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Abnormal Glucose Metabolism in Alzheimer's Disease: Relation to Autophagy/Mitophagy and Therapeutic Approaches

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Abstract

Diminished glucose metabolism accompanies many neurodegenerative diseases including Alzheimer's disease. An understanding of the relation of these metabolic changes to the disease will enable development of novel therapeutic strategies. Following a metabolic challenge, cells generally conserve energy to preserve viability. This requires activation of many cellular repair/regenerative processes such as mitophagy/autophagy and fusion/fission. These responses may diminish cell function in the long term. Prolonged fission induces mitophagy/autophagy which promotes repair but if prolonged progresses to mitochondrial degradation. Abnormal glucose metabolism alters protein signaling including the release of proteins from the mitochondria or migration of proteins from the cytosol to the mitochondria or nucleus. This overview provides an insight into the different mechanisms of autophagy/mitophagy and mitochondrial dynamics in response to the diminished metabolism that occurs with diseases, especially neurodegenerative diseases such as Alzheimer's disease. The review discusses multiple aspects of mitochondrial responses including different signaling proteins and pathways of mitophagy and mitochondrial biogenesis. Improving cellular bioenergetics and mitochondrial dynamics will alter protein signaling and improve cellular/mitochondrial repair and regeneration. An understanding of these changes will suggest new therapeutic strategies.

Keywords

Mitophagy/autophagy; fission; fusion; glucose metabolism; neurodegeneration

1. Glucose metabolism and brain function

Normal brain function requires a large and continuous supply of glucose and oxygen. The brain represents only 2% of the body's mass and consumes 20% of the body's oxygen. Further, since the energy reserves in the brain are small compared to high demand, reduced oxygen or glucose availability diminishes brain function. The high energy demand of synaptic functions links glucose consumption closely to neuronal firing. Thus, measures of

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glucose metabolism provide detailed anatomical maps of neuronal activation in the brains of animals and in humans. These maps of glucose utilization provide powerful tools to observe changes in brain activation during various diseases including neurodegeneration as the disease progresses.

Glucose metabolism is essential as a source of energy and as a carbon source of many key molecules. The brain, like other tissues, shifts metabolism in order to conserve the intracellular energy adenosine triphosphate (ATP), and preserve viability of the living cells. Although this shift in metabolism is beneficial in the short-term, the long-term consequences may diminish brain function and lead to neurodegeneration. Glucose is metabolized in the brain by the same classical pathways as in every other tissue including glycolysis, hexose mono-phosphate (HMP) shunt, tricarboxylic acid cycle (TCA) and electron transport chain (ETC). The glucose-linked metabolic pathways in brain provide many products (e.g., riboses for synthesis of DNA and RNA, the neurotransmitters acetylcholine, glutamate, gamma-amino butyric acid (GABA), serine) that are necessary for normal brain functions or can be damaging (e.g., excess lactate). Therefore, as metabolic pathways of glucose shift to maintain intracellular ATP, the resulting perturbations of glucose metabolism alter the ability of the brain to respond to further insults. This concept is very important in understanding the importance of changes in glucose metabolism in the pathobiology of neurodegenerative disorders.

The shift in metabolism can be readily modeled in animals and in cell-based experimental systems. Metabolic shift has been demonstrated by diminishing the activity of alpha-ketoglutarate dehydrogenase complex (KGDHC), a key enzyme of the TCA cycle by one-half. This reflects the KGDHC reduction in brains from AD patients. In cultured neurons, neuronal cell-lines or living mice, the reduction is associated with decreased *in vivo* and *in vitro* overall glucose metabolism and activation of the GABA shunt [1–3]. Under such circumstances, there is little overt pathology except for a dramatic decrease in the number of neuroprogenitor cells in the hippocampal zone. On the other hand, the response to neurotoxins is greatly exaggerated in these mice. The lesions from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), malonate or 3-nitropropionic acid (3-NP) are 3–10 times greater [4]. The importance of the shift in metabolism being beneficial in the short-term and damaging in the long-term has been demonstrated directly in culture of neuronal cell lines and/or primary cultures of neurons. Short-term reduction of KGDHC activity helps to facilitate the abilities of the cells to diminish external oxidative stress. On the other hand, more prolonged reduction of KGDHC impairs the ability of neurons to diminish oxidative stress. Similarly, long-term reduction in KGDHC causes Alzheimer's disease (AD) - like changes in calcium regulation whereas acute reductions do not mimic features of AD [5].

