energy metabolism could be a consequence of the altered regulation of the transcription factors controlling nuclear and mitochondrial oxidative phosphorylation (OXPHOS) genes in brain cells. Reduced levels of nuclear respiratory factor 2 (NRF2), peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) and mitochondrial transcription factor A (TFAM) are reported in hippocampal tissues from AD brain [93]. These transcription factors regulate the mitochondrial quality control system through mitochondrial biogenesis, the fission-fusion cycle of mitochondria and mitophagy.

A defective mitochondrial dynamic induces a structural change of the organelles. Baloyannis [94] described morphological alterations of the mitochondrial cristae, accumulation of osmiophilic material, and decrease of mitochondrial size to be associated with AD. The quantification of mitochondrial DNA (mtDNA) revealed low levels in AD subjects in the cortical and hippocampal areas [95, 96], which may reflect a diminished number and mass of mitochondria in AD. However, a complex picture was presented by [97], where the authors demonstrated that by measuring the mtDNA present in phagosomes together with the mtDNA in healthy mitochondria the quantification resulted in higher levels in AD subjects than in controls. The observation of an augmented number of unhealthy mitochondria in AD is corroborated by a study showing an increased number of fragmented mitochondria in Aβ stimulated astrocytes [98]. In addition to having effects on mitochondrial fragmentation, Aβ results in increased glycolysis, augmented ATP levels and the maintenance of the mitochondrial potential ($\Delta\psi m$) in exposed astrocytes [99].

Mitochondrial trafficking through the astrocytes and the localization of these organelles along the fine processes (<600 nm of diameter) of reactive astrocytes may be disrupted due to loss of genes implicated in neurodegenerative diseases. For example, PARK-2 mutations may alter the Parkin-mediated turnover of Mitochondrial Rho GTPase 1 (Miro1), a key regulator of mitochondrial trafficking. Miro1 is required to tether kinesin motor protein complexes to the outer mitochondrial membrane (OMM) and modulate the fission-fusion ratio, mitophagy and mitochondria-endoplasmic reticulum interaction [100]. Alterations to the trafficking of astrocyte mitochondria could disrupt the supportive functions of astrocytes. For example, it is well-known that astrocytes deplete the glutamate present in the synaptic left through glutamate transporters, and this is fundamental for the functionality of neurotransmission [101]. Loss of astrocyte mitochondrial function is related to the inability of astrocytes to convert glutamate to glutamine and is known to precede neuronal glutamate excitotoxicity [102]. Genda et al. [103] demonstrated the co-localization of the glutamate transporter GLT-1 with the sites of high neuronal transmission activity in hippocampal sections: furthermore, the authors observed the co-compartmentalization of mitochondria in the areas of higher concentration of glutamate transporter GLT-1. Mitochondria are not-uniformly distributed along the astrocytes but

they are an important source of energy in the contact areas with neurons to contribute to neuroprotective function against toxic insults. The mitochondria of astrocytes thereby play a direct role in glutamate-mediated synapsis homeostasis and in the hippocampal neuronal transmission: the organelles provide the ATP for the glutamate-glutamine shuttle to supply the energy demand in situ.

Very recently it was shown that human AD astrocytes have an altered display of mitochondrial encoding genes when compared to healthy controls [104]. The authors performed total RNA sequencing of the astrocytes to shed light on the molecular differences caused by the disease. PITRM1/PREP/MP1, localized in mitochondrial matrix and encoding an enzyme that degrades the Aβ peptide, was shown to be downregulated in AD. NDUFA4L2, encoding a protein that inhibits Complex I activity, was upregulated in AD astrocytes. In addition, MTND1P22, most likely a long non-coding RNA involved in the regulation of NADH dehydrogenase 1, was also altered in the AD astrocytes. This evidence pointing to the importance of mitochondria specifically in AD astrocytes is supported by further studies on the effect of Aβ on the functions of astrocyte mitochondria. Aβ induces ATP synthase uncoupling in astrocytes [105], increased β-amyloid/APP lead to reduced expression of superoxide dismutase and results in increased age-related oxidative stress in astrocytes [106], and Aβ/APP localizes on the mitochondrial inner membrane of astrocytes and disrupts Complex IV (COX) activity and APP processing by β-secretase [107]. Taken together, these studies support the evidence that exogenous Aβ treatment is sufficient to induce mitochondria-mediated apoptosis and that a dysfunction in astrocytic mitochondrial quality control is a key part of the pathophysiology associated with AD.