An inefficient interface between glycolysis and the mitochondrial pathways is also potentially damaging. For example, if the mitochondria does not consume pyruvate as fast as it is produced by glycolysis, lactate accumulates and the corresponding acidosis can be very toxic. If glucose is administered to delirious patients one must also give thiamine to shift metabolism to promote the mitochondria's ability to use pyruvate. Impaired transport of pyruvate into the mitochondria may be important in cancer cells which are very glycolytic and in AD, where aerobic glycolysis has been proposed as an early and defining feature.

Although estimations of human brain glucose metabolism are very sophisticated in measuring regional utilization of glucose, they are very limited in their capacities to identify the underlying mechanism(s). Positron emission tomography (PET) with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (^{18}F -FDG PET) provides detailed morphological map of brain glucose uptake and even temporal changes with the disease. However, ^{18}F -FDG PET only measures the first step of glucose metabolism. One can also measure the last step of metabolism by measuring oxygen consumption. The current methods fail to distinguish where the decline in synaptic activities cause or are a result of the abnormalities in glucose metabolism.

1.1 Glucose metabolism in patients with Alzheimer's disease

Glucose metabolism has been studied extensively in AD. Reduced glucose metabolism is an invariant feature and the best marker of cognitive state of this disease. The decline in glucose metabolism is highly correlated with changes in cognitive measures whereas the correlation of these measures to plaques is very poor [6]. Reduction in glucose metabolism occurs at early stages of AD. In patients with a genetic predisposition to developing AD, the decline in glucose utilization can occur when the person is in their twenties (i.e., long before the onset of the disease) [7]. However, the consequences of these reductions in glucose metabolism, in absence of overt energy failure, remains elusive. As mentioned previously, the shift in metabolism occurring in AD reflects changes in the interface between glycolysis and the mitochondrial TCA cycle. Aerobic metabolism indicates an increase in glycolysis without a corresponding increase in pyruvate oxidation by the mitochondria. Aerobic glycolysis, which can be measured in humans by PET scan, is a good predictor of the regions to be damaged in AD and the progression of the disease [8]. Although the cause of the reduced glucose utilization with AD has not been established, one possibility is a reduction in activities of the key enzymes of the TCA cycle. Both the pyruvate dehydrogenase complex (PDHC), which provides acetyl CoA, and the KGDHC are diminished in AD. The reductions in the activities of these enzymes are highly correlated to a decline in a cognitive rating scale in the patients, whereas plaques and tangles are poorly correlated to these measures [9].

The mild reduction in glucose metabolism that occur in AD due to altered mitochondrial function can be modeled by making animals thiamine (vitamin B1) deficient, by reducing E2k (the second protein of the KGDHC complex), or diminishing E3 (a protein common to KGDHC and PDHC). Although the homozygous mutation is lethal, the activity in heterozygotes declines by one-half. The E2k deficiency reduces KGDHC activity by half, and the E3 mutation diminishes activities of KGDHC and PDHC by one-half. Deficiencies of thiamine, E2k or E3 reduce neurogenesis in the hippocampal zone, but have surprisingly little effect on other phenotypes [10].

Multiple preclinical models demonstrate that the interruption of energy metabolism can be linked to the development of the pathologies that define AD, namely the plaques and tangles. Thiamine (vitamin B1) deficiency leads to a reduction in transketolase and KGDHC and causes memory deficits as well as plaque and tangle formation [11]. Reducing E2k exaggerates plaque formation and memory deficits in animal models of AD. In cell-based

models, interruption of metabolism leads to hyperphosphorylated tau and to production of amyloid-beta ($A\beta$)₁₋₄₂. In animal models, reduction of glucose metabolism leads to activation of β -secretase which is critical to plaque formation. Glycolysis in astrocytes may have a role in amyloid accumulation and cytotoxicity. Inhibiting astrocytic glycolysis results in an accumulation of amyloid protein and vulnerability to amyloid $A\beta$ cytotoxicity [12].

2. Decreased glucose metabolism and the ability of cells to repair themselves

An understanding of the link between these changes in metabolism to cell repair and cell death will enable the development of new therapeutic strategies. The above discussion details that the changes in glucose metabolism are critical in AD pathology, and suggests involvement of mitochondrial alterations to these changes. The reduction in KGDHC activity may be particularly critical in this respect. Experiments that tested the effects of reduced KGDHC on the ability of cells to buffer oxidants and on calcium regulation suggest that reductions in KGDHC may initially be protective, but with time cause AD-like changes [5]. Mild reduction in metabolism may alter mitochondrial repair, and inadequate mitochondrial repair may make neurons vulnerable to cellular insults. Removal of damaged mitochondria is critical for maintaining cellular homeostasis. If damaged mitochondria fuse with other existing healthy mitochondria, the resulting mitochondria can produce more reactive oxygen species (ROS) and release proteins that induce apoptosis. Thus, an understanding of mitochondria in cell repair and cell death is important in understanding their role in neurodegeneration and the link to altered brain metabolism.

2.1 Mitochondrial degradation by autophagy/mitophagy

Autophagy is the process of degradation of cellular components using the cells' own enzymes that is generally restorative and protective in nature. Autophagy (auto: self, phagy: eating, self-eating) is a lysosomal degradation process to recycle cellular constituents to eliminate or re-model damaged organelles. During autophagy, autophagic vacuoles/ autophagosomes engulf cytoplasmic components, such as cytosolic proteins and sub-cellular organelles including mitochondria or endoplasmic reticulum (ER). When the components targeted for degradation are only mitochondria, the process is known as mitophagy (mitochondrial-specific autophagy). There are three basic types of autophagy / mitophagy: macroautophagy, microautophagy and chaperone-mediated autophagy (Fig. 1).

2.1.1 Macroautophagy—is the formation of a double-membrane around part of cytoplasm followed by the formation of an autophagosome. This leads to engulfment of that part of cytoplasm along with the damaged organelle by the lysosomes for degradation. Upon autophagic activation, a cytoplasmic 18 kDa protein microtubule-associated protein 1A/1B-light chain (LC3-I) is processed and conjugated with phosphatidylethanolamine (PE) to form 16 kDa LC3-PE conjugate (LC3-II), which in turn is recruited to autophagosomal membranes [13]. Following autophagosome formation with the binding of LC3-II protein, engulfment of the specific cytoplasmic compartment and the fusion with lysosome for the degradation of the engulfed cytoplasmic content occurs. Macroautophagy involves phosphoinositide-3-kinase (PI3 kinase, which helps in autophagic vesicle nucleation), the

AuTophagy-related (ATG) proteins (which help to recycle membrane and to form complex with PE for membrane expansion) and ubiquitin-like conjugation reactions that leads to the formation of an isolation membrane from ER-mitochondria contact sites following the formation of autophagic vacuole and fusion with lysosome (Fig. 1) [14, 15].

2.1.2 Microautophagy—is a nonselective lysosomal degradation process that involves direct engulfment of cytoplasmic cargo at a boundary membrane by tube-like structures called autophagic tubes or by simply tubular like invaginations (Fig.1) [16].

2.1.3 Chaperone-mediated autophagy—targets proteins or organelles. For example, the huntingtin protein Htt has a pentapeptide KFERQ-like sequence that is recognized by the Hsc70 chaperone, which then associates with the integral lysosome membrane protein LAMP-2A [14, 17]. The association promotes LAMP-2A multimerization to form a translocation complex. The substrates then cross the lysosomal membrane by a luminal chaperone and enter into the lysosome. The lysosomal enzymes then degrade those substrates (Fig. 1) [18].

3. Mitochondrial fission, fusion and autophagy (mitophagy)

Healthy mitochondria are important for normal glucose metabolism and cellular health. Mitochondrial health in cells depends on their formation / rebuilding (biogenesis), their degradation (mitophagy) and remodelling (fission/fusion) [19, 20]. These processes are mediated by a variety of complex protein signaling pathways (Fig. 2). Mitochondria respond to different metabolic conditions by either repairing themselves (fission / fusion) or by degradation (mitophagy) or by increasing their mass (mitochondrial biogenesis). Depending on the cellular metabolic requirements and energy supplies, mitochondria fuse (fusion), divide (fission), fragment, swell, extend, and are recycled constantly in a regulated fashion [21]. Fission and fusion control the mitochondrial structure and function. More fission leads to more fragmented and smaller mitochondria, which are easily detected as damaged mitochondria and are degraded by mitophagy. Lower mitochondrial membrane potential diminishes fusion and promotes fission and mitophagy [22]. Unbalanced fusion leads to mitochondrial elongation while unbalanced fission leads to excessive mitochondrial fragmentation, both of which can lead to impaired mitochondrial functions (Fig. 2).