Astrocytes are an essential source of energy for neurons by providing the neurons lactate. Astrocytes also participate in the clearance of glutamate from the synaptic cleft, take up neuronal mitochondria and are an important source of antioxidant enzymes, such as GSH. In AD, these normal astrocytic functions are altered leading to increases in astrocytic intracellular calcium, reductions in the levels of GSH and mitochondrial dysfunction. The normal intracellular degradation pathway for non-functional mitochondria, mitophagy, is impaired, leading to accumulation of non-functional mitochondria. In summary, these events lead to impaired astrocytic bioenergetics and impaired glutamate uptake from the synaptic cleft, greatly influencing neuronal health and contributing to the pathology progression.

8. Therapeutic approaches targeted to modulation of mitochondrial function in Alzheimer's disease

There are a huge number of therapeutic approaches that have been trialed in AD, yet the only approved treatments only delay the inevitable and no cure for this devastating disorder exists. A critical difficulty in neurodegenerative disorders such as AD is the relative late onset of the symptoms united to a progressive degeneration, and late disease diagnosis.

At the time of diagnosis, neuronal impairment is often too far for effective intervention. Furthermore, the anatomical site affected in these disorders is often difficult to access by potential therapies.

Pharmaceutical companies have invested heavily in a variety of potential therapies to modulate AD: the well-known memantine, reducing the glutamate excitotoxicity, is considered one of the best available therapeutics for AD but still the possible long-term side effects are unknown [108]. In order for new approaches for a future therapeutic to be effective it is believed that early and better diagnosis methods are needed in order to prevent AD progression [109]. Mitochondria-targeting therapies are a novel approach that have potential to be used in the early onset of cognitive impairment. Mitochondrial oxidative damage is considered an early event of the disease process, which becomes more pronounced as AD progresses [110]. Mitochondrial dysfunction precedes Aβ plaque deposition [111] and is accompanied by a progressive reduction of the cerebral metabolic rates of glucose. Thus, several new therapeutic approaches have tested the efficacy of mitochondria-targeted molecules in delaying AD progression. For example, around ten clinical trials demonstrate that modulation of mitochondrial function rescue neuronal death and synaptic toxicity caused by Aβ exposure [112].

Mitochondrial medicine includes both life style intervention and pharmacological approaches. The Mediterranean diet [113], exercise [114] and caloric restriction [115, 116] have been shown to modulate AD risk factors including the mitochondrial healthy homeostasis. In combination with these, several preventive approaches have been studied in AD patients, for example the antioxidant N-acetyl cysteine (NAC) [117], α-lipoic acid (LA) [118] and curcumin [119] have been tested. Some clinical studies in particular demonstrate that NAC reduces brain oxidative stress through increasing GSH-mediated protective activity against Aβ deposits and lipid peroxidation, and decreasing acetylcholine levels and choline acetyltransferase (ChAT) activity [120]. In addition, several clinical trials used well-known molecules to limit oxidative damage: vitamin E (α-tocopherol) rescues cognitive impairment and oxidative stress in early phase of AD in pre-clinical studies [121] even though there are controversial results in clinical trials in human AD subjects [122]; Donepezil enhances the mitochondrial resistance by inhibiting the mitochondrial permeability transition pore (mPTP) in a mouse model of AD [123]. Other pre-clinical studies demonstrating potent mitochondrial effects have not yet been assessed in clinical trials but show great promise. For example, conjugated Coenzyme Q with a lipophilic triphenylphosphonium (TPP^+) form MitoQ that protect primary cortical neurons from Aβ toxicity, loss of mitochondrial membrane potential and ROS production [124]; Szeto-Shiller antioxidant peptides allow the localization of antioxidant molecules in the mitochondrial matrix, the major source of ROS, and in particular SS31 shows a neuroprotective effect [125, 126]. Furthermore, endogenous compounds such as peroxiredoxine (Prdx) [127] and the natural molecules such as alkaloid caffeine [128], polyphenol resveratrol [129] and gypenoside XVII (GP-17) [130] have been used to modulate the bioenergetic homeostasis at different levels in AD mouse models. The antioxidant approach may have wide applications; however, it could also present some controversial effects on mitochondrial adaptation. For example, mitohormesis, an adaptive response that