3.1. Fission

Fission is controlled by several mitochondrial and cytosolic proteins. Outer mitochondrial membrane (OMM) proteins including mitochondrial fission protein 1 (Fis1), mitochondrial fission factor (Mff), mitochondrial dynamics proteins (MiD49 and MiD51) are involved in fission. They recruit the cytosolic dynamin-related protein 1 (Drp1) to the mitochondria, which is the critical step to initiate mitochondrial fission [23, 24]. Drp1 is a guanosine triphosphatase (GTPase) that controls mitochondrial fission. It is mainly cytoplasmic and can be activated by modification at distinct sites. Phosphorylation, SUMOylation, ubiquitination, S-nitrosylation and O-linked-N-acetyl glucosamine glycosylation promote Drp1 recruitment to mitochondria, thereby increasing fission. Activated Drp1 translocates to mitochondria and assembles into helical structures that encircle and penetrate the mitochondria which induces fragmentation or fission of the organelle. Overexpression of a

dominant negative form of Drp1 (Drp1K38E) prevents mitochondrial fission [25]. Parkin ubiquitinates Drp1 and promotes its proteasome-dependent degradation [26]. Thus a loss of parkin from cytosol, as happens during parkin translocation to mitochondria, induces accumulation of Drp1 in the cytosol and increases mitochondrial fission. Drp1 is also involved in mitophagy and in cytochrome c release [27, 28], but is not involved in release of other protein signals from the mitochondria such as Smac/Diablo and Tim8a (Fig 2) [29, 30].

3.2 Fusion

Fusion is mediated by the proteins optic atrophy 1 (Opa1), mitofusins 1 and 2 (Mfn1 and Mfn2) [24]. Mitofusins are present in the OMM and Opa 1 is in mitochondrial intermembrane space [23]. Mfn1 is required for the first step of fusion, the initiation of tethering of fusing mitochondria. The second step of mitochondrial fusion requires the physical interaction between Opa1 and the two inner mitochondrial membranes (IMMs) to be fused by the hydrolysis of guanosine triphosphate (GTP). An intact mitochondrial membrane potential is required for mitochondrial fusion, and diminished mitochondrial membrane potential selectively inhibits fusion [31]. Another IMM enzyme, ATPases Associated with diverse cellular Activities (AAA) protease controls Opa 1 processing and mitochondrial protein degradation [32, 33]. Degradation or loss of Opa 1 from mitochondria inhibits the fusion of mitochondria and can alter mitochondrial structure. An increase in fusion is associated with neuroprotection (Fig. 2) [34, 35].

3.3 Mitophagy

Mitophagy protects cells from damaged mitochondria. Removal of damaged mitochondria prevent them from fusing with healthy mitochondria and from releasing proapoptotic proteins such as apoptosis-inducing factor (AIF) or cytochrome c. When the health of mitochondria cannot be restored by fusion, the unhealthy mitochondria are removed by mitochondria-specific autophagy referred to as mitophagy. Specific protein signal including LC3 are required to induce mitophagy. Depolarized mitochondria are not able to fuse and are selected for mitophagy [19]. Increased fission makes mitochondria more fragmented which are specifically designated as damaged mitochondria and are selected for mitophagy. The fragmented, small mitochondria can be easily engulfed by autophagosome/lysosome [36]. Mitophagy can be parkin-dependent or parkin-independent (Fig. 3).

3.3.1 Parkin-dependent mitophagy—Parkin is a cytosolic E3 ubiquitin ligase which plays an important role in mitochondrial degradation. Decreased mitochondrial membrane potential can trigger translocation of parkin to mitochondria which is the initiating step for mitophagy [16, 37]. Many studies suggest that parkin translocation to damaged mitochondria is responsible for inducing mitophagy in neurodegenerative diseases. Parkin induces ubiquitination and proteasomal degradation of selected mitochondrial fusion proteins [38]. It ubiquitinates Mfn2 protein present in the mitochondrial membrane to prevent fusion of that damaged mitochondria with other healthy mitochondria, and this ultimately leads to binding of mitochondria with LC3 via a protein called p62, followed by mitochondrial degradation (Fig. 3). Parkin translocation to mitochondria may reduce proteasomal activity in cytosol and that can lead to accumulation of several proteins in the

cytosol (i.e. Parkin interacting substrate (PARIS), α -synuclein, p-tau, A β etc.) [39, 40]. Parkin is involved in mitophagy following treatment with the mitochondrial uncoupler, carbonylcyanide-3-chlorophenylhydrazone (CCCP) [16, 41].

3.3.2 NIX-mediated parkin-independent mitophagy—Non-parkin mediated mitophagy mainly occurs during reticulocyte maturation through the involvement of the cytosolic NIP3-like protein X (NIX) protein [16]. In the process of erythrocyte maturation, NIX protein is upregulated and translocates to the mitochondria. At the mitochondria, NIX binds with BCL2/adenovirus E1B 19 kd-interacting protein (BNIP) and induces mitophagy, possibly through its ability to directly bind the autophagy protein LC3 [42].

3.3.3 Cardiolipin-mediated parkin-independent mitophagy—Mitophagy can also be induced by conditions that alter cardiolipin (CL) localization in mitochondria. CL is a phospholipid which is normally present only in the IMM. In compromised mitochondria, it “flips” to the outer side of the OMM. A mitochondria specific enzyme flippase/scramblase 3 is responsible for this CL movement in mitochondria. CL has specific binding site for LC3 protein. Externalized CL recruits LC3 to the OMM and induces mitophagy (Fig. 3). The increased level of LC3-II is a common marker for monitoring autophagic activity including mitophagy. RNA interference (RNAi) causing knockdown of cardiolipin synthase or of phospholipid scramblase-3 decreases mitophagy following mitochondrial damage [43]. CL flip and mitophagy can occur without increasing the Drp1 dependent-fission in a Drp1-independent manner. Mitophagy is inhibited in cells overexpressing Drp1 if mitochondrial scramblase 3 is knocked out. This supports the suggestion that CL externalization by scramblase 3 causes mitophagy and this is downstream of Drp1 [43].

3.3.4 Other possible mechanisms of mitophagy

3.3.4.1 MPT pore: The mitochondrial permeabilization transition (MPT) pore is a non-specific pore in the inner mitochondrial membrane. MPT causes mitochondria to become permeable to molecules smaller than 1.5 kDa, which, once inside, draw water in by increasing the organelle's osmolar load. This causes mitochondria to swell and may cause the outer membrane to rupture, which leads to release of cytochrome c [44, 45] (Fig. 4). Composition of phospholipids in the mitochondrial membrane also affects the MPT pore opening. Fatty acids have a role in regulating the activity of MPT pore which links lipids with mitochondrial dysfunction as well as with mitochondrial degradation (Fig. 4) [22]. Mitophagy mediated by MPT pore can also be induced by Drp1 translocation from cytosol to mitochondria. Downregulation of phosphatase and tensin homolog (PTEN) induced putative kinase 1 (PINK1) can also induce mitophagy through the MPT pore complex, though the detailed mechanism is still not very clear [46].

3.3.4.2 Mitochondria-associated ER membrane (MAM): The MAMs are a sub-compartment of the ER involved in mitochondrial function and dynamics. They are important for induction of mitophagy and autophagy, as the isolation membrane formation begins from this site [47]. In AD, there is a significant increase in both MAM function and the connections between the ER and the mitochondria and could be associated with

mitochondrial degradation (Fig. 4). The proteins involved in processing the amyloid precursor protein (APP) for the generation of A β are also located in the MAM [48].

3.3.5 Mitochondrial-cytosolic-nuclear crosstalk to apoptosis and mitogenesis/mitophagy

3.3.5.1 Release of cytochrome c: Cytochrome c is small mitochondrial protein (12 kDa) that is released to the cytosol from compromised and stressed mitochondria. Although it can induce caspase-dependent apoptosis, cytochrome c release also occurs in the absence of apoptosis [49]. Release of cytochrome c from mitochondria to cytosol can induce non-specific autophagy within the cell. Several different mechanisms can trigger the release of cytochrome c: CL peroxidation, leakage through MPT pore complex, Bax and Bac interactions with voltage-dependent anion channel (VDAC), and high K⁺ level in extra-mitochondrial matrix [50, 51].

3.3.5.2 Suppression of nuclear transcription: Mitochondria can also control the migration of proteins from the cytosol to the nucleus where they regulate transcription. Migration of parkin to the mitochondria promotes accumulation of the protein PARIS in the cytosol, which in turn promotes its translocation to the nucleus where it suppresses the expression of genes important in mitochondrial biogenesis, including peroxisome proliferator-activated receptor gamma coactivator (PGC-1 α) and its target gene, nuclear respiratory factor (NRF) - 1, as well as the nicotinamide adenine dinucleotide (NAD⁺) - dependent deacetylase sirtuin (silent mating type information regulation 2 homolog) 1 (*S. cerevisiae*) (SIRT1). PARIS mediates this action by binding to the insulin response sequences in the PGC-1 α promoter [39, 52]. P53 can translocate from the nucleus to mitochondria [53]. Mitochondrial stress changes expression of several genes in the nucleus (like PGC-1 α , cathepsin L) [54]. Oxidative stress can damage mitochondrial DNA (mtDNA) and that can alter cellular signaling by changing nuclear gene expression [54–56].