improves overall oxidative stress resistance induced by caloric restriction and exercise, may be inhibited by antioxidants [131].

The hypothesis that impaired mitophagy in both neurons and astrocytes may lead to AD neurodegeneration and the potential of the mitophagy process as a therapeutic target needs further clarification. Pre-clinical studies introduce novel therapeutic molecules such as p62-mediated mitophagy inducer (PMI) and Mitochondrial division inhibitor 1 (Midvi-1) for this purpose. PMI is a recently described compound developed to upregulate p62 via stabilization of the transcription factor Nrf2 and to promote mitophagy [132]. This molecule has not yet been tested against neurodegeneration. Midvi-1 is a small molecule non-competitive inhibitor of dynamin-related protein 1 (Drp1) GTPase activity, which attenuates Drp1 mediated mitochondrial-fission and enhances the mitochondrial rescue through inactivation of PINK1 [133]. Recently, Manczak et al. [134] proposed a Drp1 based therapy in the context of AD: the authors demonstrated that the interaction of Drp1 with Aβ increases as AD progresses and that a partial reduction of Drp1 reduces Aβ deposition, reduces mitochondrial dysfunction and enhances mitochondrial biogenesis.

It is noteworthy that most of the therapies for AD applied target neurons as the main cell type involved in neurodegeneration. Given that several therapeutic approaches have been attempted that do not completely rescue AD progression suggests that we should once more consider the cellular target against which we focus. A step towards the right direction has been taken by the scientific community in beginning to consider microglia as a therapeutic target for neurodegeneration because of their involvement in neuroinflammation. For example, the synthetic compound Midvi-1 attenuates mitochondrial-induced apoptosis in primary microglial cells in an Aβ-induced model of AD, thereby counteracting the neuroinflammation [135], and the endogenous compound melatonin has a protective role against cognitive decline and restores mitochondrial respiratory rate in microglial cells of the APPsw mouse model of AD [136].

The increasingly evident key role of astrocytes in supporting neurons against neurodegeneration suggests that probing the unexplored field of mitochondrial-targeted therapies in astrocytes is needed. Currently, there is no relevant literature about astrocyte-targeted therapies, possibly because they are thought to be more involved in the late phases of AD progression. However, modulating early changes in these cells might prove to be more beneficial than targeting downstream pathways.

9. Future aspects

Several questions remain unanswered to fully understand the mechanisms of mitochondrial function, transport, turnover and degradation in astrocytes. Given the complexity of astrocyte sub-populations and region-specific phenotypes [137] several experimental approaches and models are needed to study mitochondrial function and possible impairment in these cells.

It is important to note that very little literature exists about AD-associated mitochondrial dysfunction specifically in astrocytes, although recent reports have highlighted the importance of this cell type in neurodegeneration. In the future, it will be critically important to carry out more studies that focus on alterations of astrocytic mitochondria in AD because of the arising role of these cells in the early onset of this disease. Furthermore, the utilization of human models in AD research is expected to provide valuable tools and detailed mechanistic insight into the role of astrocytes that is central in understanding the features of this devastating human disease.

As research steers towards an in depth understanding of the molecular basis of mitochondria and the mitochondrial quality control system it is possible that this might in the future provide both a diagnostic and a therapeutic tool for neurodegeneration.

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