3.3.5.3 Apoptosis-inducing factor (AIF) and other proteins: The flavoprotein AIF is normally present within mitochondria. Following mitochondrial damage, it is released from mitochondria and translocates to the nucleus [57]. AIF translocation can take place even before the release of cytochrome c or before an alteration in the mitochondrial membrane potential. Poly (ADP-ribose) polymerase 1 (PARP-1) activation is responsible for AIF release from mitochondria [58]. Mitochondria specific enzymes, including those in the matrix, like the PDHC can also translocate from mitochondria to nucleus under stress and regulate gene expression as a transacetylase [59].

3.3.5.4 Other cellular signaling pathways: Apoptosis and mitophagy/autophagy are life and death partners that control each other. Generally autophagy blocks the induction of apoptosis, and apoptosis-associated caspase activation shuts off the autophagic process [60]. Autophagy depends on several signaling pathways, most important of which is the mammalian target of rapamycin (mTOR) pathway. Glucose metabolism and the mitochondrial signal are closely related with autophagy. Intact mitochondrial membrane potential is a necessary factor for fusion following fission. Low ATP generation from mitochondria induces adenosine monophosphate (AMP) - activated protein kinase (AMPK)

signaling pathway and inhibits mTOR [61]. Several mitochondrial proteins that go between mitochondria and cytoplasm are also connected with cellular death signal (apoptosis) activation. These vary from those involved in mitophagy and include cytochrome c, Smac/Diablo, HtrA2/Omi, Endo G, VDAC, AIF [62, 63].

3.4 Relation of mitochondrial dynamics with diseases

Alterations in mitochondrial dynamics may lead to several diseases including neurodegeneration [64, 65]. In several models of neurodegenerative diseases, changing mitochondrial fission or fusion can modify disease phenotypes [66]. Thus, a better understanding of mitochondrial biogenesis and repair and their relation to autophagy and cell death should enable development of better therapies in diseases that are accompanied by mild impairment of oxidative metabolism.

3.4.1 Autophagy / mitophagy in diseases—Autophagy has been implicated in multiple diseases including neurodegenerative diseases, cardiovascular diseases, ischemia, traumatic brain injury, pulmonary diseases and cancer [61, 67, 68]. Mitophagy has been related to AD, Parkinson's disease (PD) and Huntington disease (HD) [69]. Autophagy protects against tumors, necrosis and inflammation, and mitigate genome damage in cancer cells in response to metabolic stress [70]. The autophagy related gene, Beclin 1, is deleted in several cancers [71]. Loss of atg5 in cardiac tissue leads to more cardiac hypertrophy, abnormal contractile dysfunction, and accumulation of ubiquitinated proteins with abnormal mitochondrial structure [69]. Mice with knockout autophagy genes like atg5 or atg7 show more neurodegeneration and deficits in more functions as well as more accumulation of inclusion bodies [72]. Inducing autophagy by rapamycin removes toxic proteins from cells and is protective. In a HD model, the mitochondrial TCA cycle inhibitor 3-NP elevates apoptosis and reduces autophagic proteins LC3-II. LC3-II are significantly reduced by a p53 specific inhibitor which is protective [73].

3.4.2 PGC-1 α in diseases—Mitochondrial biogenesis is regulated by PGC-1 α - NRF - mitochondrial transcription factor A (TFAM) pathway as well as by Drp1 [74, 75]. Peroxisome proliferator-activated receptor (PPAR) is a transcriptional coactivator that interacts with a broad range of transcription factors including PGC-1 α which is involved in a wide variety of biological processes including mitochondrial biogenesis, oxidative phosphorylation, antioxidant defense, adaptive thermogenesis, glucose/fatty acid metabolism, fiber type switching in skeletal muscle, and heart development [76–78]. PGC-1 α does not bind to DNA directly, but forms heteromeric complexes with transcription factors, including NRF-1 and NRF-2, and the nuclear receptors, PPAR α , PPAR δ , PPAR γ , and estrogen related receptor α [79]. Expression levels of PGC-1 α , NRF 1, NRF 2, and TFAM are decreased in both AD hippocampal tissues and APPswe M17 cells, suggesting reduced mitochondrial biogenesis. In APPswe M17 cells diminished mitochondrial DNA/nuclear DNA ratio correlates with reduced ATP content, and decreased cytochrome c oxidase activity [80]. Thus, impaired mitochondrial biogenesis can induce mitochondrial dysfunction in AD [81].

3.4.3 Drp1 in diseases—Alterations in Drp1 are implicated in different diseases. Impaired mitochondrial biogenesis has been observed with the abnormal expression of Drp1 in postmortem AD brains, as well as in AD mouse models, and APP cell lines [82]. Inhibition of Drp1 is beneficial in cardiac dysfunction [83]. p-Tau and A β can increase Drp1 phosphorylation and Drp1 translocation to mitochondria to increase fission, resulting in more fragmented mitochondria, and mitophagy [16, 27, 84, 85]. Even mild oxidative stress can induce a Drp1-dependent increased fission which promotes mitophagy [20]. For example, in HD models, mutant Htt interacts with Drp1, elevates its GTPase activity, increases abnormal mitochondrial dynamics, and results in defective anterograde mitochondrial movement and synaptic deficiencies [86]. In systemic lupus erythematosus (SLE), HRES-1/Rab4 mediated Drp1 depletion and endocytic control is targeted in treatment [87]. Mitochondrial fission defects related to Drp1 contribute to apoptotic resistance in cancers [88]. In fibroblasts, Drp1 contributes to ABT-737-induced respiratory changes and the kinetics of cytochrome c release [89]. Thus, drugs targeted to the interaction between Drp1 and other proteins and mitochondria could be important for therapeutics.

4. Mitochondria as a therapeutic target

Mitochondrial dysfunction occurs with several diseases, thus this organelle has been suggested as a therapeutic target in several diseases including neurodegenerative diseases, heart failure, diabetes and cancer [90, 91].

4.1 Mitophagy as a therapeutic target

Treatment with a mitophagic/autophagic inducer rapamycin improves neurological outcome and mitochondrial function. These protective effects of rapamycin are reversed by treatment with an inhibitor of autophagy [13]. Benfotiamine, a thiamine derivative, largely prevents the AD pathology in a mouse model by enhancing the mitochondrial KGDHC enzyme activity [92].

4.2 Bioenergetics as a therapeutic target

Another approach to improving mitochondrial function is to enhance its bioenergetics. A shift from carbohydrate glycolytic metabolism to mitochondrial fatty acid and ketone oxidative metabolism has potential for therapeutics by modulating metabolism and signal transduction pathways [93]. Several compounds including creatine, coenzyme Q10, nicotinamide, riboflavin and lipoic acid have been proposed for use [94–97].

4.3 Activation of transcriptional pathways as a therapeutic target

Another way to improve mitochondrial function is by the activation of transcriptional pathways [98]. PGC-1 α and the other transcription factors associated with it (NRF-1, NRF-2, and the nuclear receptors, PPAR α , PPAR δ , PPAR γ) can regulate the expression of many nuclear encoded mitochondrial proteins. Therefore, pharmacological activation of the PGC-1 α pathway should be neuroprotective. One approach to activate PGC-1 α pathway is by activation of the PPARs. The PPARs are a subfamily of nuclear receptors that regulate gene expression programs of metabolic pathways. PPAR γ agonists that have been proven beneficial in *in vivo* and *in vitro* models include thiazolidinediones

like rosiglitazone. Bezafibrate is a pan-PPAR agonist that is beneficial in multiple cellular and animal models [99]. Over-expression of PGC-1 α completely rescues impaired mitochondrial biogenesis and mitochondrial deficits in APPswe M17 cells, while knockdown of PGC-1 α exaggerates deficits [80]. Cyclic AMP (cAMP) in a dose-dependent manner rescues the reduced expression of phospho-cAMP response element-binding protein (p-CREB) and PGC-1 α in APPswe M17 cells, and the effect can be diminished by the protein kinase A (PKA) inhibitor H89. Thus, the PKA/CREB pathway can play a significant role in the regulation of PGC-1 α expression in APPswe M17 cells. Resveratrol can induce biogenesis and control the interplay between apoptosis, mitophagy and biogenesis [100].

4.4 Activation of sirtuins as a therapeutic target

Another way to activate mitochondria is by activation of sirtuins, NAD⁺ dependent deacetylases. Activation of SIRT-1 activates PGC-1 α , which reduces plaque burden in plaque competent mice [101]. Resveratrol is a potent activator of SIRT-1, at least outside the central nervous system. SIRT-3 is primarily mitochondrial and is also activated by increasing NAD⁺ and it deacetylates several mitochondrial proteins, increases fatty acid oxidation, superoxide dismutase (SOD) 2 and levels of glutathione [102]. SIRT5 leads to desuccinylation in the mitochondria [103].

4.5 Activation of AMP-activated protein kinase also promotes mitogenesis

Mitogenesis is activated by increased cAMP and produces a cascade of phosphorylation dependent modification of several factors including PGC-1 α to switch on catabolic pathways to produce ATP, while simultaneously shutting down energy consuming anabolic pathways. 5-Aminoimidazole-4-carboxamide ribonucleoside (AICAR) and metformin are two compounds that activate AMP-activated protein kinase [104].

4.6. Activation by Nrf2/antioxidant response element (ARE) pathway can overcome mitochondrial deficits

After activation, nuclear factor erythroid-2 related factor 2 (Nrf 2) dissociates from Kelch-like ECH-associating protein 1 (KEAP1), translocate to the nucleus and binds to the antioxidant response promoter sequences leading to coordinated induction of a battery of antioxidant and anti-inflammatory genes known as antioxidant response element (ARE) dependent genes. These mechanisms have been extensively reviewed elsewhere [58]. Synthetic triterpenoids such as 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO) and its derivatives like CDDO-methyl ester (CDDO-Me), CDDO-methyl amide (CDDO-Ma), CDDO-ethyl amide (CDDO-Ea), and CDDO-imidazolide (CDDO-Im) are powerful inhibitors of oxidative stress and cellular inflammatory processes, and CDDO-Me (or RTA402) is very potent in activating KEAP1/Nrf 2/ARE pathway [105]. CDDO-Me has been tested in Phase III clinical trials for its therapeutic benefits in chronic kidney disease (CKD) and malignancies having inflammatory and oxidative components. It acts by activating Nrf2 and upregulating the antioxidant response while suppressing the nuclear factor (NF) κ B and proinflammatory signaling [105]. Thus it plays a promising role as a candidate drug for the diseases with defects in mitochondrial dynamics and biogenesis.

5. Conclusion and future directions

Impaired metabolism occurs in many neurodegenerative diseases. This causes changes in protein signaling that may be protective in the short-term, but are damaging in the long-term. Even mild reductions in metabolism lead to imbalanced mitochondrial fusion and fission. With more severe and prolonged impairment, these processes progress to mitophagy/autophagy which is restorative, while failure of these events lead to cell death. Thus, targeting mitochondrial changes is a potential effective therapeutic modality for many diseases including neurodegenerative disorders like AD.

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Fig. 1. Types of autophagy/mitophagy

Macroautophagy involves the formation of an autophagosome containing a portion of cytosol along with the damaged organelle (here mitochondria) within it. LC3-I is activated to LC3-II and binds to the autophagosomal membrane eventually causing it to fuse with lysosome utilizing proteins such as PI3 kinase and Atg by ubiquitin-like conjugation reactions. *Microautophagy* involves the direct engulfment of cytoplasmic material with the organelle using autophagic tubes or by simple invaginations. *Chaperone-mediated autophagy* involves the translocation of certain proteins complexed with chaperone proteins (like Hsc 70) into the lysosome by lysosomal integral membrane protein LAMP-2A (elongated oval). Lysosomal enzymes degrade the engulfed organelle and other components that need to be eliminated by the cell.

Fig. 2. Mitochondrial remodeling by fission/fusion and the proteins involved
Disruption to the balance of mitochondrial fission/fusion can lead to increased mitochondrial mass, increased mitochondrial number or induce mitochondrial degradation. Fission/fusion is controlled by the translocation of several proteins, both into and from the mitochondria. Some of the most important proteins are mentioned in the chart.

Fig. 3. Mechanisms of mitophagy induction

(a) In *Parkin-dependent mitophagy*, parkin translocates to damaged mitochondria with decreased membrane potential and ubiquitinates Mfn2 (diamond) in the mitochondrial membrane, prevents fusion with healthy mitochondria and facilitates binding with LC3 via P62, thereby inducing mitophagy of the damaged organelle. (b) In the *BNIP/NIX-mediated parkin-independent pathway*, the cytosolic protein NIX (rectangle) translocates to the mitochondria and binds with BNIP inducing mitophagy. (c) In the *cardiolipin (CL)-dependent parkin-independent pathway*, the phospholipid CL (star-shape) "flips" to the exterior surface of outer membrane of stressed mitochondria with the help of flippase/ scramblase 3 and binds with LC3 (circle) after recruiting the latter and induces mitophagy.

Fig. 4. Probable novel mechanism of mitophagy induction

Besides the pathways mentioned previously in fig. 3, there is the possibility of other pathways by different mitochondrial insults that may induce mitophagy. These could be Drp1 (diamond) translocation to mitochondria, or by the action of MPT pore (cylinder) or MAM (rectangle) or by cytochrome c (small circle) release.